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

FISCAL YEARS
2007–2008

Office of Research on Women's Health

&

NIH Support for Research on Women's Health Issues

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

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NIH SUPPORT FOR RESEARCH ON WOMEN'S HEALTH ISSUES

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), submits to the Director of the National Institutes of Health (NIH) this Biennial Report for fiscal years (FYs) 2007 and 2008. The report describes the comprehensive and coordinated efforts of the ORWH and the NIH Institutes, Centers (ICs), and Offices to address women's health issues through research and related activities in accordance with the NIH Revitalization Act of 1993. The information in this Biennial Report was prepared by the ORWH and by each of the NIH ICs and Offices to highlight significant research studies and other achievements and initiatives that have contributed to an increased knowledge of women's health. Using criteria supplied by the NIH Office of Financial Management (OFM) and the U.S. Department of Health and Human Services Office on Women's Health, and based on budget data provided by NIH ICs, this report also contains information on NIH budget allocations for women's health research during FY 2007 and FY 2008. In addition, the report contains information obtained from the NIH ICs and Offices documenting the inclusion of women and minorities in NIH-funded clinical research during the same time period.

The ACRWH has reviewed the information contained herein and believes that this Biennial Report accurately reflects the breadth and depth of research and related activities through which the NIH, in FY 2007 and FY 2008, has fulfilled its mandate from the U.S. Congress to address women's health issues and women's inclusion in research.

The ACRWH acknowledges the valuable contributions to this report of the CCRWH, which is made up of the directors of each of the ICs and Offices or their designated representatives. We are also grateful to the many NIH staff members who prepared and reviewed the reports of their ICs or Offices. We appreciate the work of the NIH Tracking and Inclusion Committee in preparing information on the inclusion of women and minorities in NIH-funded research and the work of the NIH OFM in collecting and tabulating the budgetary data published in this report.

Finally, the ACRWH wishes to acknowledge the work of ORWH staff. This Biennial Report reflects the achievements of the ORWH in fulfilling all aspects of its core mission in strengthening and enhancing research related to diseases and conditions that affect women; ensuring the appropriate representation of women in NIH research; supporting the advancement of women in biomedical careers; and building programs to ensure the development of a cadre of researchers, both women and men, in the field of interdisciplinary women's health research.

(For a full listing of ACRWH members for FY 2009, please see pages iv–vi.)

Advisory Committee on Research on Women's Health, FY 2009

Representative	*Title and Affiliation*
Vivian W. Pinn, M.D. *Chairperson*	Associate Director for Research on Women's Health Director, Office of Research on Women's Health National Institutes of Health
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Advisory Committee on Research on Women's Health, FY 2009

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Eugene P. Orringer, M.D. (2010)	Executive Associate Dean for Faculty Affairs & Faculty Development School of Medicine University of North Carolina at Chapel Hill Chapel Hill, North Carolina
Sally Rosen, M.D., M.F.S. (2011)	Special Assistant, Office of the Provost Director, Center for Women's Health Research, Leadership, and Advocacy Office of the Vice President for Research Temple University Philadelphia, Pennsylvania
Jeanne Craig Sinkford, D.D.S., Ph.D. (2013)	Professor and Dean Emeritus Howard University College of Dentistry Associate Executive Director and Director, Center for Equity and Diversity, American Dental Education Association Washington, District of Columbia
Susan P. Sloan, M.D. (2010)	Program Director, Internal Medicine Drexel University's College of Medicine Easton, Pennsylvania
Farida Sohrabji, Ph.D. (2013)	Associate Professor and Associate Department Head of Neuroscience and Experimental Therapeutics Texas A&M System Health Science Center College of Medicine Department of Neuroscience and Experimental Therapeutics College Station, Texas

Advisory Committee on Research on Women's Health, FY 2009

Representative	*Title and Affiliation*
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Debra Toney, Ph.D., RN (2012)	President, National Black Nurses Association President, TLC Health Care Service Las Vegas, Nevada
Barbara Yee, Ph.D. (2010)	Professor and Chair Department of Family and Consumer Sciences University of Hawaii at Manoa Honolulu, Hawaii

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Introduction to the Biennial Report

As directed in the National Institutes of Health (NIH) Revitalization Act of 1993,[1] the Advisory Committee on Research on Women's Health (ACRWH) submits to the NIH Director a report describing the activities of the Committee and its findings related to the mandates and funding for women's health. This report includes coordinated efforts of the NIH Institutes, Centers (ICs), and Offices to address women's health issues through research and related activities. As the 20th anniversary of the establishment of the Office of Research on Women's Health (ORWH) approaches, this FY 2007–2008 Biennial Report bears witness to the phenomenal growth in women's health research and related programs that has occurred since the formation of the Office in 1990. This report reflects major FY 2007–2008 ORWH research programs, initiatives, and activities, as well as highlights that were reported through the Coordinating Committee on Research on Women's Health (CCRWH) from the NIH ICs and Offices. This report is not a comprehensive listing of all NIH research on women's health, which would necessarily be encyclopedic; however, the report does serve to summarize, under a single cover, examples of the wealth of NIH advances in women's health research. This Biennial Report also provides information on and analysis of support for women's health research and related activities. During FY 2007–2008, NIH spent approximately $3.5 billion per year on research specifically related to women's health and approximately $23 billion on research relevant to both women and men.

The Biennial Report is divided into two major parts. Part One is based on ORWH programs and describes ORWH scientific, interdisciplinary, research, career development, and research dissemination and outreach programs. Data are also reported on the inclusion of women and minorities in NIH-funded clinical research as provided from the Office of Extramural Research. Many ORWH programs reflect the Office's roles in coordinating trans-NIH activities. Most ORWH programs are conducted in collaboration with NIH ICs and Offices. Other ORWH activities are conducted in collaboration with Federal agencies and/or with public and private partners. Part Two of the Biennial Report provides the individual reports on women's health research from 20 NIH Institutes, 4 Centers, and 7 Offices, which include highlights of some of their most promising research programs.

Office of Research on Women's Health

Information about ORWH programs is organized into six sections covering the following areas: ORWH Research; ORWH Interdisciplinary Research and Career Development Programs; ORWH Biomedical Career Development Activities; ORWH Research Dissemination and Outreach; Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research; and NIH Budget for Women's Health Research.

Section I describes FY 2007–2008 NIH women's health research priorities, developed in coordination with the CCRWH and reviewed by the ACRWH. It also provides a table of ORWH-funded projects grouped by diseases and conditions. It also provides examples of special ORWH research initiatives in FY 2007–2008 and highlights of ORWH-cofunded research projects and research workshops and conferences. A strategic planning effort, begun in 2008, is described in Section I. The effort, which will update the 1999 *Agenda for Research on Women's Health for the 21st Century*, is currently ongoing. It is anticipated that the updated research agenda will be completed in time for the 20th anniversary of the founding of ORWH in September 2010.

The Agenda for Research on Women's Health for the 21st Century recognized that women's health research is an inherently broad interdisciplinary field of endeavor, encompassing a full range of science. Since 1999, ORWH has been working to provide institutional support for interdisciplinary research and interdisciplinary research career development. Section II highlights major ORWH efforts to catalyze interdisciplinary women's health research and career development through two programs:

[1] The NIH Revitalization Act of 1993, P.L.103-43,107, Stat. 22 [codified at 42 U.S.C. 289(a)(1)] [Sec. 486(287d)(d)].

the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health, and the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Institutional Mentored Career Development Program. Section II also describes ORWH efforts to catalyze NIH interdisciplinary research and IC collaboration to advance understanding of a specific multifactorial condition predominantly affecting women, namely chronic fatigue syndrome.

Since its inception in 1990, the mandate of ORWH has included women's career development and the development of women's health researchers. The BIRCWH program is a major example of a highly successful mentored career development program that was developed and implemented by ORWH in 1999. Section III provides information on a number of other programs through which ORWH works to promote women's biomedical career development and the development of careers in research on women's health and sex/gender factors. Section III reports on the collaborative efforts of ORWH and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in supporting the Women's Reproductive Health Research Career Development program, and on the ORWH-initiated trans-NIH Reentry into Biomedical and Behavioral Careers Research Supplement Program.

Section III describes the activities of the NIH Director's Working Group on Women in Biomedical Careers to provide an NIH response to the challenges to Federal agencies posed in the 2007 National Academy of Sciences report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*. Section III also highlights FY 2007–2008 ORWH/NIH Intramural Women's Health Research programs, ranging from a summer research program for high school students interested in science to negotiation skills for tenure-track women scientists. The section ends with a summary of a wide range of other ORWH activities to promote the career development of women, some of which involve partnering with professional societies.

Section IV on research dissemination and outreach provides information on new ORWH Internet-based health information initiatives, including a collaborative effort with the NIH National Library of Medicine to create an online resource for information on women's health research; a Web-based course cosponsored with the Food and Drug Administration (FDA) on *The Science of Sex and Gender in Human Health*; and a multimedia approach to communicate advances being made from past and current women's health research. ORWH strives to ensure that the information generated from the NIH investment in research on women's health informs future research efforts and improves women's health care. Thus, outreach to the largest possible population of clinicians and researchers, women, healthcare providers, and others interested in women's health is a very important part of its mandate. Section IV describes ORWH outreach activities, including the Women's Health Seminar series and the Vulvodynia Awareness campaign.

Section V details NIH efforts to monitor the inclusion of women and minorities in NIH-funded clinical research, including data by ICs as well as NIH aggregate figures. Section VI provides information on NIH expenditures on women's health research, including a breakdown of expenditures by disease category and other major categories of interest (e.g., aging research).

NIH IC Support for Research on Women's Health

Part Two of the Biennial Report is composed of individual reports from each of 20 NIH Institutes, 4 Centers, and 7 Offices located within the Office of the Director, NIH. These IC and Office reports summarize their major initiatives and activities and provide highlights of their funded research related to women's health and sex/gender research, consistent with their specific missions.

You are invited to read this in-depth report to become acquainted with the tremendous advances in women's health research that have taken place during this 2-year period and to appreciate the promise for even greater advances in the future, not just for women's health, but also for men's health and for careers in women's health research for both men and women.

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

Office of Research on Women's Health (ORWH)

Introduction to ORWH Programs

In 1983, the Assistant Secretary for Health, Dr. Edward N. Brandt, established the U.S. Public Health Service Task Force on Women's Health Issues, in recognition of the paucity of data related to women's health. The Task Force produced a 1985 report, *Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I*.[2] The report delineated a series of criteria for differentiating a health problem, condition, or disease as a woman's issue. The criteria included the following:

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

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

Following the issuance of the Task Force report, the National Institutes of Health (NIH) established a policy for the inclusion of women in clinical research. This policy, which urged the inclusion of women, was first published in the *NIH Guide to Grants and Contracts* in 1987.[3] Later that year, minority scientists and other researchers at NIH recognized the need to address the inclusion of minority populations. As a result, a subsequent version of the NIH Guide published for the first time a policy encouraging the inclusion of minorities in clinical studies.[4]

In 1990, the Congressional Caucus for Women's Issues requested that the General Accounting Office (GAO), now known as the Government Accountability Office, conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, included in congressional testimony, indicated that the implementation of the policy for the inclusion of women was slow and not well communicated, that gender analysis was not being performed routinely, and that the impact of this policy could not be determined.[5] 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 (ICs) factored adherence to these policies into scientific merit review. GAO findings concerning the lack of consistent implementation of policies for inclusion of women in NIH clinical trials led NIH to establish the ORWH within the Office of the

[2] U.S. Public Health Service. Women's health: Report of the Public Health Service Task Force on women's health issues. *Public Health Reports* 100(1):74-106, 1985.

[3] Division of Research Grants. Inclusion of women in study populations. *NIH Guide to Grants and Contracts* 16(3):2, 1987.

[4] Division of Research Grants. Inclusion of minorities in study populations. *NIH Guide to Grants and Contracts* 16(32):3-4, 1987.

[5] *National Institutes of Health: Problems in Implementing Policy on Women Study Populations* (GAO/T-HRD-90-38, 1990). Washington, DC: *U.S. Government Accountability Office*.

NIH Director in September 1990. Since its establishment, ORWH has served as the focal point for women's health research at NIH. The responsibilities of the Director, ORWH, include the following:

(1) Advises the NIH Director and staff on matters relating to research on women's health;

(2) Strengthens and enhances research related to diseases, disorders, and conditions that affect women;

(3) Ensures that research conducted and supported by NIH adequately addresses issues regarding women's health;

(4) Ensures that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH;

(5) Develops opportunities for and supports recruitment, retention, reentry, and advancement of women in biomedical careers; and

(6) Supports research on women's health issues. ORWH works in partnership with the NIH Institutes and Centers to ensure that women's health research is part of the scientific framework at NIH and throughout the scientific community.

ORWH was established in statute in the NIH Revitalization Act of 1993.[6] An Advisory Committee on Research on Women's Health (ACRWH), composed of non-Federal members, was also statutorily mandated in the Revitalization Act as a mechanism for eliciting advice and recommendations on priority issues affecting women's health research. This Committee provides leadership to ORWH by advising the ORWH Director on appropriate research activities in women's health. ACRWH members are chosen from among health practitioners, advocates, research scientists, educators, and other professionals. Committee members are actively involved in reviewing and advising on matters related to research priorities, the women's health research portfolio for NIH, career development, inclusion of women and minorities in NIH-funded clinical research, and other ORWH or NIH programs related to women's health.

ORWH also benefits from the advice of a Coordinating Committee on Research on Women's Health (CCRWH). The CCRWH was also established in statute in the 1993 NIH Revitalization Act and is composed of Institute and Center Directors or their designees as a direct liaison for ORWH with NIH ICs. Both the ACRWH and the CCRWH provide valuable guidance, collaboration, and support for activities of ORWH in women's health research, career programs, and outreach efforts.

ORWH programs and efforts have expanded in breadth and depth over the years. The research funded or cofunded by ORWH is based on collaborative efforts with the ICs and supports peer-reviewed, science-driven initiatives. These collaborations are benefiting the health of all Americans across the lifespan, men as well as women, and all racial and ethnic groups.

[6]The NIH Revitalization Act of 1993, P.L. 103-43, 107, Stat. 22 [codified at 42 U.S.C. 289(a)(1)] [Sec. 486(287d)(d)].

I. ORWH Research

ORWH and Research on Women's Health: Identifying Priorities

The mission of the Office of Research on Women's Health (ORWH) includes stimulating and encouraging meritorious research on women's health, including the role of sex and gender in health and disease. Each year, the *ad hoc* Research Subcommittee of the Coordinating Committee on Research on Women's Health (CCRWH), composed of representatives from the National Institutes of Health (NIH) Institutes and Centers (ICs), considers continuing gaps in knowledge and emerging scientific opportunities for current research priorities in women's health. (See Appendix A for a listing of the *ad hoc* Research Subcommittee of the Coordinating Committee members.) The Subcommittee's recommendations are reviewed annually and approved by the CCRWH and the Advisory Committee on Research on Women's Health (ACRWH).

For FYs 2007 and 2008, the *NIH Research Priorities for Women's Health* are described in terms of four overarching themes, two special emphasis areas, and five areas of research interest, discussed below. These areas have been selected based on opportunities to advance the science and understanding of women's health research or the study of sex and gender differences.

Research opportunities are described in terms of overarching themes, areas of research interest, and special emphasis areas. These priorities represent areas for which there is a need to stimulate and encourage research on women's health or sex/gender factors, and the advancement of women in biomedical research careers. These research priorities are not an exclusive list of research areas important to women's health; therefore, other innovative or significant research areas should also be considered.

I. Overarching Themes

The following four overarching themes are important for addressing research on women's health: *Lifespan, Sex/Gender Determinants, Health Disparities/Differences and Diversity,* and *Interdisciplinary Research*.

Lifespan

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 frail elderly. Many women's lives and health status are also influenced by factors such as work inside and outside the home, caregiving such as childcare and elder-care responsibilities, reproductive status, marital status, and chronic illness. Each of these may influence health, disease, lifestyle and treatment choices, and response to therapy. Researchers should consider these variables in designing studies related to women's health.

Sex/Gender Determinants

Women are characterized by both sex and gender as highlighted in the *Agenda for Research in Women's Health for the 21st Century* and the Institute of Medicine report entitled, *Exploring the Biological Contributions to Human Health: Does Sex Matter*? 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 many areas of research, including basic biological, psychological, social, and behavioral studies. Consideration of these variables may be critical to the accurate inter-

pretation and validation of research affecting aspects of women's health. These variables determine how health or disease processes may differ 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 factors such as biology, genes, culture, education, effects of poverty, 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, environment, race/ethnicity, immigrant status, rural or inner city (urban) residency status, effects of poverty or low socioeconomic status, sexual orientation, and physical or mental disabilities.

Interdisciplinary Research

With our increasing understanding of the interrelatedness and complexity of health and disease, the nature of scientific investigation is shifting to an interdisciplinary collaborative approach. Advances in women's health can be better achieved by promoting partnerships across disciplines. Interdisciplinary approaches can integrate knowledge from disciplines, thus enhancing collaborations among researchers in academia, private industry, and Federal settings; and providing access to the latest scientific tools and technologies, and expertise for women's health research.

II. Special Emphasis Areas

NIH is especially interested in fostering research in women's health in the high-priority areas of prevention and treatment, and the biological and behavioral bases of sex and gender differences.

Prevention and Treatment

Increased investigation into methods to prevent conditions and diseases, or to better treat them, can result in significant improvements in the quality and length of women's lives. Prevention research spans the continuum from the most basic biological studies to understanding the basis and effects of risk behaviors across the lifespan and the interventions to change them, including a focus on wellness and healthy behaviors. Examples of needed prevention and treatment research studies in women's health include, but are not limited to, the following:

- Research in early detection and treatment, including the development of novel tools to identify and validate biomarkers, including genome-wide association studies, and functional and structural imaging in relation to disease risk, pathogenesis, and progression.
- Development of effective preventive and treatment strategies related to environmental and social factors involved in disease initiation and progression.
- Studies of the impact on health of diet and dietary supplements, hormones, exercise, weight patterns, sleep quality, toxin exposures, obesity, eating disorders, sex practices, tobacco, alcohol and drug use or abuse, occupation, violence, or trauma.
- Development of multimodal approaches to chronic diseases that contribute significantly to public health disability burden. Examples include addictions, cancer, coronary artery disease, diabetes, brain injury, stroke, neurodegenerative disorders such as Alzheimer's disease, obesity, musculoskeletal disorders, pain syndromes, chronic multisystemic diseases, and sexually transmitted diseases.
- Studies of the effects of biological, behavioral, cultural, social, economic, and environmental factors on susceptibility to, or protection from, disease and response to treatment, and where appropriate, subset analyses that can facilitate personalized medicine.

Biological and Behavioral Bases of Sex and Gender Differences

Although much research has been done to identify cellular pathways and genes, research on the effects of sex as a modifier of cellular and gene function is an underinvestigated area

of research. Systemic and cellular modeling of the influence of sex differences in biological pathways and systems is needed, including, but not limited to, the following:

- Mechanisms of sexual dimorphism in gene expression and cellular and signaling pathways in healthy women, including the impact of puberty, the menstrual cycle, pregnancy, and menopause.
- Sexual dimorphism in expression and function of genes, genetic polymorphisms, and gene defects in the risk factors, etiology, severity, and response to treatment of diseases.
- Genetic, molecular, and cellular bases of the action of pharmacologic agents in women, including differential effects between males and females.
- Sex and gender differences in disease prevention, pathogenesis, course, and response to treatment using basic, translational, behavioral, and clinical research approaches.

III. Areas of Research Interest

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

Diseases and Conditions That Affect Women

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

Basic and Clinical Research Methodology

Develop clinical trial methodology, including novel recruitment strategies, standardized outcome measures, and statistical analyses that address ethical and study design issues. Develop new methodologies for animal model studies of the normal development of women and their health and diseases, including female animal models. Encourage methodological studies related to the conceptualization, distinction, and detection of sex and gender differences in basic and clinical biomedical research. Encourage collaborations between basic scientists and clinicians to identify and test potentially relevant therapeutic approaches.

Career Development and Advancement of Girls and Women in Science

Identify and explore factors that affect the selection and advancement of women's careers in biomedical sciences; test the effectiveness of novel education programs directed at increasing the participation of girls and women in science, technology, engineering, and mathematics; and design and evaluate new approaches to reduce barriers to the sustained advancement and effective mentoring of women to senior and leadership positions in science.

Quality of Life

Elucidate the biological and behavioral factors that affect women's quality of life, especially elderly women. Develop approaches to management of disease and promotion of wellness that are unique for women, their families, and their communities.

Research Collaborations and Partnerships

Enhance trans-NIH, multi-U.S. Department of Health and Human Services (HHS) agency, public–private partnership, and community-based participatory research in women's health and career development.

Summary of ORWH-Cofunded Research

ORWH partners with the NIH ICs to fund or cofund meritorious projects that advance the mission and scientific priorities of 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 ORWH in selecting 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 ORWH is not limited to the enumerated priorities.

Tables 1 and 2 list research grants and contracts that ORWH supported with the NIH ICs for FY 2007 and FY 2008. Research summaries for FY 2007 and FY 2008 are found in Appendixes B and C, respectively. In both FY 2007 and FY 2008, ORWH collaborated with 17 NIH ICs as well as the HHS Agency for Healthcare Research and Quality (AHRQ) and the Indian Health Service. In doing so, the Office funded or cofunded more than 100 research grants and contracts. Research support is distributed across all the major scientific areas, including a focus on health disparities. Multiple grants were supported by ORWH in the areas of aging; alcohol and other substance abuse; cancer; cardiovascular disease; chronic fatigue syndrome (CFS); craniofacial disorders, such as temporomandibular joint and muscle disorders (TMJDs); diabetes; endocrinology; 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 ORWH addressed the full spectrum of a woman's lifespan, 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 cofunded by ORWH during FY 2007 and FY 2008. Research titles are grouped by broad topical subject areas, such as aging, cancer, and cardiovascular disease.

The research portfolio that derives from ORWH funding in FY 2007 and FY 2008 is extensive. ORWH and the NIH ICs use a variety of funding mechanisms to support these projects, including investigator-initiated grants, such as R01s, R03s, and R21s. However, other funding mechanisms are used as well, such as contracts and program project grants (usually P01s and P50s) and cooperative agreements (usually U01s and U10s). To stimulate research in specific areas of women's health, ORWH cosponsors with various ICs several priority Program Announcements (PAs) and Request for Applications (RFAs). They are listed in Table 3. The Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health and Building Interdisciplinary Research Careers in Women's Health (BIRCWH) programs are described in detail under Section II. Other activities deriving from the PAs and RFAs in Table 3 are described in this section.

EXAMPLES OF SPECIAL ORWH-FUNDED RESEARCH INITIATIVES

Advancing Novel Science in Women's Health Research (ANSWHR)

The two ORWH-created ANSWHR PAs were published in the *NIH Guide for Grants and Contracts* in June 2007 (FY 2007), and funded for the first time in July 2008 (FY 2008). ANSWHR has been very well received by the extramural scientific community and the ICs. Because of the complexity of working with up to 21 ICs on these two PAs, ORWH elected to have only an annual submission date of October 16. Nearly 200 applications were submitted in October 2007, with the majority as R21s. Sixteen of the ICs had one or more ANSWHR applications. Following study section reviews conducted by the Center for Scientific Review (CSR), priority scores and summary statements were carefully reviewed and combined across all of the applications and ICs. Based on the priority scores, ORWH worked with NIH scientific staff to create a funding plan that was reviewed by three Advisors from the Advisory Committee on Research in Women's Health. Based on these discussions and decisions, 11 applications were selected for funding in July 2008. Nine of

the awards were R21s and two were R03 grant mechanisms. Nine ICs partnered with ORWH for ANSWHR in FY 2008.

In terms of scientific focus, the awarded ANSWHR grants will concentrate on the genetics of reproductive life and the impact on health status; genetic pathways in systemic lupus erythematosus (SLE); sex differences in stress responsivity and psychopathology; sex differences in vulnerability to cocaine addiction; factors that regulate the timing of pubertal onset and reproductive maturation; novel ovarian cancer detection agents; evaluation of diagnostic techniques for cardiovascular events, using data from the Women's Ischemia Syndrome Evaluation (WISE study); inflammation and insulin sensitivity in obese pregnant women; sex differences and cognitive function; estrogen receptors and SLE; and sex differences in HIV/AIDS antiretroviral treatment.

Research Enhancement Awards Program

ORWH created the trans-NIH program called the Research Enhancement Awards Program (REAP) in the 1990s, and has developed very productive partnerships across NIH. The REAP program, offered once per year, supports meritorious research on women's health that has just missed the IC payline for funding. Four million dollars was available for REAP in FY 2007, and $1.5 million in FY 2008. ORWH has a policy of funding 1 year only, so all "out year" funds are provided by the primary IC. Seventeen grants were funded under the 2007 REAP, partnering with 8 ICs, and 13 REAP awards were made in 2008 to 6 ICs. Like other ORWH-funded projects, REAP spans basic, clinical, behavioral, and translational research. Some notable areas of science funded in FY 2007 include sex differences in behavior, cognition and neuroendocrine development, heart failure evaluation in postmenopausal women, autoantibody signatures as biomarkers of interstitial cystitis, fibromyalgia, smoking and pregnancy, and an animal model of long-term behavioral effects of neonatal pain and morphine treatment. Selected areas of science funded through the 2008 REAP program include decisionmaking about postmastectomy breast reconstruction, sustained skeletal benefits of adolescent exercise, effects of alcohol on gene expression, and genetic factors in SLE.

Research Dissemination Partnership With the National Library of Medicine

In March 2008, ORWH and the National Library of Medicine (NLM) announced the launch of an innovative new Web portal on women's health research. This portal, http://www.womenshealthresources.nlm.nih.gov, uses the *FY 2008 NIH Research Priorities for Women's Health* to identify overarching themes, specific health topics, and research initiatives in women's health. Within each section of the Web site are topics with links to relevant and authoritative resources and research initiatives for women's health. NLM has created specific user-friendly strategies for these topics to ease searching ClinicalTrials.gov and PubMed. Other Web resources used include AIDSinfo, American Indian Health, Arctic Health, Household Products Database, MedlinePlus, and NIHSeniorHealth. Search strategies for major studies related to women's health research have also been created and will be linked between the new Web site and the ORWH Web site. As with the topical search strategies, ClinicalTrials.gov and PubMed searches for each major report are also included.

Highlights of ORWH-Cofunded Research

The following sections highlight some of the research related to women's health. While illustrative of research supported by ORWH, these examples do not cover the full spectrum of the research portfolio on women's health. ORWH continues to develop its research base in 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 ORWH with NIH ICs, ORWH is able to provide funds for research on sex differences in health and disease in many areas, such as irritable bowel syndrome, stroke, and

the consequences and treatment of substance abuse. Additionally, ORWH cofunds innovative grants that focus on culture and cancer disparities, end-of-life care, and caregiver research.

Breast Cancer Pharmacogenomics

ORWH is cofunding 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 also serve as 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-responsive 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 promote cancer growth.

Human Papillomavirus (HPV) Vaccine

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 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 HPV 16 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.

Uterine Leiomyoma (Uterine Fibroids)

ORWH has had a longstanding interest in fostering greater research on uterine fibroids because of the high prevalence of this condition in women of all races and ethnicity, but especially for women of color. Uterine fibroids represent a health disparity that disproportionately affects African-American women. During FY 2007 and FY 2008, ORWH collaborated on a number of important projects in this area. With support from the ORWH and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the Leiomyoma Tissue Bank (LTB) was created in FY 2007. Research into the causes and treatment of fibroids has lagged behind other conditions, 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 NIH and the Department of Defense (DoD). The LTB is located in NICHD and is structured after similar tissue banks created for endometrial tissue and ovarian tissue that were established by the Specialized Cooperative Program in Reproductive Research. During this same time

period, NICHD intramural investigators have partnered with colleagues across the United States to create a comprehensive clinical classification system for fibroids that is currently being evaluated as an aid to promoting more uniform research in this area.

Additionally, NICHD and ORWH are cofunding several extramural research projects that address the molecular basis of uterine fibroids. ORWH and NICHD cofunded 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.

Vulvodynia

ORWH, NICHD, other components of NIH, public advocacy groups, and other agencies in HHS are collaborating on efforts to advance research and education on vulvodynia through a variety of methods. 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. 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. A program announcement, Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (PA-07-182), is encouraging further research that will be funded by NICHD and ORWH. In fall 2007, ORWH created a Vulvodynia Awareness Campaign (VAC) that has proved to be very successful. Working with over 40 partners across the spectrum of Federal agencies, professional societies, and advocacy groups, ORWH hosted a major press event in Washington, DC, that launched the VAC. Campaign materials include fact sheets, scientific articles, patient vignettes, and Web links for further information. (See Section IV, Outreach and Community Partnerships, for the full list of Vulvodynia Awareness Campaign partners.)

Menopause-Related Research

ORWH supports an extensive research portfolio on many aspects of the menopausal transition and symptoms. ORWH has partnered with the National Institute on Aging (NIA) on an RFA on the Biology of the Perimenopause: Impact on Health and Aging in Nonreproductive Somatic and Neuronal Tissues, from which several grants were awarded.

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 and skeletal and vascular health; the effects of cytokine secretion under follicle-stimulating hormone (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 peripheral nervous system; the estrogen-sensitive neuronal systems of the hypothalamus and effects on prolactin secretion; the survival and function of hippocampal neurons in collaboration with Insulin Growth Factor-1 (IGF-1) in a global ischemia model; and the transcriptional activation of estrogen receptors by nonestrogenic activators, as well as estrogen.

ORWH also cofunded other menopause-related grants with 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 healthcare providers and women across different racial and ethnic groups.

ORWH, the Office of Dietary Supplements (ODS), and NCCAM are partnering on several grants that focus on botanical products or other complementary and alternative medicine (CAM) methods to treat symptoms associated with 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.

New RFA on Menopausal Symptoms Follows Successful State-of-the-Science Meeting

In March 2007, the NIH 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 NIA, although other components of NIH and other Federal agencies, such as ORWH; NCCAM; NCI; National Heart, Lung, and Blood Institute (NHLBI); NICHD; NIMH; Food and Drug Administration (FDA); and Office on Women's Health (OWH) (HHS), cosponsored 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 not to be viewed as a disease. The tendency among women and their healthcare providers in the United States 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 nonhormonal treatment approaches.

The panel also found that, overall, there have been 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 related to studies of these products. More information on the SoS conference is available online. The final version of the conference report can be found at http://consensus.nih.gov/2005/2005MenopausalSymptomsSOS025main.htm.

In September 2008 (FY 2008), ORWH and other ICs partnered with NIA to fund an innovative research network entitled, Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH), to evaluate various interventions designed to reduce the vasomotor symptoms associated with menopause.

Prevention Research

While prevention has always been a component of the ORWH research portfolio, in 2007–2008, the Office emphasized it under the Special Emphasis section of the annual NIH Research Priorities. Below are selected cofunded prevention projects.

Microbicides Innovation Program (MIP)

In early 2009, an NIAID-funded clinical trial involving more than 3,000 women in the United States and southern Africa reported a finding, which for the first time demonstrated the promise of a vaginal microbicide gel for preventing HIV infection in women. According to findings presented at the Conference on Retroviruses and Opportunistic Infections (CROI), one 0.5 percent dose of a microbicide designed to prevent HIV from attaching to cells in the genital tract was 30 percent effective. While the results are encouraging, researchers on the study, known as HPTN 035, report that additional evidence is needed to determine more definitively its effectiveness.

ORWH, in collaboration with the NIH Office of AIDS Research (OAR), NIAID, NICHD, and NIMH, has funded a number of other microbicide studies, including 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. 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. Success of these tools will hinge on behavioral, cultural, and contextual factors (e.g., product characteristics, perceived risk of infection, and partner cooperation).

Other Prevention-Related Research

ORWH supports a number of research projects related to the prevention of diseases and disorders of importance to women. For example, ORWH is cofunding 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 on 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. 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.

Long-term benefits of these projects will include increases in research capacity for future HIV-related research activities in these countries.

Chronic Pain Syndromes

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. Among the chronic pain syndromes of importance to women's health are TMJDs. For example, ORWH and the National Institute of Dental and Craniofacial Research (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, ORWH cofunded 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. NIDCR and ORWH cofunded the International Research Registry Network for Sjögren's Syndrome, which is contributing valuable data from several countries, including the United States.

ORWH and the National Institute of Diabetes and Digestive and Kidney Diseases (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 nonmedical 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 United States 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, genetics, the environment, and health behaviors. Access to healthcare resources and socioeconomic differences have also been implicated in discussions of health disparities. ORWH and many other components of 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.

ORWH has funded a number of projects that fall under the category of male–female health disparities research, such as chronic pain syndromes, autoimmune diseases, and musculoskeletal disorders, and projects that focus on underserved, underrepresented minorities such as Hispanics and Native Americans. However, the Office also contributes to research on diseases that differentially affect minority women. An example of one major area is diabetes, which differentially affects women of color, especially African-American women.

ORWH has cofunded the Diabetes Prevention Program (DPP) since it was created in the 1990s. The original DPP demonstrated the efficacy of lifestyle modification and use of the drug, metformin, in decreasing 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 remained unanswered. Specifically, it was not known if the decrease in the development of diabetes would be sustained, or if the delayed onset or prevention of diabetes would 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 DPP, DPP Outcomes Study (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 5 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 inter-

vention 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 cofunded with 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. ORWH also partners with NICHD on a range of chronic gynecological conditions that affect the quality of life for many middle-aged and older women. In general, these grants focus on the etiology, prevalence, and possible treatment for these chronic conditions. ORWH participates with the HHS 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

As a focal point for women's health research at NIH, ORWH continues to encourage greater attention to autoimmunity and its impact on women of all ages, races, and ethnicity. 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 NIAID, ADCC is charged with coordinating and monitoring progress in autoimmune research across NIH.

Since its early years, ORWH has cofunded a number of grants with NIAID to advance the understanding of the underlying causes, complications, and treatment strategies for autoimmune disorders. More recently, ORWH cofunded 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.

Partnering with NIAID and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), ORWH cofunds autoimmune grants that focus on a number of conditions, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis. 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 is particularly prevalent in women of color. ORWH and NIAMS cofunded 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 SLE patients without aPL antibodies or fetal loss to non-SLE controls. 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. ORWH has been a long-term partner and cofunder with 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 genomic convergence for female osteoporosis risk genes, and comparing these identified genes in male samples. Additional projects evaluate the longitudinal changes in hip geometry and skeletal muscle, calcium absorption, factors affecting bone response or nonresponse, bone-sparing effects of soy phytoestrogens, and treatment effects on osteopenic bone loss.

Long-Term Scientific Collaborations

Most studies receive support from NIH for 3 to 5 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.

ORWH has been a collaborator with NICHD since the introduction of the Obstetrical–Fetal 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.

ORWH has also been a long-term partner with 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 6 months on incontinence in overweight women, with longer term followup of weight loss maintenance.

ORWH has collaborated with NICHD and other ICs since the initiation of the National Longitudinal Study of Adolescent Health (Add Health). Add Health is currently funded for Wave IV data collection. At the time (the project began in 1994–1995), investigators selected a nationally representative sample of adolescents in grades 7 through 12. Participants have been followed through adolescence and the transition to adulthood with three in-home interviews. Wave IV 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.

TABLE 1

ORWH Cosponsored Research, FY 2007

Subject	*Title*	*IC*	*Award Amount*
Adolescent Health	National Longitudinal Study of Adolescent Health	NICHD	$200,000
Aging	Phytoestrogens and Aging: Dose, Timing, and Tissue	NIA	97,100
	National Social Life, Health, and Aging Project	NIA	237,045
	Biological Mechanisms of Arterial Stiffening with Age and Estrogen Deficiency	NIA	48,550
	Impact of Endocrine Aging on Brain and Immune Responses	NIA	48,550
	Study of Women/Health Across Nation III	NIA	237,045
Alcohol and Substance Abuse	Reducing Alcohol & Risks Among Young Females	NIAAA	142,227
	Affect Regulation Training for Pregnant Smokers	NIDA	352,622
Cancer	Social Cognitive Theory and Physical Activity After Endometrial Cancer	NIA	106,582
	Caregivers' Strengths–Skills: Managing Older Cancer Patients	NCI	47,409
	A Topical Treatment for Genital Papillomavirus Infections	NIAID	179,897
	Pharmacogenetics Research Network and Knowledge Base	NIGMS	237,045
Cardiovascular Disease	Estrogen Dual Effects on Coronary Arteries	NHLBI	19,420
	Angiogenesis and Mechanisms of Exercise Training in Peripheral Arterial Disease	NHLBI	237,045
	Genetics of Early-Onset Stroke	NINDS	291,300
	Heart Failure Evaluation in Postmenopausal Women: The Women's Health Initiative	NHLBI	266,811
	Phytoestrogens and Progression of Atherosclerosis	NCCAM	94, 818
Chronic Fatigue Syndrome	Risk Factors Associated with CFS and CF Prognosis	NIAID	94,818
	HERV-K18 as a Risk Factor for CFIDS	NIAMS	164,058
	Chronic Fatigue Syndrome in Adolescents	NICHD	284,454
	Autonomic Nervous System in Chronic Fatigue Syndrome	NINDS	372,621
	Cognitive Behavioral Stress Management for Chronic Fatigue	NINDS	334,267
	Neuropeptide Y and Dipeptidyl-peptidase IV (CD26) in Chronic Fatigue Syndrome	NIAAA	147,653
	Mast Cells, Antidepressants, and Chronic Fatigue Syndrome	NIAAA	104,140
Complementary and Alternative Medicine	Botanical Dietary Supplements for Women's Health	NCCAM/ ODS	94,100
	Alpha-Tocopherol Modulation of Xenobiotic Metabolism	NIDDK	204,117

ORWH Cosponsored Research, FY 2007

Subject	*Title*	*IC*	*Award Amount*
Diabetes	Validity of Diabetes Self-Reports in the Women's Health Initiative	NIDDK	$244,409
	Impaired Glucose Challenge Test & Maternal–Fetal Outcomes	NIDDK	233,250
	Post-Diabetes Prevention Program Followup Study	NIDDK	284,454
	Look AHEAD: Action for Health in Diabetes	NIDDK	94,818
Endocrinology	Control of IGF-1 Gene Transcription by Growth Hormone	NIDDK	20,000
	Amygdala: Sex Differences in Behavior, Cognition, and Neuroendocrine Development	NIMH	550,926
	The Biologic Effects of Androgens in Men and Women	NICHD	194,000
Genitourinary	Role of Gene Expression in Interstitial Cystitis	NIDDK	225,000
	Autoantibody Signatures as Biomarkers of Interstitial Cystitis	NIDDK	262,500
	Epidemiology of Interstitial Cystitis/Painful Bladder System	NIDDK	195,300
	Seroprevalence and Incidence of Genital Herpes in Uganda	FIC	49,813
	PRIDE: Program To Reduce Incontinence by Diet & Exercise	NIDDK	97,000
HIV/AIDS	AIDS International Training and Research Program	FIC	50,000
	AIDS International Training and Research Program	FIC	50,000
	AIDS International Training and Research Program	FIC	50,000
	Recombinant CCR5 Inhibitors for Topical Microbicides	NIAID	13,000
	Improved Macaque Safety Model for Topical Microbicides: Postcoital Assessments	NIAID	13,000
	Implementation of a Vaginal/Rectal HIV Transmission Model To Evaluate Microbicides	NIAID	13,000
	Topical Immune Modulatory Strategies To Prevent HIV Transmission	NIAID	13,000
	Lactobacilli as a Source of Natural Microbicides Against HIV-1	NIAID	10,000
	Proteolytic Antibody HIVcides	NIAID	10,000
	Syndecan Agonists and Antagonists as Microbicides	NIAID	10,000
	Peptide Deformylase Inhibitor LBM415 for Sexually Transmitted Infections	NIAID	10,000
	CVN-12p1 Chimeras and Combinations for AIDS Microbicides	NIAID	10,000
	Engineering Simian-Derived Lactobacilli To Secrete Anti-HIV-1 Microbicides	NIAID	10,000
	Topical Microbicides Against SIV and Chlamydia	NIAID	10,000
	Development of N-Peptides for Use in HIV-1 Topical Microbicides	NIAID	10,000
	Stimulators of HIV-1 Integrase for Use in Combination Microbicides Regimens	NIAID	10,000

ORWH Cosponsored Research, FY 2007

Subject	*Title*	*IC*	*Award Amount*
HIV/AIDS (continued)	Mucosal Protection Against HIV Transmission by Combinations of Anti-HIV Antibodies	NIAID	$10,000
	Inhibitors of HIV-Dendritic Cell Interactions as Microbicides	NIAID	10,000
	Models for Testing Candidate Topical Microbicides for Cytotoxicity and Activity	NIAID	10,000
	High-Resolution Optical Imaging Assessment of Microbicide Toxicity	NIAID	10,000
	An In Vitro Model of Cell-Associated HIV-1 Transmission	NIAID	10,000
	Rational Development of Combination Microbicides Therapies	NIAID	10,000
	Development of Tissue Explant Models for Microbicides Evaluation	NIAID	10,000
	Linking Biophysical Functions of Microbicides to User Perception & Acceptability	NIAID	10,000
Immunity/ Autoimmunity	NARAC: The Genetics of Rheumatoid Arthritis	NIAMS	182,442
	Predictors of Pregnancy Outcome in SLE and APS	NIAMS	379,272
	Steroid Responsive Mechanisms in the Ear	NIDCD	19,420
	New Assay for MRBC-Specific Autoantibody Responses	NIAID	77,499
	Delineating the Role of Selected Genes in Lupus	NIAMS	76,999
	Nanoparticle Targeting of ICAM-1 as a Potential Treatment for Rheumatoid Arthritis	NIAMS	69,095
	Treatment of Autoimmune Disease by Costimulatory Signal	NIAID	58,260
	Modulation of B-Cell Responses in Autoimmunity	NIAID	55,891
	UCSF Autoimmunity Center of Excellence	NIAID	56,891
	Suppression and Exacerbation of B and T Cell Responses	NIAID	56,891
	UAB Autoimmunity Center for Excellence	NIAID	56,891
Menopause	Staging Reproductive Aging in Four Cohorts: Issues of Hormone Use Spotting Bias	NIA	472,098
	Neurobiology of the Menopausal Transition	NIA	48,550
	Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO	NIA	48,550
	Estrogen: Neuroprotection in the Perimenopause	NIA	48,500
	Menopause: Decreased Response to Increasing Inflammation	NIA	47,142
	Cytokine Modulation by Follicle-Stimulating Hormone	NIA	48,550
Mental Health	Emotions Are Emergent Events Constrained by Affective and Conceptual Processes	OD	78,625
	Antimanic Use During Pregnancy	NIMH	194,200
	Parenting and the Brain	NIMH	3,000
Musculoskeletal	Genomic Convergence for Female Osteoporosis Risk Genes	NIAMS	100,000
	Bone-Sparing Effects of Soy Phytoestrogens in Menopause	NIAMS	97,100

ORWH Cosponsored Research, FY 2007

Subject	*Title*	*IC*	*Award Amount*
Neurology/ Neurosciences	Estradiol and Glutamate in the Developing Hypothalamus	NINDS	$30,705
Obesity/Overweight	Altered Glucose and Lipid Metabolism in Obesity and CVD	NHLBI	194,200
	Estradiol Regulation of In Vivo Adipose Tissue Glucocorticoid Metabolism	NIA	48,550
	Markers of Autonomic and Metabolic Control in Childhood Obesity	NHLBI	101,842
Pain	Chemokine Receptor Function in the Nervous System	NIDA	20,000
	Brain Serotonin and Angiotensin II Systems in Migraine	FIC	39,060
	Long-Term Behavioral Effects of Neonatal Pain	NIDA	175,218
Physical Activity	Exercise-Based Motivational Interviewing for Fibromyalgia	NIAMS	493,749
	Young Adult Environmental and Physical Activity Dynamics	NCI	97,100
	Mediators and Moderators of Exercise Behavior Change	NCI	94,818
Reproductive Health/ Developmental Biology	Childhood Exposure to Disadvantage and Adult Pregnancy Outcomes	NICHD	30,096
	Protein Tyrosine Kinases in Leiomyomata Uteri	NICHD	70,427
	Finding Genes for Uterine Fibroids	NICHD	72,750
	Estrogen Dependency of Uterine Leiomyoma	NICHD	70,427
	Leiomyomata Uteri: Apoptosis and Cell Survival Pathways	NICHD	73,237
	Regulation of Uterine Fibroids by CCN5	NICHD	73,238
	Estrogen Biosynthesis and Uterine Leiomyomata	NICHD	73,237
	Molecular Etiology of Leiomyoma Uteri	NICHD	73,237
	Sixteenth Ovarian Workshop	NICHD	5,000
	Reproductive Medicine and the Law Workshops	NICHD	6,000
	17a-OH Progesterone Caproate and Progesterone Actions in Human Myometrial Cells	NICHD	226,500
	Pelvic Floor Disorders Network–Data Coordinating Center	NICHD	24,275
	The Pelvic Floor Disorders Network	NICHD	24,275
	The Pelvic Floor Disorders Network	NICHD	25,000
	Washington Obstetric–Fetal Pharmacology Research Unit	NICHD	50,000
	Obstetric–Fetal Pharmacology Research Units Network	NICHD	48,550
	Obstetric–Fetal Pharmacology Research Unit	NICHD	50,000
	Pregnancy and Drug-Metabolizing Enzymes and Transporters	NICHD	45,750
	Utah Pelvic Floor Disorders Network	NICHD	24,275
	Pelvic Floor Disorders Network	NICHD	24,275
	The Cleveland Clinic Clinical Site for Pelvic Floor Disorders	NICHD	24,275
	Pelvic Floor Disorders Network	NICHD	24,275

ORWH Cosponsored Research, FY 2007

Subject	*Title*	*IC*	*Award Amount*
Reproductive Health/ Developmental Biology (continued)	SGI Annual Meeting: Fostering a Multidisciplinary Approach to Research in Women's Health	NICHD	$5,000
	Cooperative Center for Research in Reproduction	NICHD	194,000

TABLE 2

ORWH Cosponsored Research, FY 2008

Subject	*Title*	*IC*	*Award Amount*
Adolescent Health	National Longitudinal Study of Adolescent Health (Add Health)	NICHD	$390,316
Aging	National Social Life, Health, and Aging Project	NIA	400,000
	Phytoestrogens and Aging: Dose, Timing, and Tissue	NIA	92,922
	End-of-Life Quality of Care in Nursing Homes	NINR	120,000
	Neuromuscular Fatigue in Older Adults	NIA	223,500
Alcohol and Other Substance Abuse	Effects of Alcohol on Gene Expression & Epigenetics of Progeny	NIAAA	125,000
	Sex Differences in Vulnerability to Cocaine Addiction	NIDA	230,250
	Women and Smoking: Understanding Socioeconomic Influences	NIDA	5,000
Cancer	Pharmacogenetics Research Network and Knowledge Base	NIGMS	230,171
	Novel Ovarian Cancer Detection Agents from Phage Display	NCI	184,400
	Understanding Decisionmaking in Breast Cancer Reconstruction	NCI	125,000
	Participatory Research To Understand the Translation of HPV Vaccine Policy	NCI	125,000
	Caregivers' Strengths–Skills: Managing Older Cancer Patients	NCI	46,488
	Dietary Lignan Effects on Hormone, Growth, and Signaling Factors in Breast Tumors	NCI	125,000
	Human Papillomavirus (HPV) Types 16/18 Phase III Vaccine Clinical Trial in Costa Rica	NCI	600,000
	Bench to Bedside Program	NCI	200,000
Cardiovascular Disease	Cardiovascular Events in Women's Ischemia Syndrome	NHLBI	75,357
Chronic Fatigue Syndrome	HERV-K18 as a Risk Factor for CFIDS	NIAMS	160,777
	Autonomic Nervous System in Chronic Fatigue Syndrome	NINDS	365,169
	Cognitive Behavioral Stress Management for Chronic Fatigue Syndrome	NINDS	327,582
Craniofacial	Hormonal Cycles in Women: Effects on TMD Pain & Symptoms	NIDCR	139,383
	Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?	NIDCR	5,000
Diabetes	Diabetes Prevention Program Followup/Outcomes Study	NIDDK	484,454
	Look AHEAD: Action for Health in Diabetes	NIDDK	94,818

ORWH Cosponsored Research, FY 2008

Subject	*Title*	*IC*	*Award Amount*
Dietary Supplements & CAM	Botanical Dietary Supplements for Women's Health	NCCAM ODS	$95,158
	North American Integrative Medicine Scientific Conference	NCCAM	50,000
Genitourinary	Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome	NIDDK	191,394
Global Health Partnerships	Fogarty International Clinical Research Scholars Support Center	FIC	150,000
HIV/AIDS	International Training in AIDS-Related Epidemiology	FIC	100,000
	The Risk of Cardiovascular Disease Among Women in the Women's Interagency HIV Study Initiating Abacavir	NIAID	150,000
	Gender Differences Among Women and Men Enrolled in China's National Free Antiretroviral Treatment	FIC	76,206
	Improved Macaque Safety Model for Topical Microbicides: Postcoital Assessments	NIAID	59,932
	Lactobacilli as a Source of Natural Microbicides Against HIV-1	NIAID	10,000
	Peptide Deformylase Inhibitor LBM415 for Sexually Transmitted Infections	NIAID	10,000
	Development of a Live Topical Microbicide for Women	NIAID	10,000
	Novel Stimulators of HIV-1 Integrase for Use in Combination Microbicide Regimens	NIAID	10,000
	Mucosal Protection Against HIV Transmission by Combinations of Anti-HIV Antibodies	NIAID	10,000
	Inhibitors of HIV–Dendritic Cell Interactions as Microbicides	NIAID	10,000
	Models for Testing Candidate Topical Microbicides for Cytotoxicity and Activity	NIAID	10,000
	High-Resolution Optical Imaging Assessment of Microbicide Toxicity	NIAID	10,000
	Mucus-Penetrating Nanoparticles for Sustained Microbicide Delivery	NIAID	18,182
	Novel Mucosal Models Predictive of Microbicide Safety	NIAID	18,181
	Novel Vaginal Microbicides Based on Stable AAV-Neutralizing Antibody Gene Transfer	NIAID	18,181
	HIV Integrase as a Target for Topical Microbicide Development	NIAID	18,181
	Combinations of Entry Inhibitors as Anti-HIV-1 Microbicides	NIAID	18,181
	Scalable Production of Recombinant Protein Microbicides	NIAID	18,181
	Intravaginal Ring Microbicide Formulations Comprising Multiple Anti-HIV Agents	NIAID	18,181
	HIV Sexual Transmission in Mice: Study of Microbicide Efficacy	NIAID	18,181

ORWH Cosponsored Research, FY 2008

Subject	*Title*	*IC*	*Award Amount*
HIV/AIDS (continued)	HIV Microbicides and the Vaginal Microbiome	NIAID	$18,181
	Microbicide Properties of RT Inhibitor Combinations	NIAID	18,181
	New SHIV R5 env's (based on all subtypes) for Effective Microbicide Testing	NIAID	18,181
Immunity/ Autoimmunity	Predictors of Pregnancy Outcome in SLE and APS	NIAMS	500,000
	NARAC: The Genetics of Rheumatoid Arthritis	NIAMS	175,217
	International Research Registry Network for Sjögren's Syndrome	NIDCR	300,000
	OGT Overexpression in Women with Lupus	NIAMS	196,966
	Do Estrogen Receptors in B Cells and DC Mediate Sex Bias in Murine Lupus?	NIAID	198,750
	Gender Bias in Lupus: Contribution of Sex Chromosomes	NIAMS	125,000
	Genetic Control of Renal Disease in Lupus-Prone Mice	NIDDK	125,000
	Complement Genetics and Clinical Variability of Systemic Lupus Erythematosus	NIAMS	125,000
	Innate Immunity and Allergy: Modulation by CTLA4	NHLBI	19,600
Menopause	Study of Women's Health Across the Nation III	NIA	232,304
	Neurobiology of the Menopausal Transition	NIA	47,579
	Biological Mechanisms of Arterial Stiffening with Age and Estrogen Deficiency	NIA	47,579
	Impact of Endocrine Aging on Brain and Immune Responses	NIA	47,579
	Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO	NIA	47,579
	Estrogen: Neuroprotection in the Perimenopause	NIA	47,579
	Menopause: Decreased Response to Increasing Inflammation	NIA	46,199
	Genetics of Reproductive Life Period and Health Outcomes	NIA	213,900
Mental Health	Antimanic Use During Pregnancy	NIMH	190,316
	Sex Stress Emotional Disorders: Uniting Preclinical and Epidemiologic Research	NIMH	241,800
	Sex Differences in the Entorhinal Cortex	NIMH	230,085
	Emotions Are Emergent Events Constrained by Affective and Conceptual Processes (Pioneer Award)	OD	390,000
Musculoskeletal Systems	A Study of Reduced Bone Quality as a Cause of Fractures	NIAMS	125,000
	Estrogen Effects on Atrophic Skeletal Muscle	NIAMS	125,000
	Bone-Sparing Effects of Soy Phytoestrogens in Menopause	NIAMS	97,100
	Osteoarthritis Initiative	NIAMS	800,000

ORWH Cosponsored Research, FY 2008

Subject	*Title*	*IC*	*Award Amount*
Neurology/ Neurosciences	Pathophysiology of MeCP2 Spectrum Disorders	NINDS	$125,000
	Sex Differences in Episodic Neurologic Disease	NINDS	125,000
Obesity/Overweight	DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women	NHLBI	234,000
	Bench to Bedside Program - Histaminergic Pathways and Energy Intake in Obese Women	NIDDK	80,000
Pain	Using fMRI To Evaluate CBT Treatment Response in Patients with Chronic Pain	NIAMS	150,000
Physical Activity	Sustained Skeletal Benefits of Adolescent Exercise	NIAMS	125,000
	Young Adult Environmental and Physical Activity Dynamics	NCI	97,100
	Mediators and Moderators of Exercise Behavior Change	NCI	92,977
	Social Cognitive Theory and PA After Endometrial Cancer	NCI	95,215
Reproductive Health/ Developmental Biology	Genetics of Reproductive Life Period and Health Outcomes	NIA	216,900
	The Role of GPR54 Signaling in Pubertal Disorders	NICHD	191,249
	Thyroid Function and Pregnancy	NICHD	135,000
	Washington Obstetric–Fetal Pharmacology Research Unit	NICHD	49,000
	Obstetric–Fetal Pharmacology Research Units Network	NICHD	47,579
	UW Obstetric–Fetal Pharmacology Research Unit	NICHD	49,000
	Pregnancy and Drug-Metabolizing Enzymes and Transporters	NICHD	44,835
	The History of Emergency Contraception	NLM	75,530
	ORWH–NICHD Leiomyoma Tissue Bank	NICHD	85,000
	Pelvic Floor Disorders Network	NICHD	24,500
	Pelvic Floor Disorders Network	NICHD	23,790
	Pelvic Floor Disorders Network	NICHD	23,790
	Pelvic Floor Disorders Network	NICHD	23,790
	Pelvic Floor Disorders Network	NICHD	24,500
	Pelvic Floor Disorders Network	NICHD	24,500
	Pelvic Floor Disorders Network	NICHD	23,790
	MSI-FLASH: Relative Efficacy of Hormonal and Nonhormonal Interventions for VMS	NIA	130,000
	SGI Annual Meeting: Fostering a Multidisciplinary SGI	NICHD	5,000
	Stillbirth Collaborative Research Network (SCRN) Ancillary Followup Study	NICHD	472,912
	Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH Network)	NIA	300,000

TABLE 3

FY 2007–FY 2008 List of ORWH-Related RFAs and PAs

ORWH-Developed and Implemented RFAs/PAs

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 (BIRCWH, K12)	(RFA-OD-06-004)
Advancing Novel Science in Women's Health Research (R21)	(PAS-07-381)
Advancing Novel Science in Women's Health Research (R03)	(PAS-07-382)
Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01)	(PA-08-246)
Chronic Fatigue Syndrome: Pathophysiology and Treatment (R21)	(PA-08-247)
Supplements To Promote Reentry into Biomedical and Behavioral Research Careers	(PA-08-191)

RFAs and PAs That ORWH Cosponsored

Women's Reproductive Health Research (WRHR) Career Development Program (K12)	(RFA-HD-08-014)
Leiomyomata Uteri: Basic Science, Translational and Clinical Research (R01)	(PAR-08-102)
Transdisciplinary Research on Fatigue and Fatigability in Aging (R01)	(PA-08-161)
Transdisciplinary Research on Fatigue and Fatigability in Aging (R21)	(PA-08-162)
Phase II Comprehensive International, Clinical, Operations, and Health Services Research Training Award for AIDS and TB (ICOHRTAAIDS TB) (U2R)	(PAR-08-155)
AIDS International Training and Research Program (D43)	(PAR-07-348)
Global Research Initiative Program, Behavioral/Social Sciences (R01)	(PAR-07-328)
Community Participation Research Targeting the Medically Underserved (R01)	(PAR-08-075)
Neurobiology of Migraine (R21)	(PA-07-306)
Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Comorbid Conditions (R01)	(PA-07-150)
Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Comorbid Conditions (R03)	(PA-06-267)
Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Comorbid Conditions (R21)	(PA-06-268)
Fogarty International Research Collaboration – Behavioral and Social Sciences (FIRCA-BSS) Research Award (R03)	(PAR-08-223)
Pathophysiology of Bisphosphonates-Associated Osteonecrosis of the Jaw (R21)	(PA-06-501)
Pathophysiology of Bisphosphonates-Associated Osteonecrosis of the Jaw (R03)	(PA-06-502)
Research on Social Work Practice and Concepts in Health (R03)	(PA-06-233)
Research on Social Work Practice and Concepts in Health (R21)	(PA-06-234)
NIH Support for Conferences and Scientific Meetings (R13/U13)	(PA-08-149)
NIH Clinical Trial Planning Grant Program (R34)	(PA-06-363)

Highlights of ORWH-Cofunded Research Conferences and Workshops

In addition to providing research support to ICs for women's health research, ORWH provides support for scientific workshops and conferences. A summary of all research conferences and workshops cofunded by ORWH in FY 2007 and 2008 is provided in Appendix D. Furthermore, ORWH cosponsored three major conferences on women's career development in coordination with multiple NIH ICs and other sponsors. These conferences are summarized in Section III of this report: ORWH Biomedical Career Development Activities.

In FY 2007 and FY 2008, research workshops and conferences organized by ORWH included an annual interdisciplinary symposium on research on women's health, a BIRCWH Scholars public policy training program, and two meetings for interdisciplinary researchers in chronic fatigue syndrome. Other ORWH-cosponsored research conferences of special interest included a unique partnership with the DoD and the Veterans Administration on trauma spectrum disorders, especially as these conditions affect women and men in the military. Also of special interest was a scientific conference on teen dating violence. The conference resulted from a trans-Federal agency collaboration involving the NIH, the Department of Justice (DOJ), and the Department of Health and Human Services (HHS) Office on Women's Health. The conference related directly to the reauthorization of the Violence Against Women Act (P.L. 109-162). Other ORWH-cofunded scientific workshops and conferences of special interest dealt with topics such as health disparities in women's smoking behavior and women's reproductive health. Below are summaries of these research workshops and conferences.

Annual Interdisciplinary Symposium on Research on Women's Health

The Interdisciplinary Symposium on Research on Women's Health is held annually in November in conjunction with the annual SCOR and BIRCWH Principal Investigator meetings and the BIRCWH scholar meeting in order to showcase scientific research from ORWH interdisciplinary research and career development programs.

At the Fourth Annual Interdisciplinary Women's Health Research Symposium in November 2007, Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA), gave a keynote address entitled, "Women and Substance Abuse: What Do We Know?" Platform presentations included studies of female-specific factors in stress responses; sex differences in pelvic floor conditions and urinary tract infections; health disparities research and epidemiological studies of diverse populations of women; and studies investigating sex-specific factors in relation to risk for cardiovascular diseases. A poster session provided BIRCWH scholars with an opportunity to present their ongoing research.

The Fifth Annual Interdisciplinary Women's Health Research Symposium, held in November 2008, included a keynote address by Dr. Steven Katz, Director, National Institute of Arthritis and Musculoskeletal Disease entitled, "Translating Science into Improved Patient Care." As in 2007, the 2008 Symposium had presentations of research from BIRCWH and SCOR programs and a poster session for BIRCWH scholars. Presentations included research on a wide range of topics related to women's health and sex/gender factors including substance abuse, pain, psychiatric comorbidity with perinatal depression, irritable bowel syndrome, cardiovascular disease risk factor control, urinary incontinence, and HPV vaccines.

George Washington University BIRCWH Scholars' "Day on the Hill" Training Program in Health Policy for NIH Fellows

Each year, ORWH provides support for an educational program to provide the ORWH BIRCWH scholars with a solid understanding of the health policy legislative process in Washington, DC. This Fellows Training Program is designed to educate them on the structure and processes of health policymaking. In November 2007, this unique pro-

gram focused on the development of health, healthcare, and medical research policy, with a particular focus on women's health, and was accomplished via a day-long event on Capitol Hill. The program was conducted by faculty of the George Washington University Department of Health Policy (including Dr. Carolyn Mazure, who now serves as a Professorial Lecturer, and Dr. Marsha Simon, former Staff Director for the Senate Committee on Appropriations, Subcommittee on Health). The session also included guest speakers involved with the daily workings of the legislative process.

In 2008, ORWH once again held the BIRCWH Scholars "Day on the Hill" training program, which was focused on the impact of the 2008 Presidential election on biomedical research, with particular attention to women's health research and health policy.

Grantsmanship Workshop for Research on Chronic Fatigue Syndrome

The Trans-NIH Chronic Fatigue Syndrome Working Group held a 1-day grantsmanship workshop in September 2007 to provide CFS researchers with an enhanced understanding of the NIH funding process, an overview of the diverse funding opportunities available through the NIH Office of Extramural Research (OER), and the opportunity to meet with and query Program Officers from the Institutes, Centers, and Offices represented on the Working Group. Emphasis was placed on the need to move to interdisciplinary, crosscutting research approaches. An afternoon session was devoted to explaining mechanisms appropriate for seeking research and training funding for CFS, even when the term itself is not included in the title. The 43 workshop registrants were a diverse group, both geographically and in terms of their scientific areas of interest. There was ample time for meaningful exchange and participant ratings were uniformly excellent. For more information, see http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html.

First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators

In June 2008, ORWH sponsored the First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators. The meeting brought together seven individuals who had received funding under an RFA specific to understanding the relationship of neuroimmune mechanisms and CFS. The investigators presented their results to date in the first half of the meeting and then participated in a team building exercise designed to encourage innovative collaborations. Discussions centered on how their work could be applied to understanding infection as a prototypical initial insult. Their work was seen as potentially providing insights into how systems become dysregulated and interact with one another to upset health. Other discussions focused on identifying methods that would be necessary for the investigators to function as an interdisciplinary team.

Trauma Spectrum Disorders: The Role of Gender, Race, and Other Socioeconomic Factors Conference

The goal of this conference, which was held in October 2008, was to provide a forum at which existing evidence-based science on sex, gender, race, and health disparities could be examined in the context of clinical management and care of traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD). The conference provided a unique opportunity to showcase what science could offer to the military and civilian practice and caregiver worlds. The three NIH Institutes represented—NIMH, National Institute of Neurological Disorders and Stroke (NINDS), and NICHD—provided their perspectives on the science base. Civilian and military scientists and caregivers also provided their perspectives. Potential cross-disciplinary partnerships were seen as having the potential to influence the care provided to those suffering from PTSD and TBI, as well as their family members. ORWH coordinated NIH involvement in this effort by working

closely with the Defense Centers of Excellence on Psychological Health and Traumatic Brain Injury (DCoE), and the Department of Veterans Affairs. Proceedings of the conference will be published and posted on both the DCoE and ORWH Web sites.

Joint NIH-HHS-DOJ Scientific Workshop on Teen Dating Violence

In response to the 2005 reauthorization of the Violence Against Women Act (P.L. 109–162) and the charge to the National Advisory Committee on Violence Against Women, ORWH cosponsored a 2-day meeting in December 2007 on teen dating violence along with the Department of Health and Human Services and the Department of Justice's National Institute of Justice. The goals of this workshop included the following: (1) build a consensus research and practical definition of teen dating violence; (2) discuss and review methods, measurements, and outcomes used for quantifying and defining teen dating violence, both in research and in practice; and (3) examine the research, both basic and applied, on teen, disabled youth, and particular cultural subgroups. A summary of the workshop is available at http://www.ojp.usdoj.gov/nij/topics/crime/violence-against-women/workshops/teen-dating-violence-agenda.htm.

Reproductive Medicine and the Law Workshop

With NICHD, ORWH cosponsored this joint workshop of the American Society for Reproductive Medicine (ASRM) and the Association of American Law Schools (AALS). The topic of the workshop was Reproductive Medicine and the Law. This unique educational activity brought together legal and medical scholars to develop guidance for the legal and medical professions dealing with legal issues that have arisen with the advent of assisted reproductive technologies. The workshop took take place in two parts, at the Mid-Year Meeting of the AALS in June 2007 and at the Annual Meeting of the ASRM in October 2007. The workshop was open to legal and medical scholars and professionals.

16th Ovarian Workshop, The Ovary: Signaling Mechanisms Regulating Development and Dysfunction

This workshop, organized by NICHD and cosponsored by ORWH, was held in July 2007. The goal of the workshop was to advance understanding of ovarian function so that this basic knowledge could be translated to clinical applications to enhance or control fertility and treat, reduce, and/or eliminate ovarian dysfunction and cancer. Conditions related to ovarian dysfunction under consideration at the workshop included sex reversal; metabolic disease; and steroid excess, including hyperandrogenic states leading to hirsutism, acne, and alopecia. Also considered at the meeting were other topics such as infertility treatments for women with ovarian dysfunction; preservation of fertility for women with cancer; the prevention and treatment of gynecological cancers related to ovarian dysfunction, including endometrial and ovarian cancer; and environmental threats to reproductive function. Another goal of the meeting was to provide participants with the ethical framework to understand the varying positions of the many constituents who weigh in on these issues.

The Menstrual Cycle and Adolescent Health Conference

NICHD, the American Society for Reproductive Medicine, ORWH, the NIH Office of Rare Diseases, the Food and Drug Administration Office of Women's Health and the U.S. Department of Health and Human Services Office of Women's Health cosponsored The Menstrual Cycle and Adolescent Health Conference in October 2007. A major meeting objective was to build a community of investigators, clinicians, patient advocacy groups, and governmental agencies committed to the long-term goal of focusing attention on the menstrual cycle as a marker of general health in adolescent girls. The meeting sought to define the scientific basis for the public health message that the menstrual cycle is a marker of general health in adolescent girls and to develop a related research agenda for the 21st century.

Uterine Fibroid Workshops

With NICHD, ORWH cosponsored two scientific workshops on uterine fibroids in September 2007. The first workshop focused on updating the science base. The second workshop, which followed immediately, considered a classification system for uterine fibroids that would better guide clinical treatment decisions and advance research in this area.

Preconception Care Research: Improving Birth Outcomes and Reproductive Health Workshop

Since many events before and around fertility may affect pregnancy outcomes, the workshop focused on women's health long before pregnancy begins. The purpose of this April 2008 workshop, which ORWH cosponsored with NICHD, was to bring together a broad spectrum of experts, including clinicians and basic and behavioral scientists to define a multidisciplinary framework for developing an agenda in preconception care research. The meeting covered a broad range of biological determinants that directly and indirectly influence preconception care. The diverse components of preconception care research and its specific impact on the reproductive system leading to improved birth and long-term health outcomes were explored.

Women and Smoking: Understanding Socioeconomic Influences Workshop

ORWH cosponsored a workshop with NIDA in April 2008 on Women and Smoking: Understanding Socioeconomic Influences. Health disparities in women's smoking behavior exist and there is ample sociological and epidemiological research to indicate that education moderates risk of smoking. The workshop aimed to enhance recognition of the urgency of the problem, embed the problem in a broader context with regard to other types of substance abuse as well as other non-substance-related public health problems, and foster interdisciplinary research efforts.

Strategic Planning for the Next Decade of Women's Health Research

Introduction

In 2007, ORWH began a process of exploring new dimensions and strategies for women's health and sex/gender research priorities for NIH in the coming years. Such efforts include a renewed emphasis on normal processes, developmental biology, and aging in women; reflection on the potential application of new technologies; the recognition of emerging diseases and conditions that may affect women's health or affect women differently; and integration of cutting-edge diagnostic and therapeutic strategies into healthcare delivery, among other perspectives. It is critical to ensure that future priorities for women's health research anticipate new dimensions of research and health, and incorporate innovative and successful strategies.

Since the establishment of ORWH in September 1990, enormous advances have been made in basic science and clinical applications related to women's health. It is now widely recognized that differences in sex/gender, cultural, ethnic, and socioeconomic backgrounds can influence the causes, diagnoses, progression, and treatment of disease.

ORWH, in collaboration with the ACRWH, the CCRWH, and the NIH scientific community, is once again seeking input from all concerned with women's health research, including women's health research leaders, scientists and researchers, advocacy groups, public policymakers, and the general public to consider the vast array of scientific and technologic advances, current gaps in knowledge, and emerging concepts and opportunities to develop innovative, science-driven women's health research initiatives for the future.

Regional scientific meetings include the opportunity for public testimony and provide a forum for interactive discussion among scientific, health professional, public policy, and advocacy communities of new priorities and approaches to advance the field of women's health research, ranging from clinical transla-

tion of basic research findings to the impact of behavioral, psychosocial, and societal factors on health and disease. This evolving process will consider areas of special importance for expanding current initiatives or developing new research programs in light of published research results or cutting-edge scientific advances and acknowledge nascent areas of science and/or diseases.

The challenge is revisiting a national research agenda for women's health focused on science-driven initiatives that leverages precious research resources and addresses women's health as creatively and comprehensively as possible. The goal remains to craft a research agenda that will serve as a catalyst to further advance our understanding of science and disease pathogenesis and ignite the translation of such findings to promote the health and well-being of women of all ages, races, ethnicities, and socioeconomic strata.

Initial comments have been received from a variety of sources interested in shaping the future of women's health research. One example includes correspondence received by ORWH from the American Society of Reproductive Medicine. This professional scientific society has proposed that reproductive health issues remain relevant to women's health research and should incorporate topics ranging from assisted reproductive technologies and long-term effects of oral contraceptives that stop menses for greater than 6 months at a time, to the effects of prenatal and intrauterine insults on development of disease.

Another important area of continued relevance is sex differences in aging; while the lifespan of women in general exceeds that of men, this is not the case for some regions of the country. Further, while women may live longer, the quality of life and role of disability in the health of elderly women warrant further attention.

As science and technology advance and fields such as computational biology and others demonstrate the true power of interdisciplinary research, it remains critical for sex and gender factors to be integrated into broad experimental methodologies and scientific approaches, such as genomics and the Human Microbiome Project, to maximize the value of these comprehensive and powerful approaches.

The disparities in health and disease among diverse populations of women remain critical areas in need of continued focus and renewed attention. Further biomedical and behavioral research are necessary to understand how cultural, ethnic, and racial differences influence the cause, presentation, diagnosis, progression, treatment, and outcome of disease among different populations, including women of diverse geographic locations and socioeconomic backgrounds.

In considering future priorities and strategies for research, ORWH is challenging all concerned about women's health to adopt an approach that is truly "forward thinking" in the creation of the future women's health research agenda and to consider creative strategies to address areas best poised for advancement, innovative ways to approach persistent issues of health and disease, and new questions or areas of focus. The results of the strategic planning process are anticipated to be available in 2010.

II. ORWH Interdisciplinary Research and Career Development Programs

Given the multiplicity of factors affecting women's health, a comprehensive and interdisciplinary approach to research in this area is clearly necessary. Women's health provides rich opportunities for collaboration and synergy of effort among clinical, basic, and applied scientists. To encourage collaborative interdisciplinary research, the Office of Research on Women's Health (ORWH) funds two major programs: The Specialized Centers of Research (SCOR) (P50) on Sex/Gender Factors Affecting Women's Health program, and the Building Interdisciplinary Careers in Women's Health (BIRCWH) Research K12 Institutional Mentored Career Development Program. These programs are featured in this section. A third interdisciplinary research program, the Advancing Novel Science in Women's Health Research (ANSWHR) award, has already been featured in Section I. Also in this section is a summary of the activities of a trans-National Institutes of Health (NIH) Collaboration Research on Chronic Fatigue Syndrome, coordinated by ORWH and involving multiple Institutes and Centers (ICs) in an interdisciplinary approach to a complex biomedical condition disproportionately affecting women.

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

As of FY 2008, the SCOR program of ORWH consists of 11 centers that conduct interdisciplinary research focused on major biomedical conditions affecting women, and that emphasize sex/gender factors contributing to these conditions. In both FY 2007 and FY 2008, ORWH provided approximately $10 million per year in funding to the program. The ORWH SCOR program represents an excellent model for stimulating interdisciplinary research and for human translational research, from bench to bedside, with significant applications to gender-specific human health. Each SCOR emphasizes research in an area of clinical importance to women's health. The SCOR mechanism provides for the establishment of a center program to promote collaborative research among scientists with varied expertise in order to achieve research objectives that go beyond those likely to occur through traditional grant mechanisms. An ongoing challenge is to maintain basic, clinical, and translational research within the same program.

The interdisciplinary nature of the new and continuing centers provides opportunities for innovative approaches to research on sex/gender-related health effects. The scope of research undertaken by the SCORs is based on three sources: the Institute of Medicine (IOM) report, *Exploring the Biological Contributions to Health: Does Sex Matter?*; the ORWH publication, *An Agenda for Research on Women's Health for the 21st Century*; and recommendations from NIH ICs. The IOM report highlights the critical importance of distinguishing between sex and gender factors in women's health, while recognizing the benefits of bringing both perspectives to bear on the area. The ORWH agenda stresses that a full understanding of women's health as a biomedical area could not be achieved without a consideration of multiple factors and crosscutting dimensions that provide the context for women's development and lifestyle.

Structurally, the SCORs are required to have at least three highly meritorious interdisciplinary research projects that explore an important issue related to sex/gender health differences. Individual projects must be related by a common theme, which encompasses clinical and basic research. An administrative unit at each institution oversees coordination of the individual projects.

Currently, the specialized centers are cofunded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Diabetes and Digestive and Kidney Diseases, National

Institute on Drug Abuse, National Institute of Mental Health, and the Food and Drug Administration.

SCOR Funding History

An initial Request for Applications (RFA) was issued by ORWH and participating NIH institutes in 2002. Based on the results of peer review, 11 SCORs were selected in 2002 for 5 years of funding. A second RFA was issued in 2006, resulting in 11 SCORs being selected to receive funding in 2007; 7 of these were renewal applications from the initial solicitation:

Represented in the 2007 funded SCORs are interdepartmental, intercollegiate, and even interinstitutional collaborations, which provide coverage of important thematic areas in women's health, and increase the span of impact of the mechanism. Areas represented include emerging areas of science such as the developmental impact of stress on adult health outcomes, including depression; sleep physiology and its complex interrelationships to health, obesity, and the metabolic syndrome; and new approaches to stress, health, and addiction that combine neuroscience and psychosocial areas of inquiry. These fields are further enhanced by the study of women's health. Sex/gender perspectives, in many areas, have only recently been brought to bear on the endeavors. At the same time, other SCOR programs continue to provide coverage in areas more traditionally identified as women's health, including reproductive health such as pregnancy, childbirth, pelvic floor disorders, osteoporosis, and urinary tract health. What is new in these funded SCORs is that the study of these conditions is enhanced by innovative interdisciplinary approaches, such as the impact of the central nervous system (CNS) on pelvic and visceral pain, and applications of emerging areas such as bioengineering and genomics to the problems of pelvic floor conditions and osteoporosis as well as the development of animal models to test interdisciplinary hypotheses and hasten translation from bench to bedside.

The SCORs identified in the second issuance of the RFA are currently in the second year of their funding period. In aggregate, SCORs report publishing 113 journal articles, 144 abstracts, and 30 other publications during the first year of this cycle.

SCOR I (2002–2007): Summary of Highlights of Funding Period

Eleven projects were funded as a result of the SCOR I RFA. Taken as a whole, the results of funding from SCOR I represent a large body of impressive and diverse findings related to women's health and sex/gender differences. Below is a brief summary of the research, as reported by investigators from this first 5 years of SCOR funding.

Institution: Emory University

Principal Investigator: Zachary Stowe, M.D.

Theme: *Pharmacology of Antiepileptic and Psychotropic Medications During Pregnancy and Lactation*

Models are being developed for the pharmacology of antiepileptic and psychotropic drugs during pregnancy and lactation. This information is seen as helping physicians provide risk–benefit information to pregnant and lactating women. The focus is on pharmacokinetic modeling of antidepressants and antiepileptic drugs during pregnancy and the postpartum period, with emphasis on predicting fetal exposure. The SCOR includes two clinical and one basic research project. Research highlights include a study of over 150 women with epilepsy who were treated with antiepileptic drugs (AEDs) during pregnancy. Fetal exposure to AEDs was quantified and has generated novel data with respect to the pharmacokinetics of AEDs during pregnancy, particularly lamotrigine. In another study, over 600 women with mood and anxiety disorders were enrolled to characterize the impact of pregnancy and childbirth on the clearance of these medications. Detailed studies of fetal exposure to antidepressants via amniotic fluid and placental passage were completed. Rodent studies from the group have demonstrated considerable CNS exposure both from pregnancy and breastfeeding exposure to antidepressants.

Furthermore, the group reported the development of collaborations with the SCORs at Northwestern, the Medical College of South Carolina, and the University of Florida.

Institution: Medical University of South Carolina (MUSC)

Principal Investigator: Kathleen T. Brady, M.D., Ph.D.

Theme: *Role of Sex and Gender Differences in Substance Abuse Relapse*

In this SCOR, the role of sex and gender differences in substance abuse relapse are studied, with particular emphasis on elucidating factors contributing to relapse. The substances included in this SCOR's research are tobacco, cocaine, and alcohol. A major goal of the Center is to coalesce a group of investigators across different disciplines in order to work together exploring gender differences in relapse and treatments for substance use disorders. The research includes four closely related core projects (two basic science and two clinical projects). Research highlights include findings from a rat model of cocaine-seeking behavior of clear differences between male and female animals; the response of the female animals was influenced by the estrus phase and stress. Reduced plasma progesterone levels are correlated with greater cocaine seeking in females. Other research indicating a significantly greater response was demonstrated to a psychological stressor for cocaine-dependent women as compared to cocaine-dependent men; in an exploration of gender and menstrual cycle differences in smoking cue reactivity, no gender difference in response to in vivo nicotine cues was demonstrated. In a mouse model, significant sex differences in the rewarding effects of alcohol and in the impact of medication pretreatment on these rewarding effects were demonstrated.

Furthermore, the group reported collaborations with SCORs at Yale, Emory, and University of California–Los Angeles (UCLA). A Women's Research Center was established at MUSC in 2002.

Institution: Northwestern University

Principal Investigator: Andrea Dunaif, M.D.

Theme: *Genes, Androgens, and Intrauterine Environment in Polycystic Ovarian Syndrome*

Genes, androgens, and the intrauterine environment in polycystic ovarian syndrome (PCOS) provide the theme for studies elucidating the pathogenesis of PCOS. The goal is to determine the role of genetic variation, androgens, and other factors in the intrauterine environment in the development of PCOS and the associated risk for diabetes. The unifying hypothesis that is being tested is that elevated circulating androgen levels resulting from variation in a gene regulating hormone production cause many of the phenotypic features of PCOS by prenatal androgen action. The SCOR includes two clinical and two basic research projects. Among findings reported by the group was that a genetic marker, allele 8 of D19S884, is associated with risk factors for diabetes in women with PCOS. This marker is located in a silent part of a gene known as fibrillin-3. This variant could alter the function of fibrillin-3 or of another gene, such as the insulin receptor gene, which is located in the same genetic region. Basic studies of rats indicated that intrauterine exposure to androgens causes features of diabetes by altering specific cellular K+ATP channels. In a primate model, intrauterine exposure to androgens in rhesus monkeys created the features of PCOS very early in life.

In addition to the above research findings, the group also reported the establishment of collaborations with the SCOR at Emory University, the University of Southern California, and the University of Chicago; a new fellowship program for physicians for advanced fellowship training in reproductive endocrinology and women's health; and the creation of animal resources for PCOS research.

Institution: University of California–Los Angeles

Principal Investigator: Emeran Mayer, M.D.

Theme: *Sex and Gender Factors in the Pathophysiology of Irritable Bowel Syndrome and Interstitial Cystitis*

Sex and gender factors underlying the pathophysiology of irritable bowel syndrome (IBS) and interstitial cystitis (IC) are being evaluated in this SCOR. The focus is on the interactions between the nervous system and the viscera, with special emphasis on sex-related differences in the interfaces among stress, pain, and emotions. Two common visceral pain syndromes, IBS and IC, provide the models. The SCOR includes two basic and two clinical research projects. Findings from the group in-

clude a demonstration that female IBS patients show greater responsiveness of arousal circuits, as indexed by greater startle responses and greater anxiety ratings to visceral stimuli than healthy women. A rodent study indicated that activation of CRF1 receptors are involved in the development of visceral sensitization in response to repeated colorectal distention (CRD) in rats and that females are more sensitive to CRD. In a cat study, the group found that neutering significantly reduced acoustic startle in both sexes. In contrast, cats with IC (most of which are neutered) have increased startle responses. An upregulation of the central CRF/noradrenergic mechanisms underlying stress responsiveness is suggested in IC cats.

The group also reported that research collaborations were expanded in the area of sex-based differences at UCLA and other institutions. Several junior female investigators have been mentored and assisted in obtaining their own research grants. The group's strong emphasis on characterizing central stress hyperresponsiveness and the role of abnormal CRF/CRF1R signaling has resulted in collaborative efforts with several pharmaceutical companies to develop and evaluate CRF1R antagonists in human patients.

Institution: University of California–San Francisco (UCSF)

Principal Investigator: Jeanette Brown, M.D.

Theme: *Mechanisms Underlying Female Urinary Incontinence*

Mechanisms underlying female urinary incontinence are studied using epidemiologic, biologic, and molecular approaches. The impact of diabetes on urinary incontinence is also evaluated. The Women's Urologic Research Group at UCSF fosters translational research on the female urethra, bladder, and pelvic floor. The UCSF SCOR investigators were drawn from the UCSF Departments of Obstetrics, Gynecology, and Reproductive Sciences; Urology; Epidemiology; and Family Medicine and pursued three projects. The clinical research program includes multi-institutional collaborations, including the Northern California Kaiser Permanente Division of Research. The SCOR includes one basic and two clinical research projects.

Numerous research findings were reported, among them the following:

- Reproductive Risks of Incontinence Study at Kaiser (RRISK) is a cohort of over 2,000 women (mean age of 59 ± 8 years) enrolled in a study to evaluate hormonal and reproductive risk factors for incontinence and voiding dysfunction. Several modifiable factors for voiding dysfunction and incontinence have been characterized, including obesity, estrogen use, and hysterectomy. Also, after adjustment for multiple other factors, White women have nearly three times the prevalence of stress incontinence of Black women, and about twice that of Asian women.
- Plasma samples were collected from diabetes RRISK women (98 percent collected) to determine whether markers of oxidative stress and total antioxidant potential are associated with the presence and severity of diabetic voiding dysfunction and incontinence.
- Using gene microarray analysis confirmed by Western blotting and immunohistochemical analysis, genes have been identified that are preferentially upregulated or downregulated in incontinent rats.
- Successful isolation and characterization of adipose tissue-derived stem cells from adult rats and humans may be a potential treatment option for stress incontinence by delivering growth factors.
- A comprehensive, four-channel urodynamic monitoring system that incorporates a metabolic cage and a high-resolution ultrasound device has been developed. This system enables researchers to evaluate voiding behavior in awake, freely moving rats over a 24-hour period.

The group also reported the establishment of a partnership with the UCSF National Center of Excellence in Women's Health and collaborations with the University of Washington SCOR and use of data and biologic specimens from the UCSF SCOR study of diabetic women and urinary incontinence.

Institution: University of Maryland
Principal Investigator: Joel Greenspan, Ph.D.
Theme: *Sex Differences in Pain Sensitivity*

This SCOR is focused on neuronal mechanisms underlying sex differences in pain sensitivity, with particular attention to visceral and temporomandibular pain. Basic, clinical, and translational research is aimed at identifying the biological bases for sex differences and neuroendocrine contributions to pain and analgesia. The research program is diverse, ranging from molecular studies in animal models to clinical studies. The SCOR includes one clinical and two basic research projects. Research highlights include a report that demonstrates, in the absence of any pain condition, that women's brains amplify the same pain-related signals (temporal summation [TS]) to a greater extent than men's brains, and women do so based on differences in temporal integration of those signals. Furthermore, female patients with temporomandibular disorder (TMD) pain demonstrate significantly more TS than healthy women. There are profound sex differences in visceral pain sensitivity, such that normally cycling females are significantly more responsive to visceral stimulation than males. Using a variety of immunohistochemical techniques, estrogen receptor-like immunoreactivity (ER-LI) was clearly observed and prevalent in dorsal root ganglion (DRG) neurons, but rarely observed in trigeminal ganglion neurons. This differential regulation of ERs may explain why nociceptive sensitivity varies not only as a function of estrogen level, but also with the site of stimulation (head vs. body).

Other notable activities of the SCOR included the organization and hosting of a conference, The Painful Truth: A Conference on Sex, Gender, and Pain Research, held in Baltimore, MD, September 27–29, 2006, and a number of collaborations, including with the UCLA ORWH SCOR; the University of Maryland–Baltimore Organized Research Center on Pain; and the University of Maryland–Baltimore Women's Health Research Group, which administers the University of Maryland BIRCWH program.

Institution: University of Michigan, Ann Arbor
Principal Investigator: John DeLancey, M.D.
Theme: *Birth, Muscle Injury, and Pelvic Floor Dysfunction*

Studies at this SCOR focus on stress incontinence and, more specifically, the effects of childbirth on the development of urinary incontinence. The focus is an interdisciplinary approach to address the remarkable disparities that exist in pelvic floor dysfunction between men and women owing to their different roles in the reproductive process. SCOR investigators come from the Departments of Obstetrics and Gynecology, Biomechanical Engineering, and the School of Nursing and lead one basic and two clinical research projects. Research conducted by the group found that certain pushing patterns are considerably more efficient than others in terms of delivering the fetal head in a timely manner. The generally accepted paradigm that urethral support is the primary determinant of stress urinary incontinence is not true. Maximal urethral closure pressure has the greatest effect on the occurrence of stress urinary incontinence, with women with stress incontinence having a 43 percent lower closure pressure than continent controls. A predictive model of the Knack maneuver has been developed to identify those women for whom simple conservative treatments are ineffective and cause delays in more appropriate treatment, and to correctly target those women likely to benefit from treatment.

The group sponsored Michigan Pelvic Floor Research Day—an annual symposium attracting 40 to 60 researchers in related clinical and basic science disciplines. They also initiated a National Pelvic Floor Research Forum at the American Urogynecologic Society Meeting in 2006, bringing together researchers conducting basic science research into disease mechanisms affecting the pelvic floor, including cell biology, biomechanics, genetics, epidemiology, and related areas. Three University of Michigan (UM) BIRCWH scholars and 12 urogynecology fellows have become active in pelvic floor research. The SCOR Director serves on the Executive Board of the Institute for Research on Women and Gender (IRWG) at UM. The IRWG provides an institutional umbrella for disciplinary and interdisciplinary research ef-

forts focusing on women and gender; provides stimulation, coordination, and support to increase these efforts; and heightens the presence and impact of UM in the area of women and gender scholarship.

Institution: University of Pittsburgh

Principal Investigator: Gerald Schatten, Ph.D.

Theme: *Genetic and Environmental Origins of Adverse Pregnancy Outcomes*

This SCOR is studying genetic and environmental factors that contribute to adverse pregnancy outcomes, particularly recurrent pregnancy loss. The focus was on genetic and environmental causes of adverse pregnancy outcomes. The SCOR includes one clinical and two basic research projects. Among research highlights reported was a study of mouse embryos with a known epigenetic defect; the embryos were analyzed for morphologic differences compared to wild-type embryos. There was a wide variation in developmental progression, as well as a significant incidence of anatomical abnormalities. Micro-PET imaging was adapted to in vivo studies in both pregnant mice and nonhuman primates, with the goal of developing noninvasive imaging methods that would provide insight into the effect of environmental factors on development in utero. A clinical study found that smoking during pregnancy is associated with vascular perturbations, as evidenced by increased levels of serum for intracellular adhesion molecule 1. The group also reported the establishment of collaborations with investigators at the University of Cambridge, University of California at Irvine, Johns Hopkins University, University of Pennsylvania, National Institute of Immunology at New Delhi, University of Coimbra in Portugal, and Massachusetts Institute of Technology, among others.

Institution: University of Washington (UW)

Principal Investigator: Jashvant Unadkat, Ph.D.

Theme: *Mechanisms by Which Drug Transporters Alter Maternal and Fetal Drug Exposure During Pregnancy*

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. The focus is on the mechanisms by which drug transporters and enzymes alter maternal and fetal drug exposure during pregnancy. The SCOR includes one basic and two clinical research projects. A report from SCOR investigators found upregulation of the liver drug-metabolizing enzyme, CYP3A, during pregnancy, which in turn explains the lower maternal systemic exposure to protease inhibitors (PRIs) observed in HIV-infected pregnant women. These lower plasma concentrations of PRIs are likely to result in development of viral resistance, and therefore, progression of disease. As CYP3A enzymes are important in the metabolism of approximately 40 percent of the drugs on the market, these findings have wide-ranging implications in designing dosing regimens for pregnant women. Another study reported that one of the organic cation/H+ antiporters in human placenta has been identified as MATE1 (Multidrug and Toxin Extrusion). OCT3 in the basal membrane and MATE1 in the brush border membrane seem to work in tandem to mediate the elimination of organic cationic drugs from the fetus.

Other activities include the dissemination of UW SCOR research to practitioners. The UW SCOR investigators offered a continuing education course (CME) in Seattle (April 29, 2006) titled Drugs in Pregnancy: Benchtop to Bedside and a symposium held at the Society of Gynecological Investigation (SGI) meeting in Toronto, March 21–24, 2006, titled Pregnant Women Are Therapeutic Orphans.

Institution: Washington University

Principal Investigator: Scott Hultgren, Ph.D.

Theme: *Molecular and Epidemiologic Basis of Acute and Recurrent Urinary Tract Infections in Women*

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 United States and primarily affect women. The goal is to understand the molecular and epidemiologic basis of UTIs in women. The emphasis is on delineating the interactions that uropathogenic *Escherichia coli (E. coli)* (UPEC) makes with its host and the consequences of these interactions on downstream molecular circuitries that determine whether the encounter results in symptomatic or asymptomatic infection, bacterial clearance, commensal colonization, and/or recurrence. The SCOR includes one basic and two clinical research projects. Twenty-nine positively selected UPEC gene sequences have been identified using comparative genomics and the complete genome sequence of the prototypic cystitis strain and available sequences of other *E. coli* genomes. The bacteria associated with recurrent UTI often appear to be phenotypically and/or genetically identical to the bacterial strain that caused the initial infection, suggesting that selected *E. coli* strains may become uniquely adapted for colonizing and infecting their respective hosts. A Center for Infectious Disease Research (CIDR) with a focus on women's health has been established at Washington University and the SCOR has established collaborations with the UCSF SCOR.

Institution: Yale University

Principal Investigator: Rajita Sinha, Ph.D.

Theme: *Sex, Stress, and Cocaine Addiction*

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. The goals are to assess the effects of early life stress, sex hormones, and stress hormones on cocaine reinforcement and the risk of developing cocaine dependence; and to understand the contribution of sex-based factors in the association between stress and cocaine relapse. The SCOR includes one basic and two clinical research projects. Among highlights of the SCOR's research are animal studies showing that female animals take more cocaine, binge for longer time periods, and display a loss of circadian control over intake. These effects may characterize compulsive aspects of addiction and suggest that women may have a greater biological vulnerability to addiction than men. Other studies indicate that cocaine-dependent women show a blunted hypothalamic-pituitary-adrenal (HPA) response to stress, suggesting that perhaps in women the drive to use cocaine compulsively may be related to seeking hypothalamic-pituitary-adrenal axis stimulation. Stress-induced prolactin levels that are modulated by sex hormones are involved in stress-related relapse in women, but not in men. Men and women show a different pattern of brain activation during stress and drug/alcohol cue exposure and there are specific differences as a result of chronic cocaine abuse.

The Yale SCOR has begun collaborations with other ORWH-funded SCORs that are studying stress-related mechanisms in chronic diseases affecting women's health, as well as establishing internal collaborations, including Women's Health Research at Yale, Yale Division of Substance Abuse, the Yale Research Program on Stress and Addiction, Yale Ob/Gyn, and the Child Study Center.

SCOR II (2007–2011) Funding

SCOR II represents the first reissuance of the RFA. Several SCORs funded in the first funding period resubmitted applications for competitive peer review, and of these, seven were funded. These include MUSC, UCLA, UCSF, Northwestern, Washington University, Yale, and University of Michigan. Four new SCORS funded are from Brigham and Women's Hospital/Harvard; University of Chicago; University of Miami; and University of Missouri–Kansas City. These include new studies of fetal antecedents of adult depression as mediated by changes in the CNS and hypothalamic-pituitary-adrenal axis function; developmental effects of and sex differences in prenatal exposure to cocaine; the interrelationships of sleep, sex steroids, and metabolic disorders; and a genomic study to identify

genes predisposing to osteoporosis. Below is a summary of 11 SCOR II Centers, including institution, principal investigator, SCOR theme, a description of the program taken from the applicant's abstract, and a list of the titles of the scientific projects that comprise the interdisciplinary, translational theme of each SCOR. In addition, each SCOR has an administrative core and some have specialized cores for statistical and other crosscutting methodological and laboratory support. For the convenience of the reader, a summary table (Table 4) of SCOR II-funded Centers is also provided at the end of this section.

Institution: Brigham and Women's Hospital

Principal Investigator: Jill Goldstein, Ph.D.

Theme: *Fetal Antecedents to Sex Differences in Depression: A Translational Approach*

Major depressive disorder (MDD) is the fourth leading cause of morbidity and mortality worldwide, with women having twice the incidence of men. We are proposing a translational SCOR to integrate scientists from basic, clinical neuroscience and population-level perspectives to address the question of why women are at higher risk for MDD than men. Our underlying premise is that sex differences in adult MDD are initiated during mid-gestation, a period of hypothalamic-pituitary-adrenal axis circuitry development, sexual differentiation of the brain, and a period in which fetal risk factors for MDD have been identified. We will test hypotheses regarding the roles of adrenal and gonadal signaling pathways regulating BDNF and its interactions with GABA-ergic, GLU-tamatergic, and nitric oxide (NO) mechanisms in the development of regions in stress response circuitry. Project 1, a human in vivo study of 500 Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) MDD cases and 500 normal controls from a birth cohort (followed from prenatal development to age 47) will test for genetic polymorphisms associated with these pathways and maternal serum assessment of HPA abnormalities during midgestation to understanding sex differences in MDD. Forty recurrent cases matched to 40 normal controls will be re-recruited for functional brain imaging of stress response circuitry and neuroendocrine evaluations to test our hypotheses relating abnormal maternal–fetal HPA environment and genetic polymorphisms with sex differences in adult HPA dysfunction and stress response circuitry deficits. Project 2 consists of mouse models of developmental morphology and adult behavior regarding genetic and/or hormonal sex differences in embryonic HPA circuitry neurogenesis, cell migration, and cell death and the impact of these hormones and/or genes on sex differences in adult MDD phenotypic behavior analogous to human studies. Project 3 uses rat models to study morphological and adult endocrine outcomes, after fetal and neonatal glucocorticoid treatment on sex differences in developing HPA circuitry and adult sex differences in hormonal dysregulation and MDD phenotypic behavior. This includes the role of epigenetic factors resulting from early adverse glucocorticoid exposure. Our interdisciplinary teams of senior preclinical and clinical investigators, who collaborate with each other, have spent their careers studying the roles of hormones and genes in understanding sex differences in the brain, neuroendocrine deficits, and/or the treatment of MDD. To accomplish the integration of SCOR projects, we propose an Administrative Core. Thus the SCOR would provide support to formalize our collaborations to focus on a problem of major public health significance that has etiologic implications, particularly for women, and will provide knowledge for development of sex-specific treatment and prevention strategies.

Titles for the science projects in the SCOR are as follows:

- **Project 1:** Genes and Hormonal Fetal Antecedents to Sex Differences in the Brain in Depression
- **Project 2:** Animal Models of Sex-Specific HPA Axis Development
- **Project 3:** Sex-Specific Programming of the HPA Axis by Glucocorticoids

Institution: Medical University of South Carolina

Principal Investigator: Kathleen Brady, M.D., Ph.D.

Theme: *Role of Sex and Gender Differences in Substance Abuse Relapse*

Over the past 4 years, the MUSC's SCOR has functioned as a productive, interdisciplinary research center focused on treatment and relapse in substance use disorders in women. When the MUSC SCOR was established in 2002, it filled an important gap. While MUSC had significant depth and strength in translational, interdisciplinary research in the area of substance use disorders, there was no gender-specific focus. Furthermore, the MUSC SCOR was the first women's health research initiative to be undertaken on the MUSC campus. The active, campus-wide collaborations of SCOR investigators, combined with the SCOR pilot project program, have encouraged and impacted gender-based research campus-wide. During the renewal period, we propose to more closely link our scientific projects and follow up on intriguing findings from the previous funding period. Each core research project will involve the investigation of the biological basis of sex differences in drug abuse reinstatement, craving and/or relapse, and treatment implications. The overarching goals of the center will focus not only on supporting and maximizing the translational scientific collaborations of the core and pilot research projects, but also on continuing to catalyze the growth of gender-based research throughout the MUSC campus. The Specific Aims for the years 6–10 of the MUSC SCOR are Specific Aim #1: To continue the well-established, multidisciplinary, translational program of research focused on gender-related issues in substance use disorders at MUSC. Specific Aim #2: To provide common resources through the Administrative Core to assist investigators in increasing efficiency, maximizing scientific rigor and productivity, and collecting pilot data. Specific Aim #3: To encourage and support the growth of gender-based research throughout the MUSC campus. Specific Aim #4: To attract and mentor young investigators and new faculty in the area of research, particularly patient-oriented research, in women's health issues. Specific Aim #5: To provide a regional education and training resource for research in women's health. Center funding through the P50 funding mechanism has allowed us to (1) carve out a unique identity on campus, bringing energy and visibility to the importance of gender-specific research; (2) bring together institutional and scientific leadership to form a single operational unit; (3) establish critical infrastructure support to allow for efficient operations, integration, and stability of resources; (4) coalesce a group of senior investigators to integrate their scientific expertise and research skills, and advance gender-specific research in the substance abuse area; (5) attract and train new and junior investigators in gender-specific research; (6) support the development and testing of innovative ideas through pilot project funding; and (7) provide an impressive and supportive training environment for future basic and clinical researchers interested in gender-based research. The next funding period will allow us to build on these accomplishments, expand our research program into new areas utilizing innovative techniques, enhance our outreach and dissemination efforts, and attract new investigators through the Pilot Core. Our SCOR, with a truly interdisciplinary focus on gender issues in substance use disorders, is a ready resource for inter-ORWH Center collaborations and, as such, is an asset to the ORWH program.

Scientific projects in the MUSC SCOR include the following titles:

- **Project 1:** Sex and Estrous Cycle-Dependent Differences in Cocaine-Seeking Behavior
- **Project 2:** Stress-Induced Craving: The Impact of Sex and Ovarian Hormones
- **Project 3:** Gender, Menstrual Cycle, and Smoking Cue Reactivity

Institution: Northwestern University

Principal Investigator: Andrea Dunaif, M.D.

Theme: *Metabolic Syndrome in PCOS: Precursors and Interventions*

Polycystic ovary syndrome is one of the most common conditions of young women, and it is frequently associated with insulin resistance, glucose intolerance, and other features of the insulin resistance or metabolic

syndrome (MBS). In addition, affected women have significantly elevated mean low-density lipoprotein (LDL) levels and an increased prevalence of at-risk LDL levels, independent of obesity. There is a genetic susceptibility to PCOS and we have identified a major susceptibility gene on chromosome 19p3.2 near the insulin receptor gene using the reproductive phenotype of hyperandrogenemia. We have now mapped the location of this variant (allele 8 [A8] D19S884) to an allele of a dinucleotide repeat in intron 55 of the fibrillin 3 gene. Our family studies indicate that (1) both reproductive and metabolic abnormalities are heritable, (2) male as well as female first-degree relatives (FDRs) are affected, (3) hyperandrogenemia is an independent predictor of MBS and LDL elevations, and (4) A8 is associated with a more severe metabolic phenotype in both probands and their FDRs. We have extremely exciting new data that A8 is associated with hepatic insulin resistance. The overarching hypothesis of this proposal is that (1) hyperandrogenemia plays an independent role in the pathogenesis of the metabolic abnormalities in PCOS, (2) hyperandrogenemia results from A8 PCOS susceptibility variant, and (3) hyperandrogenemia begins early in life producing metabolic abnormalities prior to puberty. There are two specific aims. Specific Aim 1: To test the hypothesis that there are premenarchal markers of PCOS that identify girls at risk for metabolic abnormalities. FDRs will be studied to determine whether there is a premenarchal phenotype and whether A8 identifies at-risk girls. Specific Aim 2: To test the hypothesis that hyperandrogenemia, alone or in synergy with insulin resistance, contributes to metabolic abnormalities in young women with PCOS. We will determine whether the androgen receptor antagonist flutamide, the insulin-sensitizing agent metformin, or a combination of these medications reduces visceral adiposity, improves insulin sensitivity, or ameliorates dyslipidemia in women with PCOS. Further, we will determine whether A8 genotype predicts response to these interventions. The proposed research has substantial scientific as well as public health implications because it promises to identify precursors of and novel therapeutic targets for metabolic abnormalities in PCOS.

Titles of the scientific projects in the SCOR are given below.

- **Project 1:** Androgens, Genotype, and Insulin Resistance in PCOS
- **Project 2:** Genetic Analysis of PCOS/ Diabetes Susceptibility Genes
- **Project 3:** Role of Androgen Excess in Provoking Oxidative Stress in Females
- **Project 4:** Fetal Androgen Induces Ovarian, LH, and B-Cell Defects

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Institution: University of California–Los Angeles

Principal Investigator: Emeran Mayer, M.D.

Theme: *A Coordinated Study of Stress, Pain, Emotion, and Sexual Factors Underlying the Pelvic Visceral Disorders of Irritable Bowel Disorder and Interstitial Cystitis*

The UCLA Center for Neurovisceral Sciences and Women's Health (CNS/WH) is composed of a cohesive group of physician–scientists, psychologists, basic scientists, and support staff who study interactions between the nervous system and pelvic viscera, with particular emphasis on the interfaces among stress, pain and emotions, and sex-related differences in these interactions. A lean and well-run Administrative Core has been an essential ingredient in the success of the Center during the past 4 years and a continuation of this Core is proposed. Primary components of the Administrative Core include the Center Director, Dr. Mayer (who also is Administrative Core Director and Principal Investigator [PI]), Center Co-Director, Dr. Tache (Co-PI) as well as the Executive Committee made up of the Directors, Project PIs, and Core Directors of the Center. An experienced administrator, Sharon Monroe, manages the Directors Office and Administrative Core, and the staff is efficient and stable. This leadership team under the direction of Dr. Mayer directs the major components of the Center operation: managerial, financial, facilitative, educational, and human information technology. The Center maintains an active External Advisory Board made up of internationally recognized thought leaders in the field of neurovisceral interactions and they provide input into scientific and administrative aspects of Center operations. The UCLA SCOR (the

CNS/WH) will continue to be placed organizationally under the umbrella of the Department of Medicine. Through this structure, the SCOR is able to maximize its visibility and its potential for interaction with relevant departments, programs, institutes, and centers at UCLA.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** Differences in Central Stress Circuit Responsiveness Between Women With and Without Chronic Pelvic Visceral Symptoms (IBS, IC) and in an Animal Model of Chronic Stress
- **Project 2:** Sex Differences in Mucosal Neuroendocrine-Immune Interactions in IBS Patients
- **Project 3:** CRF Signaling Pathways in Stress-Related Visceral Manifestations
- **Project 4:** Role of the Peripheral CRF Signaling System

Institution: University of California–San Francisco

Principal Investigator: Jeanette Brown, M.D.

Theme: *Lower Urinary Tract Function in Women*

The proposed renewal of the UCSF SCOR on Lower Urinary Tract Function in Women is an exceptional opportunity to continue the unique and productive translational center. The UCSF SCOR 2002–2007 achieved our overriding goal of innovative translational research by enhancing the productivity of our basic and clinical investigators, resulting in 41 published manuscripts and grant support through a U01, four R01s, and an NIH Merit award. Catalyzing "Knowledge Synthesis" on lower urinary tract function in women, our research programs are actively contributing to improved patient care. For our SCOR renewal, we are building on strong leadership and senior scientists from many disciplines with a growing foundation of funded, successful research programs. The greatest strengths of our UCSF SCOR include the close proximity of internationally recognized laboratory and clinical researchers, the productive achievements of our current SCOR projects, and effective translational research collaborations. The UCSF SCOR multidisciplinary, multi-institutional program proposes three new projects and continuation and expansion of the Biostatistics and Data Management and Administrative Cores. The four major areas of scientific integration and collaboration include (1) Advancing novel treatments for stress incontinence: Characterizing adipose-derived stem cells for treatment; (2) Identifying mechanisms by which obesity, prediabetes, and diabetes cause incontinence: In a realistic type 2 diabetes rat model and prospective population-based ethnically diverse cohorts; (3) Exploring genetic risk factors for incontinence: Using our population-based DNA bank and gene expression in a unique incontinent rat model; (4) Understanding the effects of hormones and selective estrogen receptor modulators on incontinence: Including basic mechanism investigations and linkage to pharmacy records and use of phytoestrogens. To achieve our overall goal of innovative translational research on the female lower urinary tract, the UCSF SCOR has strong institutional support, collaborations with UCSF senior scientists and other internationally recognized researchers, outstanding leadership, and a cadre of senior and junior investigators with a record of excellent productivity. The UCSF SCOR will continue to accelerate the pace at which discoveries in basic science can serve the health of our patients and populations.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** RRISK (Reproductive Risks of Incontinence Study at Kaiser) Prospective Cohort
- **Project 2:** Diabetic Voiding Dysfunction and Stem Cell Therapy for Stress Urinary Incontinence
- **Project 3:** Diabetes RRISK Prospective Cohort: Urinary Incontinence and Diabetic Voiding Dysfunction

Institution: University of Chicago

Principal Investigator: David Ehrmann, M.D.

Theme: *Sex Steroids, Sleep, and Metabolic Dysfunction in Women*

The prevalence of obesity and chronic sleep loss are at record levels among Americans and evidence continues to emerge to support a causal link between the two conditions. Metabolic and cardiovascular abnormalities related to sleep disruption are particularly evident in individuals with obstructive sleep apnea (OSA), a disorder traditionally associated with male gender. While more prevalent in men, OSA is underrecognized in women in part because its clinical and polysomnographic features differ from those of men. Women with PCOS are particularly susceptible to OSA with at least a fivefold higher risk for its development compared to obese women without PCOS. The overarching aim of this SCOR application is to therefore establish the basis for the apparent gender difference in prevalence of OSA by focusing on the mechanistic role of sex steroids in the pathogenesis of the disorder as well as its metabolic complications. Four projects sharing integrated hypotheses, aims, and methods, plus an Administrative Core, are proposed. In Project 1 (Van Cauter, PI) and Project 2 (Ehrmann, PI), subjects with and without OSA will have detailed assessments of sleep, metabolic, and cardiovascular function; studies will be conducted in serum and urine for metabolomics and in fat biopsies for adipocyte function. Obese men and women with and without OSA will participate in Project 1: those with OSA will be treated with continuous positive airway pressure (CPAP) and its impact on baseline measures will be assessed. Project 2 will enroll obese women with PCOS, with and without OSA. Those with OSA will receive CPAP or will be randomized to receive depot leuprolide to suppress ovarian steroid output over 12 weeks, reassessed at 6 weeks, and then randomized (double-blind, placebo controlled) to 6 weeks of either micronized estrogen + placebo or micronized progestin + placebo. The independent effects of androgen, estrogen, and progesterone on OSA and metabolic function will be assessed. Project 3 (Mittendorfer, PI) will focus on mechanisms responsible for increased plasma triglyceride (TG) concentration, a finding common to both OSA and PCOS. Studies of VLDL-TG kinetics will be undertaken before and after modulation of plasma glucocorticoid, progesterone, and testosterone concentrations. In Project 4 (Brady, PI) primary human adipocytes will be prepared from fat biopsies obtained in Projects 1–2. Insulin sensitivity will be determined by phospho-specific immunoblotting in conjunction with glucose uptake and antilipolysis assays. In parallel, adipocytes from these subjects will be cultured for 1–5 days prior to metabolic assays to ascertain if removal of circulating factors will improve insulin signaling, or if insulin resistance persists in vitro. Finally, the Administrative Core will have oversight of all project functions, interface with the Metabolomics Laboratory at Duke University (C. Newgard, Lab Director), and coordinate meetings of the External Advisory Committee.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** Sleep and Metabolism in Obesity: Impact of Gender
- **Project 2:** PCOS, Sleep Apnea, and Metabolic Risk in Women
- **Project 3:** Sex Steroids, Sleep, Body Fat, and Plasma Triglycerides in Women
- **Project 4:** Assessment of Adipocyte Function in Women with PCOS
  Administrative Core

Institution: University of Miami

Principal Investigator: Emmalee Bandstra, M.D.

Theme: *Sex and Gender Influences on Addiction and Health: A Developmental Perspective*

This proposal seeks to establish a SCOR on the overarching theme of sex and gender factors affecting addiction and health. The Center's mission is to address the health concerns of women and their developing offspring affected by drug abuse by providing the optimal environment to encourage and facilitate clinical and translational research. The approach will be to use interdisciplinary translational and clinical studies to assess sex/gender-specific differences in vulnerability to drug taking and drug effects across development in adolescent and adult females and

males with and without prenatal exposure to cocaine and other drugs. Project #1 (Dow-Edwards, PI), Sex Differences in Drug Effects: The Prenatal Trajectory, is a series of preclinical translational studies using an established rat model of prenatal drug exposure. This project will examine the roles of prenatal cocaine exposure, postnatal environment, and polydrug exposure (cocaine with nicotine, THC, and alcohol) in the development of drug-taking behavior in male and female adolescent rats, emphasizing sex differences in conditioned place preference for cocaine and elucidating the potential biologic basis for sex differences by functional imaging and neurochemical assessments. Project #2 (Izenwasser, PI), Sex Differences in Drug Effects: The Adolescent Trajectory is a series of preclinical translational studies, the focus of which is to study the effects of nicotine, marijuana (A9-THC), and cocaine in male and female adolescent and adult rats on behavior and neurochemistry during adolescence and later during adulthood. Project #3 (Bandstra, PI), Sex and Gender Influences on Adolescent Drug Involvement is a clinical investigation of sex and gender differences affecting risk for drug abuse in adolescents (and ultimately as adults) with and without prenatal exposure to cocaine and other drugs. Subjects were enrolled in the Miami Prenatal Cocaine Study (n = 476), and assessed through early adolescence (retention 85 percent) for neuropsychological and other outcomes. In this proposal, subjects will be assessed at age 16 and 18 years by self-report and biomarkers for drug involvement; caregiver and self-report of psychosocial risk factors; and laboratory measures of stress reactivity, risk taking, and decisionmaking. Analyses will include consideration of the influence of prenatal cocaine exposure on later drug involvement in the female and male adolescents. The Administrative Core will host a Scientific Steering Committee and Internal and External Advisory Committees of interdisciplinary investigators with relevant expertise. Enhanced understanding of the differential effects of drugs of abuse in females and males across development (from prenatal to postnatal exposures during adolescence and adulthood) should lead to improved sex-, gender-, and age-specific preventions and treatments for drug addiction and related conditions.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** Sex and Stress Mechanisms of Vulnerability to Addiction
- **Project 2:** Sex Differences in Drug Effects: The Adolescent Trajectory
- **Project 3:** Sex and Gender Influences on Adolescent Drug Involvement

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Institution: University of Michigan–Ann Arbor

Principal Investigator: John DeLancey, M.D.

Theme: *Birth, Muscle Injury, and Pelvic Floor Dysfunction*

This proposal seeks to improve care for the women who suffer the priority health conditions of pelvic floor dysfunction, problems that arise due to women's unique role in giving birth. It addresses the sex disparities that exist in these problems. Each year in the U.S., 3 million women deliver babies and 300,000 women need surgery for pelvic floor dysfunction. A lack of basic understanding of the mechanisms of birth-related injury and recovery during reproductive years and mechanisms of prolapse later in life block efforts to prevent damage, improve recovery, or improve treatment. We seek continued support for a broadly interdisciplinary group of researchers from four schools and two institutes that have expedited development of new knowledge needed to improve treatment and prevention. Project 1: Birth Biomechanics will test hypotheses concerning basic mechanisms of pelvic floor injury during vaginal birth, the single largest factor in causing pelvic floor dysfunction, to identify specific situations that may increase or decrease injury risk. Project 2: Injury Recovery will identify risk factors associated with levator injury; test the hypothesis that these injuries are, in fact, related to vaginal delivery; and determine early predictors of eventual recovery. Project 3, Mechanisms of Posterior Vaginal Prolapse will use advanced imaging and deformation analysis to test hypotheses concerning the basic disease mechanisms responsible for posterior vaginal wall prolapse, one of the most common and strongly birth-associated pelvic floor dysfunctions. Core A: Administrative/Human Subjects/Biostatistics core provides project support by recruiting subjects, compiling and analyzing data, and

protecting subject safety. In Core A, two study groups will be formed concerning (1) Gender Impact, and (2) Basic Science Futures to discuss expanding the issues raised by this research. Core B: Measurement and Imaging core will provide technical support for the projects along with integrated analysis for two- and three-dimensional spatial data gathered across projects. This research will produce insights to address the women's health problem of pelvic floor dysfunction.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** Biomechanics of Birth-Related Injuries
- **Project 2:** Maternal Birth-Related Neuromuscular Injury and Recovery: Phase II
- **Project 3:** Mechanisms of Posterior Vaginal Prolapse

Institution: University of Missouri–Kansas City

Principal Investigator: Hong-Wen Deng, Ph.D.

Theme: *Genome-Wide Scans for Female Osteoporosis*

Osteoporosis is the most prevalent metabolic bone disease responsible for a major public health problem. Osteoporosis is mainly characterized by low bone mineral density (BMD). In general, women have lower BMD and higher risk of osteoporosis than men. Most BMD variation is determined by genetic factors with heritability greater than 60 percent. However, the specific genes involved are largely unknown. Our studies and the studies of others have demonstrated that some osteoporosis risk genes/genomic regions are gender specific.

The goal of this SCOR is primarily to identify osteoporosis risk genes and their functional aspects in females and, secondarily, to assess the female specificity of these identified genes/functions in male samples. In addition, we will also perform in-depth molecular and cellular functional studies for specific mechanisms and confirmation of the risk genes identified by studying two novel genes we discovered recently.

This SCOR will pioneer a comprehensive and novel approach in bone genetics by investigating osteoporosis at the genome-, transcriptome-, and proteome-wide levels simultaneously. We will use the samples largely recruited or archived for targeted recruitment and adopt state-of-the-art technologies proved successful in our recent pilot studies. This genomic convergence approach will pinpoint and consolidate the most significant genes identified in each of the individual projects. The genes identified will be subject to replication studies within and across populations. All the genes identified in the genomic convergence approach will be subject to in-depth functional studies for confirmation and functional mechanisms as exemplified in Stage 2 of Project 2 of this SCOR. This SCOR is composed of three projects, all aimed at identifying osteoporosis risk genes, but from different genomic approaches. Project 1 is to perform a whole-genome association scan using dense SNPs to identify those genes/regions that are associated with risk of osteoporosis. Project 2 is to perform a DMA microarray study to scan > 40,000 known human genes and ESTs to identify those mRNAs and corresponding genes associated with osteoporosis. Project 3 is to perform proteomics studies to identify those proteins (and corresponding genes) associated with osteoporosis. The SCOR has three cores: (1) Administrative Core; (2) Clinical Core; and (3) Biostatistics and Bioinformatics Core. Each core serves all the three projects. For example, the Clinical Core recruits samples that are shared by Projects 2 and 3 and provides support for clinical-related issues (e.g., choice of important medical and environmental factors for covariate analyses) and for human subject research issues in Project 1. Identifying genes and their functions for human BMD variation, especially for women, is important for (1) gaining insights into the fundamental molecular mechanisms underlying risk of osteoporosis; (2) discovering new pathways and targets for therapeutic cures; and (3) identifying genetically susceptible individuals, so that future preventions and interventions can be targeted to and based on individuals' specific genotypes.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** Genome-Wide Scans for Female Osteoporosis Genes

- **Project 2:** Genome-Wide and Specific Gene Expression Study of Osteogenic Cells
- **Project 3:** Proteome-Wide Expression Study of Osteogenic Cells

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Institution: Washington University

Principal Investigator: Scott Hultgren, Ph.D.

Theme: *Molecular and Epidemiologic Basis of Acute and Recurrent Urinary Tract Infections (UTIs) in Women*

This interdisciplinary SCOR program seeks to understand the epidemiology, pathogenic strategies, and resultant host responses of UTIs caused by uropathogenic *E. coli*, one of the most common diseases affecting women. This knowledge will be applied to critically evaluate all aspects of clinical UTI management, including diagnosis, treatment, and prevention. We have proposed an integrative and translational set of experiments that capitalizes on the complementary expertise found in each of the three projects. Basic scientists in Projects 1 and 3 have access to uropathogenic strains collected from women in Project 2 at different clinical stages of UTI. Working together, Projects 1, 2, and 3 will identify genetic and molecular markers and correlates of the different clinical UTI syndromes associated with Uropathogenic *Escherichia coli* (UPEC) infection. These will be pursued both in humans (Project 2) and mice (Project 1) for prognostic indicators of disease outcome: bacterial clearance, asymptomatic infection, chronic colonization, or recurrence. Genotypic and phenotypic profiles of UPEC strains from well-characterized UTI cases will be generated in Projects 1 and 3 by blending a powerful genetic system with functional and comparative genomics, defined in vitro and murine models, comparative immunoproteomics, biochemistry, cell biology, laser capture microdissection, antigen discovery techniques, and high-resolution electron microscopy. The host response to intracellular bacterial communities (IBCs) and quiescent intracellular reservoirs (QIRs) formed by different UPEC isolates will be examined in detail both in a mouse model (Project 1), using gene and cytokine expression profiling, and in humans (Project 2), by monitoring the adaptive immune response and metabolite profiles in human urine. In addition, exfoliated bladder epithelial cells in mouse and human urine will be screened for evidence of IBC formation, allowing parallel correlation of microscopic assays with clinical outcome in both mice and humans. These efforts promise to connect specific measurements made at the bench to clinical outcomes observed at the bedside. Project 3 will also address primary prevention of UTI by using comparative pangenomics to study the mechanism by which UPEC emerge from the distal gastrointestinal tract and traverse the perineum to the urethra to cause infection. Completion of these interwoven projects promises to address questions in the clinical management of this ubiquitous disease.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** Host–Pathogen Interaction in Acute and Chronic Urinary Tract Infections
- **Project 2:** Host-Response to Recurrent Urinary Tract Infections in Women
- **Project 3:** Pangenome of *E. coli* in Bladder and Gut of Women with Recurrent Urinary Tract Infection

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Institution: Yale University

Principal Investigator: Rajita Sinha, Ph.D.

Theme: *Sex, Stress, and Cocaine Addiction*

Competitive Renewal of the Yale SCOR on Women's Health: Sex, Stress, and Substance Abuse. Substance Use Disorders (SUDs) are chronic relapsing illnesses with devastating psychosocial, health, and societal consequences. Differential susceptibility to SUDs in men and women is well known. Historically, prevalence of disorders such as cocaine abuse is higher in men than women, but emerging evidence indicates that adolescent girls are as likely or slightly more likely to use and abuse substances, such as cocaine, than adolescent boys. Stress is a major factor increasing the vulnerability to develop SUDs in girls and in women. Our current SCOR findings indicate that females are more vulnerable to the addictive properties of abusive drugs and that stress markers such as early trauma and altered stress neurobiology play a pivotal role in the continued drug use and relapse cycle in women. In this SCOR competitive renewal, we propose translational research that will systematically examine mechanisms of such increased vulner-

ability in girls and in women. Continued support is requested to conduct interdisciplinary studies to address the following three scientific goals: (1) to examine sex differences in the neural and psychobiological effects of prenatal cocaine exposure on stress responses affecting risk of developing SUDs; (2) to evaluate the effects of sex-specific factors in the association among stress, drug seeking, and vulnerability to cocaine relapse; and (3) to build scientific collaborations through consultation and research support so as to increase the study of sex-specific effects on stress and drug abuse among investigators locally, regionally, and nationally. These goals will be accomplished by means of basic science and clinical studies conducted in animals and in humans. A greater understanding of these interactions will directly affect the development of sex-specific prevention and treatment approaches that will enhance the health of addicted women and their families. The following Specific Aims will be achieved by the SCOR: (1) To conduct a series of translational research projects on the interdisciplinary study of sex-specific effects in the association between stress and SUDs across the lifespan; (2) To extend the SCOR collaborative research program utilizing SCOR core scientific resources to facilitate the investigation of sex-specific factors in ongoing independently funded research relating to the etiology, neurobiology, and treatment of SUDs that includes faculty and research at other institutions; (3) To assist a range of young investigators from different disciplines both at Yale and at other institutions in conducting sex-specific research on stress and drug abuse through mentorship, research support, and scientific consultation; and (4) To establish inter-SCOR collaborations on common stress mechanisms to study similarities and differences in biological and social factors that contribute to stress-related disorders affecting women's health.

Titles of the scientific projects in the SCOR are given below:

- **Project 1:** Sex and Stress Mechanisms of Vulnerability to Addiction
- **Project 2:** Sex Differences in Stress Arousal in Cocaine-Exposed Youth at Risk for Addiction
- **Project 3:** Sex Differences in fMRI of Stress in Cocaine-Exposed Youth at Risk for Addiction
- **Project 4:** Sex Differences in Progesterone Effects on Responses to Stress and Drug Cues

TABLE 4

SCOR II Summary Table

Institution and Investigator	SCOR Theme
Brigham and Women's Hospital **Jill Goldstein, Ph.D.**	Fetal antecedents to sex differences in depression: A translational approach
Medical University of South Carolina * **Kathleen Brady, M.D., Ph.D.**	Role of sex and gender differences in substance abuse relapse
Northwestern University * **Andrea Dunaif, M.D.**	Excess male hormones (androgens) as the key to explaining polycystic ovarian syndrome (PCOS)
University of California–Los Angeles * **Emeran Mayer, Ph.D.**	A coordinated study of stress, pain, emotion, and sexual factors underlying the pelvic visceral disorders of irritable bowel disorder and interstitial cystitis
University of California–San Francisco * **Jeanette Brown, M.D.**	Lower urinary tract function in women
University of Chicago **David Ehrmann, M.D.**	Sex steroids, sleep, and metabolic dysfunction in women
University of Miami **Emmalee Bandstra, M.D.**	Sex and gender influences on addiction and health: A developmental perspective
University of Michigan–Ann Arbor * **John DeLancey, M.D.**	Birth, muscle injury, and pelvic floor dysfunction
University of Missouri–Kansas City **Hong-Wen Deng, Ph.D.**	Identifying the genes that put women at risk for osteoporosis
Washington University * **Scott Hultgren, Ph.D.**	Molecular and epidemiologic basis of acute and recurrent urinary tract infections (UTIs) in women
Yale University * **Rajita Sinha, Ph.D.**	Sex, stress, and substance use disorders

* The asterisk indicates that the program is a renewal project.

BUILDING INTERDISCIPLINARY RESEARCH CAREERS IN WOMEN'S HEALTH PROGRAM

The BIRCWH program supports junior faculty members who have recently completed clinical training or postdoctoral fellowships, and who are beginning basic, translational, clinical, and/or health services research related to women's health researchers in an interdisciplinary mentored environment in women's health research by pairing junior researchers with senior investigators. BIRCWH is designed to increase the number and skills of investigators through a mentored research and career development experience leading to an independent interdisciplinary scientific career that will benefit the health of women, including research on sex/gender similarities or differences in biology, health, or disease.

Programs accomplish these goals by ensuring that mentors represent diverse disciplines needed to carry out interdisciplinary projects that will bridge training with research independence for BIRCWH scholars. The BIRCWH program was established in 2000. Since that time, ORWH and cosponsors have made 50 total awards, including competitive renewals. In FY 2007, 15 new and continuing awards were made.

The first BIRCWH grants were awarded in FY 2000. Since that time, ORWH has issued three additional RFAs, and has made a total of 50 awards to 38 institutions (12 institutions were competitively renewed in the third and fourth round of funding). The BIRCWH Program has been supported by many NIH Institutes and Centers, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); NIAMS; National Institute on Aging (NIA); National Institute of Mental Health (NIMH); National Institute of Neurological Disorders and Stroke (NINDS); National Cancer Institute (NCI); National Heart, Lung, and Blood Institute (NHLBI); and by the Agency for Healthcare Research and Quality (AHRQ). ORWH provided approximately $10 million per year in funding to the program in FY 2007 and FY 2008. This report focuses on accomplishments from BIRCWH III and BIRCWH IV.

BIRCWH Scholar Demographics

As of August 2008, a total of 335 individuals (78.8 percent female, 21.2 percent male) had participated in the BIRCWH program as BIRCWH scholars. Of these, 126 were active and 178 completed the BIRCWH program. Of the total number of scholars, 34.9 percent had a Ph.D. only, 28.7 percent had an M.D. only, 14.6 percent held an M.D. and a master's-level degree (OSPAC data), 12.2 percent had an M.D. and a Ph.D., and 3.6 percent had a Ph.D. and an M.P.H. In addition, approximately 6 percent held other doctoral degrees, including D.V.M., D.D.S., Dr.P.H., Pharm.D., and D.O. degrees. The fields represented among BIRCWH Scholars included internal medicine (22.7 percent), psychology/psychiatry (12 percent), and obstetrics and gynecology (11 percent). The single largest research area reported by scholars was obstetrics/gynecology, followed closely by oncology. Mental health/substance abuse, cardiovascular health, diabetes, and allergy and infectious disease topic areas were also substantially represented.

There are currently 26 active BIRCWH Centers in BIRCWH III and IV.

1. BIRCWH III (2005–2009)

In FY 2005, the third BIRCWH solicitation (RFA-OD-05-002) was funded by ORWH with support from several NIH ICs, including NICHD, National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Allergy and Infectious Diseases (NIAID), National Institute on Drug Abuse (NIDA), NIDDK, National Institute of Environmental Health Sciences (NIEHS), NIMH, Office of Dietary Supplements, NIH (ODS), and AHRQ. Eleven BIRCWHs were funded. The following is a description of programs supported under the BIRCWH III program.

Institution: Harvard University

Principal Investigator: 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 lifespan 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 childbearing years, perimenopause, and menopause.

Institution: University of California–Davis (UC Davis)

Principal Investigator: 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 nontraditional, 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) lifespan biology and transitions, such as early development, adolescence, and menopause, which bring unique risks to females.

Institution: University of California–Los Angeles

Principal Investigator: 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.

Institution: University of California–San Francisco

Principal Investigator: Deborah G. Grady, M.D., M.P.H.

In this program, UCSF 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.

Institution: University of Cincinnati

Principal Investigator: 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.

Institution: University of Kansas Medical Center

Principal Investigator: 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 5-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.

Institution: University of Kentucky

Principal Investigator: James E. Ferguson, M.D.

The primary goal of this BIRCWH program is to provide Interdisciplinary Women's Health Research (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 in-depth 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 lifespan, and (4) oral health and its impact on cardiovascular and endocrine health and pregnancy outcomes.

Institution: University of Michigan

Principal Investigator: 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.

Institution: University of North Carolina (UNC)–Chapel Hill

Principal Investigator: 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.

Institution: University of Texas Medical Branch, Galveston

Principal Investigator: 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.

Institution: Washington University

Principal Investigator: 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.

2. BIRCWH IV (2007–2011)

In FY 2007, the fourth BIRCWH solicitation (RFA-OD-06-002) was funded by ORWH with support from several NIH ICs, including NICHD, NIAAA, NIAID, NIDA, NIDDK, NIEHS, NIMH, ODS, and AHRQ. Fifteen programs were funded. They are described below.

Institution: Boston Medical Center

Principal Investigator: Karen Freund, M.D., M.P.H.

The Boston University (BU) BIRCWH has demonstrated the ability to expand women's health research and the number of excellent investigators in women's health. The BU BIRCWH will build upon the strengths of our existing program to recruit, select, and train junior faculty in conducting clinical and health services research on women's health issues. The focus of research training and research will be addressing the needs of underserved, minority, and elderly women. The long-term goals of the BU BIRCWH are to mentor an identified cadre of outstanding scholars and to provide them with the support and training needed for them to develop independent research careers in women's health. The BU BIRCWH will train selected clinician investigators in health services research, clinical research, and clinical epidemiology to address a focus of important questions in the care of women.

Institution: University of Colorado, Denver

Principal Investigator: Lorna Moore, Ph.D.

The broad objective of the BIRCWH program at the University of Colorado at Denver and Health Sciences Center (UCDHSC) is to develop and increase the pool of highly qualified young scientists and clinician–investigators pursuing independent interdisciplinary scientific careers in women's health. The BIRCWH grant at UCDHSC focuses on three interrelated areas affecting women's health across the lifespan, from preconception to aging. These areas are (1) pregnancy, fetal programming, and lactation, (2) aging, cardiovascular disease, diabetes, and obesity, and (3) women's cancers. These are fields in which the UCDHSC has strong interdisciplinary research programs, extending from molecular research into the basic mechanisms of disease through clinical studies to epidemiological analyses of etiology and outcomes.

Institution: Northwestern University

Principal Investigator: J. Larry Jameson, M.D., Ph.D.

The BIRCWH program at Northwestern University will be used to develop a group of independent, tenure-track scientists with backgrounds in clinical medicine or basic science disciplines whose research will address high-priority areas relevant to women's health. We have identified five focus areas that have been historically strong within Northwestern and that are fundamental to the understanding and treatment of women's health and disease—differences in cardiovascular disease risk, ovarian biology, obstetrical and gynecological disorders, sex differences in sleep, rheumatology, and osteoporosis. In order to develop expertise outside the Ob/Gyn specialty, faculty members who have interdisciplinary training in basic reproductive science and gender-specific disease research must be cultivated. Northwestern has a longstanding and rich tradition of interdisciplinary excellence in the reproductive sciences and in disorders that affect women.

Institution: University of Illinois–Chicago

Principal Investigator: Stacie Geller, Ph.D.

The University of Illinois at Chicago (UIC) BIRCWH program is a collaborative effort between the UIC's National Center of Excellence in Women's Health (CoE) and its six health colleges: including the Colleges of Medicine, Nursing, Pharmacy, Dentistry, Applied Health Sciences; and the School of Public Health. The overall purpose of this BIRCWH program is to institutionalize a generative scholar training program that will optimize the success of junior faculty in developing a substantive

and sustained research program in women's health science. The program will contribute substantially to the development of a diverse multidisciplinary basic science, clinical, and community research work force through the interdisciplinary training, mentorship, and career development of junior investigators. These investigators will accelerate the translation of research findings into evidence-based policies and practices that improve the health of women and girls in the United States. A diverse group of scholars is selected who focus on research in one of five areas in which UIC has particular strengths: reproductive health, midlife and aging, cancer in women, heart disease in women, and underserved populations. These areas encompass health and illness issues that are unique to women, more prevalent in women, or different in women than in men. Health disparities are an underlying theme in much of the research on women's health, regardless of level of analysis, reflecting the diverse urban environment in which UIC is situated. UIC's conceptual approach to women's health and to research about women's health is to view women's health in terms of life stages and on a continuum. Work in women's health ranges from the molecular and cellular level to the community level; these levels are interrelated.

Institution: Tulane University

Principal Investigator: Jeanette H. Magnus, M.D., Ph.D.

The Tulane BIRCWH program is dedicated to promoting research and the transfer of findings to promote women's health by promoting research independence among junior researchers. To improve the quality and increase the quantity of women's health research, Tulane BIRCWH proposes to bridge the period between advanced training and research independence, as well as link professions, scientific disciplines, and areas of interest for selected scholars. The common theme running throughout the various research areas is interdisciplinary research on cardiovascular disease, hypertension, and renal disease. The long-term objectives of the Tulane BIRCWH program are to increase the number of skilled, independent interdisciplinary investigators with a focus on sex, gender, and women's health research; promote, through the BIRCWH program's illustration, the awareness of the need to ensure a strong pipeline when fostering independent researchers and taking advantage of interdisciplinary and multidisciplinary clinical and translational research efforts; promote collaborations with traditionally non-research–focused entities; establish institutional and individual renown both nationally and internationally for the BIRCWH program's findings on cardiovascular disease (CVD) and women's health; and improve the cardiovascular health of Louisiana women across the lifespan, particularly African-American women, by effectively training the next generation of conscientious, culturally competent, and independent academic women's health researchers.

Institution: University of Maryland–Baltimore (UMB)

Principal Investigator: Patricia Langenberg, Ph.D.

The University of Maryland's BIRCWH program will continue our already highly successful program that was designed to foster interdisciplinary research in women's health among junior faculty. Scholars worked together with a team of senior faculty mentors to bridge the gap between specialized training and independent research careers. To achieve this goal, we have refined and adapted our current program to provide scholars with in-depth career development training in three focused and interactive research theme areas: (1) Women's Health and the Brain; (2) The Aging Woman; and (3) Conditions Specific to Women. These theme areas build on existing strengths in research at UMB and are fertile ground for interdisciplinary basic science, translational, behavioral, clinical, epidemiological, and/or health services research. They are an extension of the theme areas offered in our current program, allowing many of those mentors from the current program to participate, and allowing former scholars the opportunities to serve on mentor teams as coaches, providing a support network for new scholars. An important strength of our BIRCWH program is that scholars are able to draw from a multidisciplinary pool of senior faculty mentors for their mentor teams, but are also able to engage in research that is truly interdisciplin-

ary. For example, a scholar could access expertise in genetics, epidemiology, and neurology to conduct clinical research on central nervous system contributions to the menopausal transition. Our former and current scholars all have benefited immensely from our rich research environment and frequently cite the interdisciplinary nature of their training experience as an extraordinary advantage to their research.

Institution: University of Minnesota–Twin Cities

Principal Investigator: Nancy Raymond, M.D.

Three aspects of the University of Minnesota make it a unique environment for a BIRCWH program: (1) based on substantial empirical research by one of our faculty members, we have developed a comprehensive model of mentoring that systematizes the vagaries of the interdisciplinary mentoring process; (2) With our six health science schools and other health-related departments, we have an extremely diverse institution. This diversity of disciplines reveals itself in our mentors, our course offerings, and the scholars themselves. Few universities can offer such a wide range of career development opportunities; and (3) The University of Minnesota is a leader in women's health. Based on the work of the Deborah E. Powell Center of Excellence in Women's Health, we have a strategic plan related to women's health research, the goals of which are to (1) build academic capacity; (2) increase interdisciplinary collaboration; (3) increase funding opportunities; and (4) increase the visibility of women's health research.

Institution: Duke University

Principal Investigator: Eugene Z. Oddone, M.D.

The Duke/North Carolina Central University (NCCU) BIRCWH program is designed to develop highly skilled researchers investigating women's health issues, with a strong emphasis on interdisciplinary scholarship. The overarching theme for the Duke/NCCU program will be women's health across the lifespan, with areas of research interest that include maternal consequences of childbearing conditions that affect women, and healthcare use and disparities. A group of experienced core mentors will support the scholars, and a distinguished advisory committee will provide oversight as well as regular evaluations of the program and scholar progress. The collaboration between Duke and NCCU, a Historically Black University, will strengthen our goal of training minority scholars. The Duke/NCCU BIRCWH program is relevant to public health because it trains researchers whose work will lead to improved treatments for a wide range of conditions affecting women.

Institution: Oregon Health & Science University

Principal Investigator: Lesley Hallick, Ph.D.

The goal of the Oregon BIRCWH program is to create a stimulating and nurturing environment for junior faculty to develop into leading physician–scientists in women's health. Our program recognizes that research can modify the course of disease at one point in a woman's lifespan, which will affect the rest of lifelong development and aging. The program pairs basic and clinical junior faculty scientists with established mentors from different backgrounds who have expertise in women's health issues in order to enhance the scholar's research capabilities. The mix of career paths and backgrounds is integral to increasing collaboration and invigorating research in women's health across the lifespan. The extensive intellectual and research resources at the Oregon Health & Science University are available and committed to developing BIRCWH scholars. Integration is interdepartmental and is center driven to enhance collaborations between scientists and trainees in the Center for Women's Health, the Heart Research Center, the Primate Research Center, the Cancer Institute, and the Center for Gender Biology and Medicine. Sophisticated research core laboratories specializing in molecular biology, cell culture, DNA analysis, imaging, statistics, assisted reproductive techniques, endocrine assays, laboratory animals, transgenic and molecular genetics cores, among others, are established and available to the BIRCWH Scholars. Advanced training in designing clinical studies and statistical evaluation for clinician scientists will be coordinated through the highly successful Human Investigations

Program. Writing skills are enhanced through structured workshops.

Institution: Magee Women's Hospital of the University of Pittsburgh Medical Center

Principal Investigator: James M. Roberts, M.D.

The BIRCWH program at the University of Pittsburgh seeks to improve women's health research at the University of Pittsburgh with several strategies. The first has been to provide excellent interdisciplinary research training in women's health to as many beginning investigators as possible. Scholars funded by the program are encouraged to obtain alternative K funding and, when successful, to continue to participate in the BIRCWH career development program. The program has publicized the availability of components of the BIRCWH program to other beginning investigators. In addition, we have recruited many of the research leaders of the University of Pittsburgh to become actively involved in the program through membership in the Advisory Committee. The training program emphasizes interdisciplinary research, and exposure to this strategy is provided through projects and also by selecting a group of scholars with diverse research interests and approaches, and encouraging their interaction.

Institution: Pennsylvania State University

Principal Investigator: Carol Weisman, Ph.D.

The goal of the BIRCWH program at Pennsylvania State University is to increase the number and skills of investigators in women's health through a mentored research and career development experience leading to an independent interdisciplinary scientific career that will benefit the health of women. The expanding research agenda in women's health is informed by multiple scientific disciplines, including the biological, physical, and social sciences. Research integrating knowledge from multiple perspectives is needed to advance the field of women's health and to improve women's health and health services. The interdisciplinary research conducted by BIRCWH scholars may be basic, translational, behavioral, clinical, and/or health services research relevant to women's health or to sex/gender factors related to health. At Penn State, 21 senior faculty mentors have been identified in four core research areas: (1) Precursors and Consequences of Obesity; (2) Reproductive Health; (3) Sex and Gender Issues in Health and Disease; and (4) Cancer Prevention, Screening, and Treatment.

Institution: Medical University of South Carolina

Principal Investigator: Kathleen Brady, M.D., Ph.D.

The overall objective of the MUSC BIRCWH Program is to promote the performance of research in women's health by bridging advanced training with research independence. The Interdisciplinary Women's Health Research program at MUSC will encourage interdisciplinary study of differences between women and men that impact the prevention, diagnosis, and treatment of disease in two major focus areas—aging and mental health. The convergence at MUSC of substantial expertise in these two critical areas assures our ability to mentor junior faculty to study women's health issues across the lifespan. Our faculty mentors have a broad skills basis in both aging and mental health, especially pertaining to dementia, substance use disorders, posttraumatic stress disorder (PTSD), and depression. In addition, we have specific expertise in the study of gender differences in pharmacokinetics, pharmacodynamics, and pharmacogenomics.

Institution: Vanderbilt University

Principal Investigator: Nancy Brown, M.D.

The Vanderbilt BIRCWH program has supported the career development of scholars engaged in basic, translational, and epidemiological women's health research in collaboration with investigators from among 15 departments or centers within Vanderbilt, Meharry Medical College, and other institutions. At the same time, the BIRCWH has served as a catalyst for recruitment and growth in the area of women's health research at Vanderbilt and for collaboration between Vanderbilt and Meharry Medical College. During the next 5 years, the BIRCWH program will focus on developing outstanding investigators in six major areas of women's health research: cardiovascular risk and gender, clini-

cal pharmacology and vaccine development, disparities and health outcomes, endometrial biology and reproductive toxicology, neoplasia and cancer, and neuroscience and behavioral health. We strive to create a new generation of creative, successful leaders in scientific areas that will improve the health of women.

Institution: Virginia Commonwealth University (VCU)

Principal Investigator: Jerome Strauss, M.D., Ph.D.

The VCU BIRCWH program enjoys superb leadership from its PI (School of Medicine dean) and its program codirectors, both highly successful female faculty (one basic scientist, one physician–scientist). The BIRCWH program intersects with several interdisciplinary matrix organizations, such as the Institute for Women's Health National Center of Excellence, Center for Health Disparities, and Center for Translational and Clinical Science. VCU BIRCWH scholars will have the opportunity to investigate the pathogenesis and develop preventive and therapeutic interventions for preeclampsia, PCOS, perinatal depression, preterm birth, low birthweight, vaginal bacteriosis, breast and ovarian cancer, and substance abuse. Scholars will learn innovative methods of conducting community-based health research, statistical analyses focused on distinguishing sex and gender differences in data, and culturally competent research methodology. Scholars will be required to integrate training experiences in clinical and laboratory settings and community outreach. All scholars will attend monthly group lunch brainstorming sessions at which they will make informal presentations on their research and solicit advice and assistance.

Institution: University of Wisconsin–Madison

Principal Investigator: Gloria Sarto, M.D., Ph.D.

The goals of the Building Interdisciplinary Research Careers in Women's Health Scholars Program at the University of Wisconsin (UW) are (1) to increase the diversity of academic leaders in the field of women's health, and (2) to promote interdisciplinary research that addresses disparities in health status and health outcomes among diverse populations of women throughout the lifespan, and chronic disease prevention. We will accomplish these goals by selecting diverse and talented applicants and providing them with dual scientific mentorship with established investigators in both biomedical and behavioral/social sciences; a rigorous 2- to 3-year didactic curriculum (biostatistics and study design, ethics, leadership/management, presentation and teaching, and scientific writing); and individual guidance in a safe environment that values cultural diversity. We believe that the integration of biomedical sciences, public health sciences, and sociocultural and behavioral sciences is prerequisite to addressing the linkages of macro-societal levels of being with pathogenesis of disease, so important in addressing health disparities. Thus, the UW BIRCWH provides interdisciplinary and multifaceted opportunities for research that include not only biomedical and behavioral sciences, but also investigation into quality of care, cost, access, and satisfaction with services; causes of and barriers to reducing health disparities; social context; and identification of assessment measures for outcomes. To address not only the broad array of research areas outlined above, but also the interdisciplinary nature of the possible candidates, the faculty is interdisciplinary and consists of physician–scientists, perinatal researchers, sociologists, nurse–scientists, nutritional scientists, epidemiologists, and economists. The outstanding research mentors selected for the BIRCWH are enthusiastic about the opportunity to mentor more advanced scholars through the BIRCWH.

3. BIRCWH Scholars Early-Stage Outcomes

A primary goal of the ORWH BIRCWH program is for scholars to receive independent grant funding. Of the total number of scholars who completed the BIRCWH program (178), 46 percent received at least one subsequent NIH grant. Men and women were equally likely to obtain NIH funding. In terms of the prestigious R01 grant, 29 percent of NIH R01 applications that were submitted by scholars who completed the program were funded.

In total, scholars have successfully competed for over 200 NIH research grants,

which include 83 R Awards, 39 K Awards, and 9 center grants. The following NIH Institutes have funded BIRCWH Scholars: NIDDK, NICHD, NIAMS, NIAID, NIA, NIMH, NINDS, NCI, National Institute of Nursing Research (NINR), and NHLBI. Scholars have also received Federal funding from AHRQ, Centers for Disease Control and Prevention (CDC), Department of Defense (DoD), and Department of Education (ED). Furthermore, scholar research has been supported through numerous academic, foundation, and industry grants. Below are a few examples of BIRCWH scholar funding. They describe three major NIH Office of the Director Awards to Dr. Kristen Jacobson, a former Virginia Commonwealth University scholar, and Dr. Rajita Sinha, a former Yale University scholar.

NIH Director's New Innovator Award Program (DP2)

Principal Investigator: Kristen C. Jacobson, Ph.D.

Institution: University of Chicago

Grant Title: From Neighborhoods to Neurons and Beyond

Award: $2.3 million per year for 5 years

In 2007, the NIH Director's New Innovator Award was created to support new principal investigators who propose highly innovative research projects that have an unusual potential to impact a significant biomedical or behavioral problem, yet may not have the preliminary data that are required for an R01 grant application. Dr. Jacobson was one of 29 New Innovator Award recipients. The award will allow the Principal Investigator to conduct a multidisciplinary-based investigation of the effects of individual, family, peer, and neighborhood characteristics on individual differences in adolescent problem behavior. The study will be conducted in three phases to address the following: (1) What are the environmental and psychosocial factors that account for socioeconomic and racial and ethnic differences in problem behavior? What factors predict resilience? (Phase I); (2) What are the environmental, biological, and psychosocial variables that account for individual differences in problem behavior among two siblings in the same family? To what extent are the relationships between these risk and protective factors and problem behavior genetically versus environmentally mediated? (Phase II); and (3) What are the underlying neurobiological substrates that account for within-family differences in problem behavior? To what extent do within-family differences in behavior and neurobiological functioning reflect the effects of differences in environmental experiences and exposures (i.e., neurobiological mediation of environmental influences on behavior)? (Phase III).

ORWH Specialized Centers of Interdisciplinary Research on Sex and Gender Factors Affecting Women's Health (P50) Program

Principal Investigator: Rajita Sinha, Ph.D.

Institution: Yale University

Grant Title: Yale SCOR on Women Health: Sex, Stress, and Substance Abuse

Award: $1 million per year for 5 years

ORWH implemented its second interdisciplinary program, Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health, in 2002. The SCOR Program was designed to bridge basic and clinical research on sex/gender factors underlying a health issue that affects women. Dr. Sinha was among the first cohort of SCOR Principal Investigators, and she was successfully renewed in FY 2007. During the next 5 years of funding, the investigator's goals are as follows: (1) to examine sex differences in the neural and psychobiological effects of prenatal cocaine exposure on stress responses affecting risk of developing SUDs; (2) to evaluate the effects of sex-specific factors in the association between stress, drug seeking, and vulnerability to cocaine relapse; and (3) to build scientific collaborations through consultation and research support to increase the study of sex-specific effects on stress and drug abuse among investigators.

NIH Roadmap Interdisciplinary Research Consortia (U54)

Principal Investigator: Rajita Sinha, Ph.D.

Institution: Yale University

Grant Title: Interdisciplinary Research on Stress, Self-Control, and Addiction

Award: $4.7 million per year for 5 years

In FY 2007, Dr. Sinha competed against 100 applicants to become one of nine new NIH Roadmap Interdisciplinary Research Consortia awardees. The interdisciplinary program supports projects that address complex biomedical problems that require novel approaches. The Yale consortia will bring together more than 50 investigators from 20 disciplines to address stress, self-control, and addiction by (1) identifying mechanisms involved in the development of stress-related effects on self-control in the addictive behaviors of smoking, drinking, and overeating; (2) evaluating self-control mechanisms in the pathophysiology of chronic stress and addiction; and (3) developing social, behavioral, and pharmacological strategies to increase self-control and decrease addictive behaviors.

4. BIRCWH Scholar Publications

Another measure of the success of the BIRCWH program can be seen in the quality and diversity of research publications. To date, the scholars have produced over 1,300 publications, including abstracts, journal articles, and book chapters. Listed below are selected recent publications from BIRCWH Scholars in 2006 and 2007.

2006 Selected Scholar Publications

1. Vahratian, A., Troendle, J. F., Siega-Riz, A. M., & Zhang, J. (2006). Methodological challenges in studying labour progression in contemporary practice. *Paediatric and Perinatal Epidemiology* 20(1), 72-78.
2. Black, B., Holditch-Davis, D., Schwartz, T., & Scher, M. (2006). Effects of antenatal magnesium sulfate and corticosteroid therapy on sleep states of preterm infants. *Research in Nursing and Health* 29(4), 269-280.
3. Berges, I., Ottenbacher, K., & Ostir, G. V. (2006). Perceived pain and satisfaction with medical care after hospital discharge, 2006. *Clinical Rehabilitation* 20, 724-730.
4. Ardeshiri, A., Kelley, M. H., Korner, I. P., Hurn, P. D., & Herson, P. S. (2006). Mechanism of progesterone neuroprotection of rat cerebellar Purkinje cells following oxygen-glucose deprivation. *The European Journal of Neuroscience* 24, 2567-2574.
5. Liu, N. J., vonGizycki, H., & Gintzler, A. R. (2006). Phospholipase Cbeta1 modulates pain sensitivity, opioid antinociception and opioid tolerance formation. *Brain Research* 1069(1), 47-53.
6. Charbonneau, A., Greiner, K. A., Born, W., Hall, S., Rhode, P., James, A., et al. (2006). Concordance of patient–physician obesity diagnosis and treatment beliefs in rural practice settings. *Journal of Rural Health* 22(4), 364-366.
7. Tsai, A. G., Wadden, T. A., & Berkowitz, R. I. (2006). Pharmacotherapy for overweight adolescents. *Obesity Management* 2, 98-102.
8. Meich, R. A., Kumanyika, S. K., Stettler, N., Link, B. G., Phlelan, J. C., & Chang, V. W. (2006). Trends in the association of poverty with overweight among U.S. adolescents, 1971-2004. *Journal of the American Medical Association* 295(20), 2385-2393.
9. Ayala, G. X., Mickens, L., Galindo, P., & Elder, J. P. (2007). Acculturation and body image perception among Latino youth. *Ethnicity and Health* 12(1), 21-41.
10. Kallianpur, A. R., Hulgan, T., Canter, J. A., Haines, J. L., Ritchie, M. D., Robbins, G. K., et al. (2006). Hemochromatosis (HFE) gene mutations and peripheral neuropathy during antiretroviral therapy. *AIDS* 20, 1503-1513.
11. Dong, B. J., & Cocohoba, J. M. (2006). Tipranavir: A new protease inhibitor for HIV salvage therapy. *The Annals of Pharmacotherapy*, 40(7-8) 1311-1321.

12. Duffy, C. M., Clark, M. A., & Allsworth, J. (2006). Health maintenance and screening among breast cancer survivors in the U.S. *Cancer Detection and Prevention* 30, 52-57.

13. Buckanovich, R. J., Sassaroli, D., Jenkins, A., Botbyl, J., Conejo-Garcia, J. R., Benencia, F., et al. (2006). Use of immuno-LCM to identify the in situ expression profile of cellular constituents of the tumor microenvironment. *Cancer Biology and Therapy* 5(6), 635-642.

14. Williams, D. M., Papandonatos, G. D., Napolitano, M. A., Lewis, B. A., Whiteley, J. A., & Marcus, B. H. (2006). Perceived enjoyment moderates the efficacy of an individually tailored physical activity intervention. *Journal of Sport and Exercise Psychology* 28, 300-309.

15. Lane, N. E., Yao, W., Balooch, M., Nalla, R. K., Balooch, G., Habelitz, S., et al. (2006). Glucocorticoid-treated mice have localized changes in trabecular bone material properties and osteocyte lacunar size that are not observed in placebo-treated or estrogen-deficient mice. *Journal of Bone and Mineral Research* 21, 466-476.

16. Dumont, D. M., Behler, R. H., Nichols, T. C., Merricks, E. P., & Gallippi, C. M. (2006). ARFI imaging for noninvasive material characterization of atherosclerosis. *Ultrasound in Medicine and Biology* 32(11), 1703-1711.

17. Stanic, A. K., Stein, C. M., Morgan, A. C., Fazio, S., Linton, M. F., Wakeland, E. K., et al. (2006). Immune dysregulation accelerates atherosclerosis and modulates plaque composition in systemic lupus erythematosus. *Proceedings of the National Academy of Sciences of the United States of America* 103(18), 7018-7023.

18. James, A. H., Jamison, M. G., Biswas, M. S., Brancazio, L. R., Swamy, G. K., & Myers, E. R. (2006). Acute myocardial infarction in pregnancy: A population-based study. *Circulation* 113(12), 1564-1571.

19. Bazzano, L. A., Reynolds, K., Holder, K. N., & He, J. (2006). Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association* 296(22), 2720-2726.

2007 Selected Scholar Publications

20. Jeyabalan, A., Novak, J., Doty, K. D., Matthews, J., Fisher, M. C., Kerchner, L. J., et al. (2007). Vascular matrix metalloproteinase-9 mediates the inhibition of myogenic reactivity in small arteries isolated from rats after short-term administration of relaxin. *Endocrinology* 148, 189-197.

21. Gunderson, E. P., Lewis, C. E., Wei, G. S., Whitmer, R. A., Quesenberry, C. P., & Sidney, S. (2007). Lactation and changes in maternal metabolic risk factors. *Obstetrics and Gynecology* 109(3), 729-738.

22. Dassow, P. (2007). Measuring performance in primary care: What patient outcome indicators do physicians value? *Journal of the American Board of Family Medicine* 20(1), 1-8.

23. Renner, R. M., Eden, K. B., Osterweil, P., Chan, B. K. S., & Guise, J. M. (2007). Informational factors influencing patient's childbirth preferences after prior cesarean. *American Journal of Obstetrics and Gynecology* 196(5), e14-e16.

24. Modesitt, S. C., Tian, C., Kryscio, R., Thigpen, J. T., Randall, M. E., Gallion, H. H., et al.; Gynecologic Oncology Group. (2007). Impact of body mass index on treatment outcomes in endometrial cancer patients receiving doxorubicin and cisplatin: A Gynecologic Oncology Group study. *Gynecologic Oncology* 105(1), 59-65.

25. Buckanovich, R. J., Sassaroli, D., O'Brien-Jenkins, A., Botbyl, J., Hammond, R., Katsaros, D., et al. (2007). Tumor vascular proteins as biomarkers in ovarian cancer. *Journal of Clinical Oncology* 25(7), 852-861.

26. Zinser, G. M., Leonis, M. A., Toney, K., Pathrose, P., Thobe, M., Kader, S. A., et al. (2006). Mammary-specific ron receptor overexpression induces highly metastatic mammary tumors associated with beta-catenin activation. *Cancer Research* 66(24), 11967-11974.

27. Berges, I. M., Ottenbacher, K., Kuo, Y.-F., Smith, P., Smith, D., & Ostir, G. V. (2007). Satisfaction with quality of life post-stroke: Effect of sex differences in pain response. *Archives of Physical Medicine and Rehabilitation* 88(4), 413-417.

28. Pettee, K. K., Kriska, A. M., Johnson, B. D., Conroy, M. B., Mackey, R. H., Orchard, T. J., et al. (2007). The relationship between physical activity and lipoprotein sub-class levels in post-menopausal women: The influence of hormone therapy. *Menopause* 14(1), 115-122.

29. Magkos, F., Patterson, B. W., Mohammed, B. S., Klein, S., & Mittendorfer, B. (2007). Women produce fewer but triglyceride-richer very low-density lipoproteins than men. *Journal of Clinical Endocrinology & Metabolism* 92, 1311-1318.

30. DeSalvo, K. B., Hyre, A. D., Ompad, D. C., Menke, A., Tynes, L. L., & Muntner, P. (2007). Symptoms of posttraumatic stress disorder in a New Orleans workforce following Hurricane Katrina. *Journal of Urban Health* 84 (2), 142-152.

31. Musatov, S., Chen, W., Pfaff, D. W., Mobbs, C. V., Yang, X. J., Clegg, D. J., et al. (2007). Silencing of estrogen receptor alpha in the ventromedial nucleus of hypothalamus leads to metabolic syndrome. *Proceedings of The National Academy of Sciences of the United States of America* 104(7), 2501-2506.

32. Solomon, M., Hessl, D., Chiu, S., Hagerman, R., & Hendren, R. L. (2007). A genetic etiology of pervasive developmental disorder guides treatment. *American Journal of Psychiatry* 164(4), 575-580.

33. Friocourt, G., Liu, J., Antypa, M., Rakic, S., Walsh, C. A., & Parnavelas, J. G. (2007). Both doublecortin and doublecortin-like kinase play a role in cortical interneuron migration. *Journal of Neuroscience* 27(14), 3875-3883.

34. Napoli, N., Thompson, J., Civitelli, R., & Armamento-Villareal, R. (2007). Effects of dietary calcium compared with calcium supplements on estrogen metabolism and bone mineral density. *American Journal of Clinical Nutrition* 85(5), 1428-1433.

35. Bhattacharya, D., Carleton, H., Tsai, C., Baron, E. J., & Perdreau-Remington, F. (2007). Differences in molecular characteristics of skin and soft-tissue (SSTI) methicillin-resistant staphylococcus aureus (MRSA) isolates between two hospitals in northern California. *Journal of Clinical Microbiology* 45(6), 1798-1803.

Trans-NIH Collaboration on Chronic Fatigue Syndrome

The multisystemic nature of chronic fatigue syndrome (CFS) calls for multidisciplinary and interdisciplinary approaches that cut across the missions of multiple NIH ICs. ORWH coordinates NIH research on CFS through its leadership role in the Trans-NIH Working Group for Research on CFS (CFSWG) (see Appendix E). The CFSWG develops and promotes multidisciplinary and interdisciplinary approaches to the study of CFS by holding thought-provoking meetings and by issuing collaborative funding opportunities.

Throughout FY 2007 and FY 2008, ORWH and other NIH ICs continued to fund a diverse range of investigator-initiated research programs that hold promise for developing biological markers and potential treatments for CFS. In addition, to ensure that the pipeline of promising studies in CFS remains full, ORWH and cosponsors from the CFSWG issued two new Program Announcements to encourage new research applications entitled, "CFS: Pathophysiology and Treatment" that were published on August 22, 2008, PA-08-246 (R01) and PA-08-247 (R21).

In its lead NIH role, ORWH takes an active role in working with and providing information on CFS to the scientific and lay communities. It continues to maintain and update the CFSWG page on its Web site, http://orwh.od.nih.gov/cfs.html. In addition, ORWH continues to serve as the NIH representative on the Department of Health and Human Services (HHS) Chronic Fatigue Syndrome Advisory Committee. It is expected that these continued efforts to plan and publish interdisciplinary initiatives for CFS at the NIH will attract new researchers to the field. Some highlights of accomplishments, including two major meetings on which future activities were based, are provided below.

Grantsmanship Workshop for Research on Chronic Fatigue Syndrome

The Trans-NIH Chronic Fatigue Syndrome Working Group held a 1-day grantsmanship workshop in September 2007 to provide CFS researchers with an enhanced understanding of the NIH funding process, an overview of the diverse funding opportunities available through the NIH Office of Extramural Research (OER), and the opportunity to meet with and query Program Officers from the Institutes, Centers, and Offices represented on the Working Group. Emphasis was placed on the need to move to interdisciplinary, crosscutting research approaches. An afternoon session was devoted to explaining mechanisms appropriate for seeking research and training funding for CFS, even when the term itself is not included in the title. The 43 workshop registrants were a diverse group, both geographically and in terms of their scientific areas of interest. There was ample time for meaningful exchange, and participant ratings were uniformly excellent. For more information, see http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html.

First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators

In June 2008, ORWH sponsored the First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators. The meeting brought together seven individuals who had received funding under an RFA specific to understanding the relationship of neuroimmune mechanisms and CFS. The investigators presented their results to date in the first half of the meeting and then participated in a team building exercise designed to encourage innovative collaborations. Discussions centered on how their work could be applied to understanding infection as a prototypical initial insult. Their work was seen as potentially providing insights into how systems become dysregulated and interact with one another to upset health. Other discussions focused on identifying methods that would be necessary for the investigators to function as an interdisciplinary team.

The following section summarizes individual studies funded in 2007–2008. With the exception of the first two listed, all were funded in response to the ORWH-initiated RFA on Neuroimmune Mechanisms and CFS. The following section summarizes individual studies funded in 2007–2008. With the exception of the first two listed, which were cofunded with NICHD (Taylor) and NIAID (Jason), all were funded in response to the ORWH-initiated RFA on Neuroimmune Mechanisms and CFS. ORWH fully funded two (Antoni and Biaggoni) through NINDs and provided 50 percent funding for two (Fletcher and Theoharides) through NIAAA. NINDS fully funded one study, Light, and NIEHS another, Baraniuk. NIAMS fully funded one study, Lorton.

Leonard Jason of De Paul University in Chicago was funded to elucidate the risk factors associated with CFS and CFS prognosis. CFS and chronic fatigue (CF) are severe, disabling conditions. Few studies have examined the natural history course of CFS and CF over time, particularly in random, community-based, multiethnic populations. In the past, almost all studies with samples of CFS and CF patients have relied on referrals from physicians or health facilities, which biased the sample by illness, help-seeking behaviors, or differential access to health care. In contrast, a recent community-based study found the prevalence rate of CFS to be 4 percent among adults, and the prevalence of CFS among adults was higher among Latino and African-

American samples than among the White sample (Jason et al., 1999). These findings might be because this sample was collected from an urban area, and a community-based approach was used, thus minimizing the influence of biased data collection procedures. The proposed study will rigorously evaluate the natural history of CFS and CF in an ethnically and socioeconomically diverse sample unbiased by illness and help-seeking behaviors, or by differential access to the healthcare system. Increasingly, the studies suggest that a variety of socioenvironmental and psychological risk factors are associated with CFS and CF maintenance over time. Followup will be undertaken for Wave 1 subjects with CFS and chronic fatigue to determine if the associations identified in Wave 1 between CFS and a variety of risk factors will be associated with poorer prognosis in Wave 2. Similar comparisons will be conducted for those with chronic fatigue. Major benefits of this grant application are the diversity of the population, identification of cases from the community rather than the healthcare system, and the use of a medical exam to confirm CFS and CF diagnoses. Funding for this grant ended in 2008, but the PI and colleagues continue to publish reports that elucidate and enhance identification of specific subgroups of CFS patients, as well as reports that help clarify changes in CFS terminology and the controversy regarding changing the name of CFS.

Renee Taylor from the University of Illinois in Chicago was funded to study CFS in adolescents in a prospective, case-control study based on research that documented development of a fatigue syndrome following mononucleosis in adults. One objective of the investigation was to prospectively study the relationship between infection with mononucleosis and the onset and course of CFS over time in adolescents. The following hypotheses were tested using a prospective, case-control design: (1) Baseline predictors of postinfectious CFS and fatigue severity at 6 months will include greater levels of psychological distress, having a psychiatric diagnosis, a greater degree of stressful life events, and higher levels of activity prior to initial infection; (2) Adolescents with CFS, compared with matched controls, will also report higher levels of psychological distress, higher rates of psychiatric diagnoses, a greater degree of stressful life events, and lower levels of physical activity following infection at the 6-, 12-, and 24-month time points; (3) Compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol (peak and trough), reduced natural killer cell function and count, and elevated proinflammatory cytokines at the 6-, 12-, and 24-month time points. At the 6-month time point (clinic visit), adolescents with CFS will also demonstrate higher rates of orthostatic intolerance; and (4) In response to an exercise challenge test at the 6-month time point, compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol and plasma ACTH, and elevated cytokines, illustrating impaired communication between neuroendocrine and immune systems with physical stress. An exploration of the nature and timing of these relationships would provide a preliminary model of etiology and natural course of illness for adolescents with postviral CFS. Results from this investigation may assist physicians in identifying adolescents at high risk for CFS and allow them to initiate preventative measures. Although funding ceased in 2008, the PI is sharing this prospective dataset of 400 published reports based on these studies.

Mary Fletcher from the University of Miami Medical School in Florida conducted research to clarify the etiology and pathogenesis of CFS. No unanimity of opinion regarding the etiology of CFS currently exists. Several etiologies have been proposed—immunological, neuroendocrine, and autonomic—and yet no physiological mechanism has been consistently and uniquely related to CFS. It is probable that CFS encompasses subpopulations that share a common symptom profile yet are mediated by different factors. Neuropeptides such as neuropeptide Y (NPY) have long been proposed to play a role in the pathogenesis of inflammatory diseases. NPY is a 36 amino acid neuropeptide, which participates in the regulation of a large number of physiological and pathophysiological processes in the cardiorespiratory, immune, nervous, and endocrine systems. In the periphery, NPY is concentrated in sympathetic nerve endings and is released alone or with catecholamines. NPY receptors are present

on most cells of the immune system, including natural killer (NK) cells. NPY suppresses natural killer cell cytotoxicity (NKCC). Given the potential for adverse effects with a constant stimulus, downregulation mechanisms are essential for neuropeptides, including NPY. A regulator of NPY is dipeptidyl peptidase IV (CD26). Preliminary data from the investigator's lab indicate that CD26 concentrations on lymphocytes are abnormally low. The role of NPY in CFS is undefined. A goal of the research is to improve the understanding of CFS pathophysiology and to develop biomarkers useful in diagnosis, in defining subsets, and in therapeutic trials. A study with four Specific Aims examines the neuroimmune relationship in CFS. Aim 1: to determine the extent to which patients, or a subset of patients, who meet the CFS case definition have elevated NPY, as compared to healthy, sedentary controls. Aim 2: to determine the relationship of NPY to the cell surface concentration of CD26 in patients with CFS as compared to controls. Aim 3: to define the relationship of NPY and CD26 to NKCC in CFS. Aim 4: to determine the relationship of NPY and CD26 to clinical severity in CFS patients. Funding for the project ended in 2008, but the research has created the potential for the development of a specific treatment for CFS in the near future.

Theoharis Theoharides of the Tufts Medical School in Boston conducted a study on mast cells, antidepressants, and CFS. CFS is characterized by fatigue, malaise, sleep, and autonomic disturbances; it is considered a neuroimmune disorder with dysregulation of the HPA axis, precipitated by stress and associated with high disability. CFS often occurs with comorbid diseases such as fibromyalgia, irritable bowel syndrome (IBS), interstitial cystitis, and migraines, all of which also worsen with stress. There are no reliable animal models for CFS. Mast cells have emerged as major regulators of neuroimmune endocrine processes affected by stress and have been implicated in the comorbid diseases associated with CFS. The PI and colleagues have shown that (1) mast cells have functional associations with nerve endings; (2) acute stress activates mast cells, an action blocked by pretreatment with corticotropin-releasing hormone (CRH) neutralizing antiserum; (3) stress increases blood-brain-barrier (BBB) permeability, which is inhibited by the CRH-receptor-1 (CRH-R1) antagonist Antalarmin and does not develop in mast cell-deficient W/W mice; (4) human mast cells express CRH receptors, activation of which leads to selective release of vascular endothelial growth factor (VEGF); and (5) some of the stimulatory effects of CRH on mast cells are mediated by neurotensin (NT), which has been shown to regulate the HPA axis. Tricyclic antidepressants are helpful in CFS and in the other comorbid diseases, but their mechanism of action is unknown. Preliminary results show that the tricyclic antidepressant amitriptyline can inhibit rat mast cell secretion and intracellular calcium ion levels. It is hypothesized that CRH, or the structurally related urocortin (Ucn), secreted by stress, activates diencephalic mast cells, either alone or together with other neuropeptides such as NT, leading to release of molecules that contribute to the central pathogenesis of CFS, and secretion of which can be inhibited by tricyclic antidepressants.

The following aims will be investigated: Aim 1: the dose-response (0.1–100 uM) and time-course (0.5, 1, 6, 24 h) effects of three different classes of antidepressants, tricyclics (amitriptyline, imipramine), selective serotonin reuptake inhibitors (fluoxetine, sertraline), and bupropion on secretion of histamine, IL-1, IL-6, IL-8, IL-13, TNF, tryptase, and VEGF from normal human umbilical cord-derived cultured mast cells. Aim 2: the effect of those antidepressants shown to be effective in Aim 1 in inhibiting "brain mast cells" developed by culturing human umbilical cord matrix stem cells. Results from these studies will further understanding of molecules released in response to stress hormones and which antidepressants may be useful in inhibiting these effects. Future studies will build on these findings to develop in vitro and in vivo models of CFS and lead to clinical trials with select antidepressants or other molecules that inhibit brain mast cells.

Brigitte Huber from Tufts University in Boston was funded to study a human endogenous retrovirus, HERV-K18, as a risk factor for chronic fatigue and immune dysfunction syndrome (CFIDS). The etiology of CFS is far from understood and is likely due to multiple genetic components. Infection with Epstein-Barr virus (EBV) and treatment with Interferon

alpha (IFN-a) have been implicated in the pathogenesis. Findings from the investigator's laboratory have shown that EBV infection, and exogenous IFN-a, activate transcription of the env gene of HERV-K18. This provirus is normally silent, but when induced, it encodes a superantigen (SAg), which is a class of proteins capable of deregulating the immune system. Three alleles of HERV-K18 env have been documented, K18.1, K18.2, and K18.3, whose gene products have SAg activity, but are predicted to differ biochemically and functionally. A working hypothesis is that HERV-K18 is a risk factor for CFS. In a pilot study, the allele and genotype distributions of the HERV-K18 env gene were compared between various groups of CFS patients and healthy controls. Although only a limited number of samples were available in the various cohorts, the odds ratios that were obtained were statistically significant. The most intriguing interpretation of these data is that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the coinvestigator, Dr. Renee Taylor. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T-cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during the course of the disease, will be tested ex vivo, using a T-cell hybridoma reporter assay that has been developed in the investigator's lab. Since SAg-activated T-cells produce massive quantities of chemokines, lymphokines, and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of CFS whose underlying mechanism(s) of pathogenesis as yet remain unclear.

Italo Biaggioni of Vanderbilt Medical School is conducting studies to determine the role of the autonomic nervous system (ANS) in abnormalities associated with CFS. The investigator proposes to test the hypothesis that the sympathetic nervous system contributes to the cardiovascular and inflammatory abnormalities present in CFS, and in particular, in the subset of patients characterized by postural tachycardia (POTS). CFS and POTS are seen mostly in otherwise normal young women, and are a cause of significant disability. Preliminary data indicate a decrease in plasma volume in patients with POTS, which can contribute to and be the consequence of sympathetic activation. Preliminary studies also indicate an interaction between the sympathetic nervous system and NO mechanisms; this may also create a negative feedback mechanism whereby a decrease in NO results in sympathetic activation, and increased sympathetic activity results in impaired NO mechanisms. The PI and his associates have developed a paradigm that will allow them to define selectively the contribution of endothelial NO to blood pressure regulation and will apply this approach to patients with CFS and POTS. In addition, their preliminary studies indicate that sympathetic activity is associated with inflammatory processes. In particular, C-reactive protein is increased in patients with POTS and, conversely, it is decreased in patients with low sympathetic tone due to pure autonomic unsuccessful undertaking. They propose to measure validated indices of sympathetic activity, inflammation, and oxidative stress in patients with CFS and POTS, and compare them to appropriate control groups, including patients with CFS without POTS, POTS without CFS, and normal controls. If their hypothesis is correct and sympathetic activity contributes to the pathophysiology of CFS, then chronic inhibition of sympathetic tone will result in improvement of symptoms, cardiovascular alterations, volume defects, and inflammatory abnormalities present in CFS.

Michael Antoni from the University of Miami Medical School in Florida was funded for his clinical trial of Cognitive Behavioral Stress Management for Chronic Fatigue Syndrome. This is a 4-year study that uses a 10-week, telephone-based cognitive behavioral stress management intervention (T-CBSM) to illuminate neuroimmune mechanisms underlying the effects of stress and stress management on physical health status and immune

regulation in individuals with CFS relative to participants receiving a health promotion telephone (T-HP) intervention. CFS is characterized by physical symptoms that bring about severe limitations in lifestyle behaviors and vocational activities. Associated symptoms include debilitating fatigue, low-grade fever, lymph node pain and tenderness, cognitive difficulties, and mood changes. There is growing evidence that CFS patients may also show abnormalities in HPA axis functioning and on several indices of immune functioning. Chronic stress is also associated with a flattened diurnal secretion pattern for cortisol. An inability to maintain regulation in the HPA axis may contribute to the pathophysiology of CFS via diminished control of proinflammatory cytokines and associated physical symptoms related to chronic immune activation and inflammation. Given the debilitating nature of CFS, we propose to deliver the T-CBSM intervention through a telecommunications system (i.e., Telecare) designed to enhance access to formal and informal care for a population that may have difficulty accessing traditional psychotherapeutic settings. In our prior work with individuals with CFS, we have shown that individuals in a structured-group CBSM intervention report significantly improved quality of life, perceived stress, fatigue, memory, muscle pain, and postexertional malaise compared to individuals in the control condition. The Telecare system has been successful in delivering a supportive intervention for older caregivers of dementia patients. This study is novel in expanding our prior work to individuals with CFS who have reported difficulty participating in structured groups due to physical burden. The study design is a 2 X 3 randomized experimental design with group (T-CBSM, n = 60 vs. T-HP, n = 60) as the between-group factor, and time (preintervention, postintervention, and 6-month followup) as the within-group factor. Our primary objective is to evaluate the extent to which a T-CBSM intervention aimed at building skills in anxiety reduction, distress tolerance, stressor appraisals, and adaptive coping strategies may improve physical health status and immune regulation in CFS by modulating neuroimmune interactions.

III. ORWH Biomedical Career Development Activities

Section III of this Biennial Report provides information on Office of Research on Women's Health (ORWH) initiatives and support for a wide range of career development activities. A major ORWH interdisciplinary mentored research career development program, the Building Interdisciplinary Research Centers in Women's Health (BIRCWH), has already been described in Section II. Additionally, ORWH works with many valued National Institutes of Health (NIH) and professional society partners in activities and initiatives to facilitate scientific career development and training. In FY 2007 and FY 2008, ORWH provided more than $1 million per year in support to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Women's Reproductive Health Research (WRHR) Career Development Program, which provides mentored research experiences for postdoctoral obstetrician/gynecologists, women and men, thereby enabling them to obtain the scientific skills necessary for a successful academic career in patient-oriented clinical women's health research. ORWH also provided support to multiple NIH Institutes for the Reentry into Biomedical and Behavioral Careers Research Supplement Program, which aims to facilitate the reentry of individuals into scientific careers after a hiatus due to family obligations such as childrearing or elder care. The activities and achievements of these two programs in FY 2007 and FY 2008 are summarized below.

Section III also provides a summary of the activities of the NIH Working Group on Women in Biomedical Careers, which was convened in 2007 by then-Director Dr. Elias Zerhouni, with ORWH designated as NIH lead. Dr. Vivian W. Pinn, Associate Director for Women's Health and Director, ORWH, cochaired this group with Dr. Zerhouni in 2007 and 2008, and she continues in this role with NIH Deputy Director and current Working Group Chair, Dr. Raynard Kington. The Working Group's activities are varied, but all aim to enhance the career development of women in biomedical science. Also in Section III is a summary of activities and accomplishments of ORWH/NIH Intramural Women's Health Programs. Activities include seminars to highlight intramural research on women's health and sex/gender differences as well as initiatives—many developed in parallel with the Working Group—to facilitate a successful combination of family responsibilities with a scientific career and to promote the career development of female intramural scientists. A final summary in Section III provides information on Other ORWH Career Development Activities, including partnering activities with professional societies to enhance the career development of women in science.

Women's Reproductive Health Research Career Development Program

The WRHR Career Development Program was initiated by the NICHD in 1998. ORWH joined NICHD in cosponsoring this program. This institutional career development award uses the K12 mentored career development mechanism to support research career development of WRHR Scholars, who are obstetricians/gynecologists who have recently completed postgraduate clinical training and are commencing basic, translational, and/or clinical research relevant to women's reproductive health. The goal of this initiative is to promote research that will benefit the health of women by bridging clinical training with research independence, and by increasing the number and skills of obstetrician/gynecologist investigators at awardee institutions through a mentored research experience leading to an independent scientific career addressing women's reproductive health concerns.

Twenty WRHR program sites are located in departments of obstetrics and gynecology throughout the Nation, with the primary goal of increasing the research capacity of clinically trained obstetricians/gynecologists. Since 1998, a total of 157 scholars have been appointed to the program. The 5th Annual WRHR Scholars' Research Symposium was convened on June 1–3, 2008, at the University

of Rochester School of Medicine and Dentistry, Rochester, NY.

Information on the WRHR program may be obtained by visiting http://www.nichd.nih.gov/research/supported/wrhr.cfm and the national Web site hosted by the University of Rochester WRHR program at http://www.wrhrscholars.org/. Below is information on the 20 WRHRs that are currently funded. In addition to NICHD support, for FY 2007 and FY 2008, ORWH contributed approximately $1.1 million per year to support the program.

2004 WRHR Sites

Ten WRHR sites funded for 5 years in 2004 include the following:

- University of Pennsylvania, Philadelphia, PA
- University of Cincinnati College of Medicine, Cincinnati, OH
- Wayne State University, Detroit, MI
- University of Texas Medical Branch, Galveston, TX
- University of California, Los Angeles, CA
- University of California, San Francisco, CA
- Stanford University School of Medicine, Stanford, CA
- Oregon Health & Science University, Portland, OR
- University of Washington School of Medicine, Seattle, WA
- Yale University School of Medicine, New Haven, CT

2005 WRHR Sites

The following are descriptions of the 10 WRHR sites that were funded for 5 years in 2006.

Program Director: Joe L. Simpson, M.D.

Institution: Baylor College of Medicine

Title: *Baylor WRHR Program*

This application offers career development for Ob/Gyn clinicians pursuing molecular research related to women's reproductive health. The program is a partnership involving M.D. Anderson Cancer Center that offers scholars greater access to clinical resources and core laboratories, as well as a full range of training opportunities to facilitate a seamless transition to research independence for scholars. A major strength includes the mentoring program that complements a formal didactic curriculum consisting of five required courses. Dr. Simpson has arranged for each scholar to have two mentors and an individualized training plan expressly designed for their professional backgrounds. These are important strengths of the program. The primary research mentor's role is to secure the development of solid investigative expertise. The secondary Ob/Gyn academic mentor's responsibilities are to maintain the clinical perspective and monitor academic progress.

Program Director: Robert L. Barbieri, M.D.

Institution: Brigham and Women's Hospital/ Harvard Medical School

Title: *Development of Scholars in Ob/Gyn for the 21st Century*

This continuing program builds on a long tradition of investigation and teaching in women's reproductive health. Dr. Barbieri has put together an outstanding plan that will make available biomedical resources in the extensive Harvard-affiliated system. The didactic component, along with the clinical breadth and biomedical research capabilities of the system, will provide a rich foundation for career development. Individualized plans are personalized for each scholar and could include enrollment in a Master's or Ph.D. program. In particular, assignment to one of three career tracks based on the scholar's background can only optimize a quality research experience. Mentoring from both a research and academic career advisor makes up a cohesive plan to solidify career development. Strengths include the five core strategies and key functional components that leverage the full potential of

research training to ensure successful career development of Ob/Gyn physician–scientists.

Program Director: Donald R. Coustan, M.D.

Institution: Women and Infants Hospital, Rhode Island (WIHRI)/Brown Medical School

Title: *Brown Medical School/WIHRI Dept of Ob/Gyn WRHR Program*

This proposal presents a very strong program dedicated to the career development of physician–scientists and clinical investigators. Dr. Coustan has a flexible program that will provide each scholar with a core curriculum, essential for his/her development as an independent investigator in women's health; a suitable mentor who can provide the guidance and expertise to ensure successful academic development and skills as an independent investigator; and the research infrastructure in an environment conducive to investigation into women's health. The scholars will be able to capitalize on a diverse group of senior scientific mentors and supporting investigators providing academic career advice. A major strength of this program is the focus on the translation of basic research into patient-oriented, clinical research to improve women's health. Their goal of creating independent investigators who will be committed to research careers in women's reproductive health should be realized.

Program Director: Mary D'Alton, M.D.

Institution: Columbia University Health Sciences

Title: *Columbia University Center for Career Development in Reproductive Sciences*

This ongoing program offers a unique opportunity for scholars to learn experimental concepts and techniques that will provide the necessary basics for a fruitful academic career. Dr. D'Alton plans to attract mentors primarily from the Center for Reproductive Sciences within the Department of Obstetrics and Gynecology. An important strength of the program is its long-standing history of combining basic investigation and training in the reproductive sciences. With this objective in mind, the program intends to recruit scholars who have an interest in and passion for basic investigation. The underlying theme is to maintain an essential clinical link to encourage a bridge between basic research process and its application and relevance to clinical principles related to women's health concerns. Clinical advisors will be available to facilitate this linkage. This program appears well positioned to train the next generation of outstanding physician–scientists in women's reproductive health.

Program Director: Sherman Elias, M.D.

Institution: Northwestern University

Title: *Research Career Development in Obstetrics and Gynecology*

This proposal has a highly innovative approach for establishing a training program for Ob/Gyn physician–scientists. Dr. Elias proposes a custom-designed research training and career development plan for each scholar. Scholars will be 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 will enter a basic science or clinical track based on their interests and previous research experience. The program provides an outstanding pool of experienced translational, basic science, 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 strength of the program is its location, surrounded by six medical schools in the Chicago area, which has one of the largest concentrations of highly qualified potential scholars.

Program Director: John C. Hauth, M.D.

Institution: University of Alabama at Birmingham

Title: *Ob/Gyn Faculty Research Career Development Program*

This renewal application is based on a research infrastructure that can accommodate and sustain an independent program dedicated to future generations of physician–scientists. Dr. Hauth plans to include the program as a division within the Center for Research in Women's Health, thereby allowing scholars access to 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 application offers a formal structured pathway by which entry-level or advanced scholars at different levels of development and expertise can be expected to acquire research skills appropriate to their ultimate goal of becoming independent investigators. A major strength is the critical mass of senior academicians with enhanced interdisciplinary research skills to assist in the development of physician–scientists capable of sustaining independent research careers.

Program Director: Thomas R. Moore, M.D.

Institution: University of California–San Diego

Title: *Reproductive Sciences Research Career Development Center*

This ongoing proposal includes a flexible two-phase program to accommodate the needs of potential scholars with a broad range of scientific backgrounds and experience. Dr. Moore plans to increase the opportunities for creative interdisciplinary approaches to diseases by bringing together basic scientists and Ob/Gyn clinical collaborators interested in the application of research advances specific to women's reproductive health. Scholars who enter this program have access to clinical, translational, and basic science collaborators with expertise in applying scientific findings to bedside medicine. A major strength is the Mentoring Committee, which represents a unique approach to providing scholars with an optimal research environment, and assists in sharpening their research skills as they move toward independence. Required didactic courses and opportunities for advanced degrees round out the training experience.

Program Director: Ronald S. Gibbs, M.D.

Institution: University of Colorado Health Sciences Center, Denver

Title: *Colorado WRHR Career Development Center*

This continuing program has a flexible plan focused on basic cellular and molecular mechanisms and translational research for scholars seeking an independent research career in women's reproductive health. Dr. Gibbs has established milestones for advancement in the program, including an ongoing dialogue with mentors, successfully completing a model curriculum for scholars with varying degrees of experience, and writing 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 for a multifaceted approach to the challenges of career development. A major strength of the program is the new interdisciplinary Graduate Program in Reproductive Science that is expected to foster interactions among scientists and clinicians and offers scholars exposure to multiple disciplines in a rich intellectual environment.

Program Director: Robert C. Cefalo, M.D., Ph.D.

Institution: University of North Carolina, Chapel Hill

Title: *WRHR Career Development at UNC*

This application builds on the institution's climate of research growth and commitment to patient-oriented translational research. Dr. Cefalo has a program with a long tradition of preparing Ob/Gyn physicians for careers in clinical research and a track record of interdisciplinary reproductive health research. One objective is to orient new investigators toward large-scale collaborative research teams. Scholars entering this program will convene a mentor panel to access scientific expertise, consultation, 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. A major strength of the program is the proposed partnership with the Morehouse School of Medicine to identify eligible members of the Ob/Gyn faculty to participate in the program. Didactic components and a tailored program of training increase the likelihood of future research independence.

Program Director: James R. Woods, M.D.

Institution: University of Rochester

Title: *Rochester Women's Reproductive Health Research Program*

This renewal application presents an outstanding pathway for Ob/Gyn physician–scientists to commence their research careers. Scholars entering this program complete a basic core of didactic courses emphasizing clinical research design, data processing and analysis, writing, and ethics. Dr. Woods believes that a core curriculum of knowledge, skills, and research perspectives will be important in clinical investigation and practice. With this in mind and taking into account the experience of the scholars, the program offers two individualized tracks: laboratory science and clinical science. Both tracks will provide scholars with the underpinnings needed to maximize the benefit from mentored research. The environment offers a longstanding multidisciplinary research focus, including a pool of mentors who are leaders in their respective fields and experienced educators. This approach to training is the cornerstone of a program that has been successful in training physician–scientists.

Reentry into Biomedical and Behavioral Careers Research Supplement Program

The ORWH Reentry Supplement Program helps fully trained scientists (women and men) to reestablish careers in biomedical or behavioral science after taking time off to fulfill familial responsibilities. It was originally developed in FY 1992 and is a supplement to an existing NIH research grant.

In parallel with efforts of the NIH Working Group on Women in Biomedical Careers, ORWH led an effort to broaden eligibility to postdoctoral fellows for *Research Supplements to Promote Reentry into Biomedical and Behavioral Research Careers*. ORWH initiated a clarification of the eligibility requirements so that individuals who were postdoctoral fellows at the time they left active research will be specifically eligible to apply. The new Program Announcement (PA) states that candidates "must have been in a postdoctoral or faculty position at the time they left active research" (NOT-OD-07-068) and is supported by the National Cancer Institute (NCI); National Eye Institute (NEI); National Human Genome Research Institute (NHGRI); National Heart, Lung, and Blood Institute (NHLBI); National Institute on Aging (NIA); National Institute on Alcohol Abuse and Alcoholism (NIAAA); National Institute of Allergy and Infectious Diseases (NIAID); National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); National Institute of Biomedical Imaging and Bioengineering (NIBIB); *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); National Institute of Dental and Craniofacial Research (NIDCR); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Institute of Environmental Health Sciences (NIEHS); National Institute of General Medical Sciences (NIGMS); National Institute of Mental Health (NIMH); National Institute of Neurological Disorders and Stroke (NINDS); National Institute of Nursing Research (NINR); National Library of Medicine (NLM); Fogarty International Center (FIC); National Center for Complementary and Alternative Medicine (NCCAM); National Center for Research Resources (NCRR); and Office of Dietary Supplements (ODS), with ORWH as the lead. It also extends the deadline for applications for another year.

PA-08-191 was issued in July 2008 with support from 23 Institutes and Centers and states that candidates with a postdoctoral or faculty position at the time they left active research are eligible to apply.

FY 2007 Reentry Awardees

In FY 2007, ORWH supported a total of seven individuals in the Reentry Program. They are briefly described below.

NIDCD: Carol McArthur, M.D. (Year 2)

Institution: Oregon Health & Science University (OHSU)

PI: Dennis R. Trune, Ph.D.

Grant: R01DC005593

Title: *Steroid Responsive Mechanisms in the Ear*

Dr. Carol McArthur received her M.D. from University of California–Los Angeles (UCLA) School of Medicine in 1984. She trained at University of California–Davis for her residency, and she received a fellowship from Harvard School of Medicine in Pediatric Otolaryngology. In 1996, she left academic medicine to raise two young children. She gave up her clinical practice to move to Portland with her husband, at which time she turned to academic medicine at OHSU. In 2002, she reestablished her clinical practice on a half-time basis and at the same time, she began volunteering in Dr. Trune's laboratory within the otolaryngology department. This supplement will be used to facilitate her reentry into academic science.

NHLBI: Mary Owen, Ph.D. (Year 2)

Institution: Medical College of Georgia

PI: Richard E. White, Ph.D.

Grant: R01HL73890

Title: *Molecular Basis of Estrogen Dual Effects on Coronary Arteries*

Dr. Mary Owen obtained her Ph.D. from Medical College of Georgia in 1979. After 2 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 became an Associate Professor at Philadelphia College of Pharmacy and Science in 1988. Due to her mother's illness, Dr. Owen took a leave for 7 years and recently returned to the Georgia Campus of Philadelphia College. Prior to her leave, Dr. Owen had been an active researcher in the cardiovascular field. Her research was supported by NHLBI and the American Heart Association.

NHGRI: Pia Abola, Ph.D. (Year 1)

Institution: The Molecular Sciences Institute, Berkeley, CA

PI: Roger Brent, Ph.D.

Grant: P50HG002370

Title: *Center for Genomic Experimentation and Computation*

Prior to her hiatus, Dr. Abola had acquired many of the qualities and skills necessary to develop an individual research program, with 4 years as a postdoctoral fellow and 1 year as a research associate. She has taken a hiatus since 2001 to care for her children while keeping current with scientific research by acting as an informal consultant to a scientist at Scripps Institute, as well as by keeping up with scientific literature and colleagues. She will continue her reentry process with Dr. Roger Brent, purifying proteins to measure kinetic parameters of the MAP kinase signaling complex.

NHLBI: Ann Celi, M.D., M.P.H. (Year 1)

Institution: University of California–San Diego

PI: Patricia W. Finn, M.D.

Grant: R01HL081663

Title: *Innate Immunity and Allergy: Modulations by CTLA4*

Until 2003, Dr. Ann Celi was involved in research on breastfeeding issues in Project Viva and was a Co-PI of Smoke-Free Moms, a randomized trial of buproprion to prevent postpartum smoking relapse. After giving birth to her third child in 2003, she took time off from research to care for her family. During the 3 years from 2003 to 2006, she kept her clinical appointment at Brigham and Women's, but did not perform research activities. She will be reentering research under the mentorship of Patricia Finn, M.D., and Ellice Lieberman, M.D., Dr.P.H., on allergic asthma and inflammation.

NIDA: Huan Ngo, Ph.D. (Year 1)

Institution: Northwestern University

PI: Richard Miller, Ph.D.

Grant: R01DA013141

Title: *Chemokine Receptor Function in the Nervous System*

Dr. Ngo took leave from scientific research at Yale University to contribute to urban education, working with underprivileged children as a teacher, for the past 5 years to "repay" his debt for the support given him. As a child in Vietnam, Dr. Ngo was homeless. Despite his underprivileged background, he achieved his professional training goals, becoming a researcher at Yale University with more than 20 publications. Having built a model educational science program and having worked with the urban poor, he will move forward with reentry into a full-time scientific research career under the mentorship of Richard Miller, Ph.D., and Rima McLeod, M.D.

NIMH: Kristin Wilcox, Ph.D. (Year 1)

Institution: Johns Hopkins University School of Medicine

PI: Michael R. Weed, Ph.D.

Grant: U01MH75378

Title: *Oral Self-Dosing/Behavioral Assessment*

Dr. Wilcox focused on examining the neurochemical and behavioral effects of cocaine self-administration in nonhuman primates until 2002, when she took a hiatus to focus on caring for her infant children. During her hiatus, she remained scientifically active through consulting activities and publishing 14 articles. She has also been working as a consultant with Dr. Weed at Johns Hopkins University, with whom she will continue her reentry process, with co-mentoring from Nancy Ator, Mark Riddle, and Dean Wong on examining the effects of chronic methylphenidate and amphetamine administration on physiological, behavioral, and neurochemical function in a pre- and postadolescent nonhuman primate model for Attention Deficit Hyperactivity Disorder.

NIDDK: Kathryn Ann Woods, M.D. (Year 1)

Institution: Oregon Health & Science University

PI: Peter S. Rotwein, M.D.

Grant: R01DK069703

Title: *Control of IGF-1 Gene Transcription by Growth Hormone*

Prior to her hiatus, Dr. Woods was active in basic and clinical research for 7 years in the molecular biology of hormone receptor pathways. She was an international presenter at many scientific meetings and the recipient of the Best Original Research Proposal award from the British Endocrine Society. She took a hiatus from 2000 to 2003 to care for her children, and returned half-time as a Senior Research Associate in 2003. She has been involved in several small-scale, nonlaboratory research projects and will continue her reentry process under the mentorship of Dr. Peter Rotwein.

FY 2008 Reentry Awardees

In 2008, the reentry awardees were as follows:

NIDDK: Kathryn Ann Woods, M.D. (Year 2)

Institution: Oregon Health & Science University

PI: Peter S. Rotwein, M.D.

Grant: R01DK069703

ORWH Contribution: $20,000

Title: *Control of IGF-1 Gene Transcription by Growth Hormone*

Prior to her hiatus, Dr. Woods was active in basic and clinical research for 7 years in the molecular biology of hormone receptor pathways. She was an international presenter at many scientific meetings and the recipient of the Best Original Research Proposal award from the British Endocrine Society. She took a hiatus from 2000 to 2003 to care for her children, and returned half-time as a Senior Research Associate in 2003. She has been involved in several small-scale, nonlaboratory research projects and will continue her reentry process under the mentorship of Dr. Peter Rotwein.

NHLBI: Ann Celi, M.D., M.P.H. (Year 2)
Institution: University of California–San Diego
PI: Patricia W. Finn, M.D.
Grant: R01HL081663
ORWH Contribution: $19,000
Title: *Innate Immunity and Allergy: Modulations by CTLA4*

Until 2003, Dr. Ann Celi was involved in research on breastfeeding issues in Project Viva and was a Co-PI of Smoke-Free Moms, a randomized trial of bupropion to prevent postpartum smoking relapse. After giving birth to her third child in 2003, she took time off from research to care for her family. During the 3 years from 2003 to 2006, she kept her clinical appointment at Brigham and Women's, but did not perform research activities. She will be reentering research under the mentorship of Patricia Finn, M.D., and Ellice Lieberman, M.D., Dr.P.H., on allergic asthma and inflammation.

NHLBI: L. Maria Belalcazar, M.D. (Year 1)
Institution: Baylor College of Medicine
PI: Christie M. Ballantyne, M.D.
Grant: R01HL090514-01
ORWH Contribution: $20,000
Title: *Long-Chain Omega-3 Fatty Acid Intake and the Modulation of Atherothrombotic Risk in Obese Diabetics*

Dr. Belalcazar received her M.D. and completed her residency in Bogota, Colombia, then migrated to the University of Pittsburgh, where she did a fellowship. She then went to the University of Texas Medical Branch and did another residency in internal medicine. Following her second residency, she did a 3-year fellowship at Baylor College of Medicine in endocrinology, diabetes, and metabolism. At the time of Dr. Belalcazar's career hiatus, she was a full-time tenure-track Assistant Professor. Due to family care issues, Dr. Belalcazar was away from research for several years. Her current position is that of a part-time Clinical Assistant Professor of Medicine. Under the mentorship of Dr. Ballantyne, Dr. Belalcazar will be clarifying the associations among obesity, inflammation, and coagulation balance in diabetics; and determining the impact of weight loss, diet, and physical activity on these parameters. Dr. Belalcazar will be doing a project entitled, "Long-Chain Omega-3 Fatty Acid Intake and the Modulation of Atherothrombotic Risk in Obese Diabetics."

NHLBI: Tracy Baker-Herman, Ph.D. (Year 1)
Institution: University of Wisconsin
PI: Gordon S. Mitchell, Ph.D.
Grant: 5R37HL069064-07
ORWH Contribution: $20,000

Dr. Baker-Herman had begun her post-doctoral research in Dr. Gordon Mitchell's laboratory, but the birth of her three children, periods of full-time parenting, and relocation of the family and then back due to her husband's jobs interrupted her research career. She is currently reestablishing her research career in Dr. Mitchell's lab. Dr. Mitchell is conducting research on respiratory plasticity and spinal cord injury. Under the mentorship of Dr. Mitchell, Dr. Baker-Herman will be conducting research on respiratory memory and neuronal plasticity.

NIH WORKING GROUP ON WOMEN IN BIOMEDICAL CAREERS

Background

A component of the mandate of ORWH within the NIH Office of the Director is to develop opportunities and programs to support recruitment, retention, reentry, and advancement of girls and women in biomedical careers (P.L. 103–43, Section 486e). Soon after the Office was established in 1990, ORWH sponsored public hearings and a workshop on women in biomedical careers to identify barriers to women's professional advancement in the biomedical community. The resulting report, *Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century*, inspired the development of a wide variety of programs and strategies at NIH to support women's careers.

ORWH also provided the initial funding to The National Academies Committee on Science, Engineering, and Public Policy and

The National Research Council standing committee, Committee on Women in Science and Engineering, to address issues relevant to women in academic science and engineering. Later funding was provided by Eli Lilly and Co., the National Science Foundation, the Ford Foundation, and The National Academies. With this funding, The National Academies created the ad-hoc Committee on Maximizing the Potential of Women in Academic Science and Engineering, chaired by Donna Shalala, Ph.D., President of the University of Miami and former Secretary of the U.S. Department of Health and Human Services, and charged the committee to review and analyze the best data available on the women in academic science and engineering and to develop specific recommendations on "...how to make the fullest possible use of a large part of our Nation's talent: women in academic science and engineering." The committee hosted a public convocation to explore the impact of sex and gender on cognitive and intellectual abilities and attitudes and institutions that affect career advancement for women in science and engineering. The committee published its findings and recommendations in *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*.

The National Academies report noted that women today comprise an increasing proportion of science and engineering majors; nonetheless, the representation of women in leadership positions in academic institutions, scientific and professional societies, and honorary organizations is low relative to the number of women qualified to hold these positions. The report put forth a challenge to Federal funding and Government agencies, foundations, universities, and professional societies to take decisive action and called for an urgent, broad national effort to maximize the potential of women scientists and engineers in academia.

Establishment of the NIH Working Group on Women in Biomedical Careers

In response to The National Academies report, NIH Director Dr. Elias A. Zerhouni created the NIH Working Group on Women in Biomedical Careers (see Appendix G) in early 2007 to examine the issues raised in The National Academies report and to address the challenges issued to government funding agencies to maximize the potential of women scientists and engineers; give attention to the NIH intramural community and the concerns of intramural women scientists; consider the broader context of girls and women in science; and provide special attention to issues of barriers, minority women scientists, and mentoring.

The Working Group was cochaired by Dr. Zerhouni and Dr. Vivian W. Pinn, Associate Director for Research on Women's Health and Director of the Office of Research on Women's Health. Following Dr. Zerhouni's departure from NIH in late 2008, Dr. Kington also became cochair of the Working Group. The Working Group is composed of individuals from across NIH at different career levels, including both men and women, individuals from underrepresented groups; postdoctoral fellows; early-stage investigators; a dual-career couple; directors of Institutes, Centers, and Offices; and NIH Deputy Directors.

The Working Group has created a Web site, hosted by ORWH, to provide a central focus for career development resources for women, both from NIH and from other organizations. For example, the Web site includes a comprehensive working document, created by the Working Group, which identifies NIH Career Development and Mentoring Programs available to both the intramural and extramural communities. In addition, the Working Group maintains a listserv, *NIH Updates on Women in Science (NUWS)*, which is a monthly e-newsletter containing articles and items pertaining to women in science. The Web site can be found at http://www.womeninscience.nih.gov.

ORWH/Working Group Workshops

ORWH and members of the Working Group organized two major meetings in 2007 and 2008. Descriptions of the meetings follow:

- The National Leadership Workshop on Mentoring Women in Biomedical Careers was held in November 2007. With nearly 600 registrants from government, academia, industry, and other organizations,

this workshop provided attendees with innovative tools to improve or initiate effective mentoring programs in their institutions or organizations. The purpose of the Workshop was to provide leadership in mentoring to sustain the advancement of women in biomedical careers. Goals of the workshop were to provide attendees with innovative tools to improve or initiate effective mentoring programs in their institutions or organizations. Among specific aims of the Workshop were the following: (1) Define mentoring as it applies across the career span of women in biomedical research careers; (2) Determine best ways to evaluate the effectiveness of mentoring programs; (3) Learn lessons from established biomedical research mentoring programs; (4) Develop new models for successful mentoring programs; (5) Design new pathways for mentoring women in the private and public biomedical research sectors; and (6) Construct leadership strategies for success in the global biomedical research environment. Full proceedings of that meeting are available at http://womeninscience.nih.gov/mentoring/documents/National_Leadership_Workshop_on_Mentoring_Women_in_Biomedical_Careers.pdf.

- The Women in Biomedical Research: Best Practices for Sustained Career Success Workshop was held in March 2008. This workshop had over 500 registrants and highlighted the "best practices" of organizations that are successfully addressing major barriers in the career development of women scientists. Conference committees developed a list of real or potential "best practices," along with consideration of potential programs that can be adapted or piloted by academic health centers to improve the retention and advancement of women in biomedical careers. The conference attendees discussed the specific roles of NIH and other organizations in increasing the career success of women in the biomedical sciences. Videocasts from the plenary session of ORWH Initiatives and full proceedings are available at http://womeninscience.nih.gov/bestpractices/docs/BestPracticesReport.pdf.

Based on these workshop activities and recommendations, several initiatives have been developed and implemented by the Extramural Program.

Extramural Career Initiatives

On July 14, 2008, NIH released a Request for Applications (RFA) entitled, *Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering*. The full announcement is available at http://grants.nih.gov/grants/guide/notice-files/NOT-GM-08-126.html. The intent of the RFA is to develop the evidence base that will inform policy decisions that will help to bring about the institutional changes necessary to promote and support women in biomedical careers. Rigorous research will help define the critical issues and provide guidance on the development of effective interventions and strategies.

This RFA was developed by a Subcommittee of the Working Group under the direction of Raynard Kington, M.D., Ph.D., Deputy Director, NIH. The RFA is sponsored by the National Institute of General Medical Sciences (NIGMS) with awards to be funded in 2009.

ORWH established a Reentry Supplement Program in 1992 as a pilot program to assist fully trained scientists (women and men) to reestablish their careers in biomedical or behavioral science after taking time off to fulfill familial responsibilities. After 3 years as a successful pilot program, it was expanded to a trans-NIH program.

The Reentry Supplement Program was reissued in July 2008, and is supported by NCI, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, and NIAMS. To address suggestions for improving the Reentry Supplement Program, ORWH initiated a clarification of the eligibility requirements so that individuals who were postdoctoral fellows at the time they left active research are also eligible to apply. The new program announcement states that candidates "must have been in a postdoctoral or faculty position at the time they left active research." The full text of the announcement can be found at http://grants.nih.gov/grants/guide/pa-files/PA-08-191.html.

The parental leave policies for one of the NIH major training awards, the Ruth L. Kirschstein National Research Service Awards (NRSA), have been modified to extend paid family leave for the birth or adoption of a child from 30 days to 60 days. The doubling of the period of parental leave available to NRSA recipients will encourage institutions to examine their own parental leave policies for all students and postdoctoral fellows. More information on this change can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-064.html.

The Working Group Subcommittee on extramural funding mechanisms and policies created a PowerPoint presentation that summarizes data on women in NIH extramural research, training, and career development programs. The group has also developed answers to common questions about parental leave and childcare policies. Both items are posted on the Office of Extramural Research, NIH and Working Group Web sites.

Intramural Career Initiatives

A number of initiatives have been developed in conjunction with the Office of Intramural Research (OIR) and the Council of Scientific Directors aimed at supporting investigators with family responsibilities to advance in their careers. These initiatives include an extension of the tenure clock by 1 year and a mechanism to employ a temporary lab manager to continue lab operations for a PI while on family or medical leave.

To increase the availability of child care, the Foundation for Advanced Education in the Sciences is funding a program to grant the children of new tenure-track hires priority placement at a daycare center very close to campus.

In addition, NIH is one of four institutions that helped to establish the Mid-Atlantic Higher Education Recruitment Consortium, which maintains a regional (Baltimore to Richmond) Web-based search engine of all job listings at member institutions. The purpose is to enhance and facilitate dual-career job searches.

The Trans-NIH Mentoring Committee has been formed to examine methods used for annual progress reviews for fellows to ensure that they are beneficial for both the fellow and the PI and to determine how mentoring by PIs can be evaluated and enhanced. Parental leave policies for NIH intramural trainees have been modified to allow 60 days of family leave for the birth or adoption of a child. Finally, focus groups were held with tenure-track intramural scientists, staff clinicians and scientists, and postdoctoral fellows to address issues of recruitment and retention of minority and women scientists.

ORWH/NIH Intramural Women's Health Research Programs

In 2006, ORWH supported an 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 determine the need for mentoring and support networks. This survey addressed 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 identified impediments to the recruitment of women into tenure-track investigator positions and tenured senior investigator positions at NIH. The task force also examined impediments to the retention and tenure of female tenure-track investigators, and career tracks and appointment mechanisms chosen by men versus women as well as the underlying reasons for the choices. Based in significant part on the activities of the Task Force, in 2007–2008, the Intramural Subcommittee of the NIH Working Group on Women in Biomedical Careers considered changes to the work culture at NIH. The Subcommittee, co-chaired by Michael Gottesman, M.D., and Ruth Kirschstein, M.D., made a number of recommendations for changes to NIH culture, many of which have been implemented. Highlights of the subcommittee's activities can be found earlier in this Section under the summary of the activities of the *NIH Working Group on Women in Biomedical Careers*. A full summary of the Working Group's reports can be accessed at http://womeninscience.nih.gov/. A number of other ORWH/Intramural Women's

Health Research Initiatives are highlighted in the next section.

Intramural Seminars

Intramural Women's Health Scientific Interest Group (WHSIG) Seminar Series

The WHSIG Seminar Series, sponsored by ORWH and the Intramural Research Program on Women's Health, began in October 2002. Lectures on both basic science and clinical research topics of relevance to women's health have been presented by experts in a wide variety of scientific disciplines from within the NIH intramural program as well as the outside scientific community.

The WHSIG is a forum for researchers across NIH to meet, establish collaborations, and learn about sex-based differences beyond the effects of sex hormones that are relevant to molecular, cellular, genetic, and developmental processes, and affect organ systems, behavior, and the organism as a whole. This lecture series has provided an important avenue for scientific interchange, and has resulted in the formation of new scientific collaborations between NIH intramural researchers with scientists around the world, highlighting the value of an interdisciplinary research approach to sex and gender differences in biology and disease from the molecular level to therapeutic clinical trials.

In 2007, some examples of lectures include Menstrual Cycle; Preeclampsia and Cardiovascular Disease; Changing Models of Biomedical Research or Interregnums Are Tough for Young Investigators; and the Griff Ross Memorial Lecture on Reproductive Endocrinology, New Genes that Control Reproduction in Humans.

In 2008, seminars included HPV Infection and Cervical Cancer: Applying What We Have Learned About Natural History to Prevention; Uterine Fibroids—An Understudied Condition: Epidemiologic Research at NIEHS; Integrating Genomics and Behavioral Science: Opportunities & Challenges for Women's Health; Sex Matters: A Tale of Two Bones—Sexual Dimorphism in the Skeleton; Depression and Osteoporosis: The Magnitude of Bone Loss Is Substantial; and Sex Differences in Obesity and Osteoarthritis of the Knee.

Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH

The NIH Women Scientist Advisors Committee, with support from ORWH, announced a new seminar series to highlight outstanding research achievements of women scientists in the Intramural Research Program. The seminar series is dedicated to the memory of Dr. Anita B. Roberts, and honors her role as an exceptional mentor and scientist. In 2007, the speaker was Dr. Nora Volkow on "Why Is It So Hard for the Addict's Brain to Just Say No?" In 2008, Dr. Susan Gottesman spoke on "Small RNAs and Adapting to Stress."

Intramural Fellowships

ORWH/NICHD Fibroid Fellowship

The ORWH/NICHD Fibroid Fellowship was established to provide for the support of continued studies of the molecular derangements associated with uterine fibroids. This fellowship was awarded in 2006 to Chantal Mayers, a participant in the NIH Graduate Partnerships Program (GPP). The GPP, established in 2000, links the NIH Intramural Research Program with Ph.D. programs at U.S. and international universities.

A graduate of Salisbury State University, Mayers sought and was awarded one of the highly competitive postbaccalaureate Intramural Research Training Awards and worked with Dr. James Segars in NICHD. After doing research with Dr. Segars and colleagues at the Uniformed Services University of the Health Sciences for 3 years, she joined the Johns Hopkins Graduate Partnership Program to pursue her Ph.D. She elected to continue working with Dr. Segars for her dissertation, which was based on her ongoing fibroid research in his lab. In 2007, she completed her second year in this program. In Dr. Segar's lab, she is studying factors that contribute to fibroid cell growth.

NIH Women's Health Fellowships in Intramural Women's Health Research (Public–Private Partnership)

In 2006, ORWH and the NIH Intramural Program for Research on Women's Health announced the first recipients of the NIH Women's Health Fellowships in Intramural Women's Health Research. This intramural program is supported jointly by ORWH and OIR. The Fellowships are funded through the Foundation of the NIH. Sponsors of the fellowships were Batelle and AstraZeneca. Two fellows were selected: Suzanne C. O'Neil, Ph.D., University of North Carolina, Lineberger Comprehensive Cancer Center; and Shannon K. Laughlin, M.D., Loyola University.

Dr. O'Neil, awarded the Shared Postdoctoral Fellowship, examined the emotional and behavioral responses of women seeking genetic testing for BRCA1/BRCA2 breast and ovarian cancer susceptibility genes. Dr. O'Neil obtained her Ph.D. in clinical psychology from the University of Delaware and did a clinical internship in behavioral medicine at the Medical University of South Carolina. She had been a postdoctoral fellow at the University of North Carolina's Lineberger Comprehensive Cancer Center.

Dr. Laughlin, recipient of the Clinical/Translational Fellowship, completed a residency in obstetrics and gynecology at Loyola University. Dr. Laughlin worked with the epidemiology branch of the National Institute of Environmental Health (NIEHS) in Research Triangle Park, NC. Her research plan was focused on factors that place women at high risk of developing fibroids. She explored early identification and treatment of high-risk women, with prevention and reduction in the need for surgical intervention as the goal.

Clinique—Women's Health Summer Research Internship (Public–Private Partnership)

A partnership was created with the cosmetics firm, Clinique Laboratories, Inc., through the Foundation for the NIH to provide support for a summer internship program for individuals interested in pursuing a career in nursing or science. Candidates were selected from the pool of applicants who had applied for the NIH Summer Internship Program in Biomedical Research based on enrollment in an undergraduate program and an expressed interest in skin, skin cancer, and/or dermatology. Three outstanding interns were selected to participate in the Program. This Women's Health Summer Internship Program provided an 8- to 10-week intensive biomedical research experience for the three students in laboratories of the National Cancer Institute, the National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of Dental and Craniofacial Research. The Selection Committee included individuals from the Intramural Program on Research on Women's Health Steering Committee, the National Institute of Nursing Research, and the Office of Intramural Training & Education. At the end of the summer, the interns presented their research findings at the NIH Summer Poster Day and then joined their mentors for a day in New York at Clinique headquarters for a second presentation of their work.

The students in 2007 selected for this fellowship were as follows:

- **Recipient:** Neha Agarwal, University of Maryland–College Park
  Institute: NCI
  Mentor: Drs. David Solomon and Barbara Vonderhaar
- **Recipient:** Laurel Cumming, University of Maryland–College Park
- **Institute:** NIAMS
  Mentor: Dr. Maria Morasso
- **Recipient:** Jean Suh, John Hopkins University
  Institute: NIA
  Mentor: Dr. David Schlessinger

In 2008, the students were as follows:

- **Recipient:** Bonnie Chen, Stanford University
  Institute: NIA
  Mentor: Dr. Ashani Weeraratna
- **Recipient:** Caroline Loftus, University of Minnesota
  Institute: NIDCR

Mentor: Drs. Peter Burbelo and Mike Ladarola

- **Recipient:** Subha Perni, Princeton University
  Institute: NCI
  Mentor: Dr. David Solomon

ORWH/Intramural Programs on Women's Health

ORWH provides support for a variety of Intramural Programs. In FY 2007, ORWH provided the Office of Intramural Training and Education (OITE) with $377,900 and $410,000 in FY 2008 to support a series of educational programs for postdoctoral fellows, graduate students, summer students, and postbaccalaureate trainees, as well as a workshop for tenure-track women on assertiveness and management. These programs are summarized below. (See Appendix H for Steering Committee members.)

Assertiveness Training

In 2007, a test-pilot course on Assertiveness–Managing Up training for women tenure track was developed. Entitled, How to Succeed as a PI at the NIH, the course was well received by the women who participated, many of whom wrote the course organizers to tell them how they were able to successfully apply lessons learned in negotiations with their supervisors. A few female postdoctoral trainees attended as well, and based on their enthusiastic evaluation, it was decided to offer a similar workshop to fellows in January 2008. This type of training has been perceived as extremely valuable and a prototype of the type of training that should be offered to women scientists.

Fellows Award for Research Excellence (FARE) Program

The FARE program was established by the NIH Fellows Committee in 1994 as a mechanism for promoting and recognizing research excellence in the intramural program. All graduate students and postdoctoral and clinical fellows with less than 5 years' total research experience at 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, 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 for presenting his/her work at a scientific meeting during the fiscal year.

Predoctoral and Postdoctoral Courses and Workshops

A number of training courses have been developed for predoctoral and postdoctoral students in the NIH Intramural program. For postdoctoral Fellows, programs include (1) Survival Skills Workshops: a series of half-day workshops that addressed the topics of resume writing, job interviewing, negotiating a job offer, grant writing, and establishing a laboratory; (2) a Career Series consisting of panels of experts in career fields for which a biomedical research background is essential, including biodefense, teaching, patents, and technology transfer. Many of the speakers for the career series were former NIH fellows, who are particularly effective with the fellows and can offer them up-to-date information and networking for the jobs; (3) courses on Speaking and Writing about Science, each a 4- to 5-week course offered three times per year; (4) an advanced course: Speaking about Science, offered twice last year, as a forum for in-depth, individualized assistance to each participant; (5) an NIH Job Fair held annually in conjunction with the NIH Research Festival, which brings together NIH scientists across campus and science and biotech companies. More than 800 fellows participated; and (6) the Improved Language Skills course, offered to first-year Visiting Fellows to improve the English skills necessary for professional development. This course proved so popular it was offered twice.

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 NIH in cooperation with the Office of Intramural Research, Fogarty

International Center, and 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 NIH; and trains promising students for postdoctoral studies at NIH. Each year, a joint TAU–NIH committee chooses about five of the best students to join the program. They then perform research in the Israeli laboratory (10 months/year) and the NIH laboratory (2 months/year) for 3 years. The students who participated in the program have covered many aspects of cutting-edge research, with a special emphasis on women's health.

Postbaccalaureate Programs

For postbaccalaureate trainees, the programs offered include Career Enhancement Seminars designed to assist postbaccalaurate trainees to prepare for careers in research. These include sessions on speaking about science, tips on scientific poster presentations, preparation for the Medical College Admission Tests and Graduate Record Examinations, and the Myers-Briggs personality inventory. A Premed Advising Workshop for postbaccalaureate trainees who plan to apply for admission to medical school was also provided.

Undergraduate Scholarship Program

ORWH provided $75,000 to the Office of Intramural Training & Education, Undergraduate Scholarship Program in FY 2007. These funds were used in collaboration with others in the OITE to establish a Scientific Career Counseling Center for NIH trainees. Specifically, ORWH funding was used to support Dr. William Higgins, a pregraduate/preprofessional advisor who assists Undergraduate Scholarship Program scholars and other undergraduate trainees with their applications to graduate and medical schools. Funds were also used to support Melanie Sinche, a certified career counselor with a specialization in science careers. She also prepares and delivers career development workshops on CV/resume writing and networking.

ORWH–FAES–NIH High School Summer Student Program

This is a program that the Office of Intramural Research considers to be of high importance because it exposes Washington-area high school students from a diverse background, including at least 50 percent women and a high percentage of minorities and underrepresented minorities, to biomedical research at a time when they are still forming their future plans. The program thereby enhances the possibility that they will choose science careers. In the summer of 2007, the program had 24 new high school students and 13 returning students; and in the summer of 2008, 26 students enrolled in the program. The program included presentations at which students learned about the structure of NIH, the Intramural Research Program, and ORWH, and received guidance on how to make research presentations. Students met as a group for a lunch-time session over a 5-week period, during which they were offered the opportunity to make presentations on their research to each other. Included in the audience were their preceptors; some of the advisors for the program (all members of the NIH scientific staff); and either Dr. Michael Gottesman, Deputy Director for Intramural Research, or his Assistant Director, Dr. Joan Schwartz. The presence of these NIH senior scientific staff ensured a lively discussion of each presentation, and put each research project into a broader biomedical context. The students also presented posters at the NIH Summer Student Poster Presentations day. They learned not only how to carry out a research project, how to ask important questions, and how to design experiments to answer those questions, but also how to communicate their results to other scientists. Among signs of the success of the program are that one of the students won one of the three grand prizes in the Intel Science Competition, and that several have had publications result from their work.

OTHER ORWH CAREER DEVELOPMENT ACTIVITIES

From Doctorate to Dean or Director: Sustaining Women Through Critical Transition Points in Science, Engineering, and Medicine

In September 2008, the Committee on Women in Science, Engineering, and Medicine of The National Academies hosted a workshop sponsored by ORWH and the Kauffman Foundation. This 1½-day workshop explored crucial transition points in women's career paths in academia and industry, as well as the increasing importance of interdisciplinary work and how it impacts women's career choices.

Panel discussions outlined critical transition points in academic careers, proven strategies for helping women transition in industry, and the impact of the changing nature of science, engineering, and medicine—specifically the growth in interdisciplinary research fields—on career progression now and in the future. Representatives from professional scientific societies submitted oral testimony to the committee addressing critical transition points in their fields of expertise. Information on the Workshop can be found at http://www7.nationalacademies.org/cwsem.

NIH/National Medical Association Partnership Travel Award Program

Since 1998, NIH and the National Medical Association (NMA) partnership committee have worked collaboratively to provide travel awards to support residents and fellows interested in academic medicine to attend the Annual Convention and Scientific Assembly of the NMA. The awardees participate in a special 2-day academic skills workshop held in conjunction with the Annual Convention and Scientific Assembly. The topics of the workshop range from how to write a grant to time management skills.

The intent of this award is to enhance the potential careers of residents and fellows of all medical and surgical specialties interested in an academic career, and secondly, to encourage research in disease areas that disproportionately impact the health of underserved communities. NIH anticipates that through this scientific opportunity, a greater number of physicians from communities that are underrepresented in science will enter into and remain in academic research positions.

The applicant must be a member of a nationally underrepresented group in biomedical or behavioral research and must have a strong interest in academic medicine. A special review committee composed of NIH professional staff evaluates and assesses each application. The committee makes recommendations for awards based on the selection criteria and policies and provisions of the NIH governing administrative awards. In 2007, 60 Travel Fellowships were made to residents and fellows and 40 were made in 2008.

Minority Faculty Student Partnership (MFSP); MFSP Biotechnology Training Course

The goal of the partnership is to train minority students and faculty members, primarily from Historically Black Colleges and Universities, Hispanic Serving Institutions, and Indian Tribal Colleges or Universities, in the nature and application of the latest principles and techniques of biotechnology. For the MFSP Biotechnology Training Course, 12 faculty members, along with 12 second-, third-, or fourth-year biology majors were selected and trained at NIH for a 1-week period. Through the Bio-Trac program, a series of 1-week lecture and "hands-on" laboratory training workshops were provided in different areas of biotechnology that are topical and in demand in the sciences.

Association for Women in Science Annual Seminar Series

The Association for Women in Science (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 over 150 members. Its members are actively engaged in scientific research, education, administration, and policy activities, and are employed in Federal agencies, academia, business, and nonprofit organizations. In FY 2007, ORWH provided support for the 14th Annual Seminar Series, Strategies for Success in Science. Seminars included Analyzing the Leaky Pipeline: Why are Women Scientists Underrepresented on the Faculties of U.S. Medical Schools?; Science & Policy: Making the Connection, Expanding Your Horizons, Survival Skills workshop; Assessing the Status of Women Scientists in the NIH Intramural Program; and Have a Meal With Your Mentor.

Women in the Environmental Mutagen Society (WEMS)

ORWH provided funding to support the programmatic activities of the newly organized Women in the Environmental Mutagen Society (WEMS) during the 39th annual meeting of the Environmental Mutagen Society (EMS). The mission of the WEMS is to (1) create opportunities for networking and mentoring for women; (2) encourage leadership and career development; and (3) encourage and support representation of women throughout the society and in the broader scientific community. Together with the Education and Student Affairs and the Membership and Professional Development Committees of EMS, this year, WEMS is also holding a special mentoring workshop that will introduce a new mentoring program to nurture students, postdoctoral fellows, and early career investigators in the environmental health sciences. This program will connect more seasoned scientists working in academia, industry, and regulatory agencies with young female scientists to help them in establishing connections that will allow them to flourish.

American Society for Cell Biology (ASCB) Activities

American Society for Cell Biology Publications

In FY 2008, ORWH provided funding to support the production of copies of three ASCB publications and development of a new publication for young investigators. Funds were used for reprinting *Career Advice for Life Scientists (CALS) I and II* (into one volume) and compiling, editing, designing, laying out, and printing CALS III. This edition will also be prepared as a downloadable PDF on the ASCB Web site and will be on the ORWH Web site.

American Society for Cell Biology, Women in Cell Biology Workshops

Women in Cell Biology (WICB) is a longstanding committee of the ASCB. WICB provides year-round career support and advice. They respond to reports of discriminatory practices, offer a speaker referral service to help program organizers identify women speakers, and produce monthly columns for the ASCB newsletter. In addition, WICB has a traditional presence at the ASCB Annual Meeting, providing networking and workshop opportunities. In FY 2007, ORWH provided funding to support the workshop, Developing Leadership Skills, which was held at the 46th Annual Meeting in San Diego, CA, in December 2006 and was led by the WICB committee. In 2008, ORWH supported the Career Development activities at the 47th annual meeting in San Francisco.

American Psychological Association (APA): Committee on Women In Psychology

In FY 2008, in partnership with the APA Committee on Women in Psychology, ORWH provided support for a Leadership Development Needs Focus Group. The goal of this leadership program was to prepare and support women psychologists to advance and excel in positions of institutional and organizational leadership where they can effect positive changes. Increasing the diversity, number,

and effectiveness of women psychologists as leaders should help advance psychology as a science and profession and as a means of promoting health, education, and human welfare.

Dr. Ruth Fassinger, Interim Chair and Professor, Department of Counseling and Personnel Services, University of Maryland—College Park, conducted this formal evaluation of leadership training needs. The focus-group portion of the day allowed participants to be divided into small groups for discussion, each with one facilitator and a note taker. Each group was also audiotaped. All of the information was treated as confidential and all identifying characteristics in the transcript were redacted. In addition, all information was reported in aggregate form only.

ORWH and the NIH Office of Science Education Program

Women Are Scientists is a series of video presentations that showcases successful female scientists in their respective specialties, and informs students about educational requirements, rewards, and challenges of careers in the biomedical sciences. Each video presentation gives a detailed view of three women scientists from various backgrounds as role models for their particular career. This series is designed to motivate middle school students to take more challenging advanced science and math courses and to enable them to successfully direct their own career paths. ORWH has provided cofunding for the series, including in 2007–2008, support for a fifth video entitled, "Women in Dental Research," which completes the series of videos. In addition, ORWH supported the conversion of the Women Scientists With Disabilities video into DVD format and packaging. A process is underway to digitize all five videos for Web site use.

The titles in the series include the following:

- Women Are Surgeons
- Women Are Researchers
- Women Are Pathologists
- Women Scientists With Disabilities
- Women in Dental Research

More information about the series and other educational activities are available at the Office of Scientific Education (OSE), NIH Web site, http://science.education.nih.gov/home2.nsf/feature/index.htm.

IV. Research Dissemination and Outreach

The Office of Research on Women's Health (ORWH) works in partnership with the National Institutes of Health (NIH) Institutes and Centers (ICs), other Federal agencies, and various national, State, and community organizations using a variety of outreach efforts to disseminate information on research on women's health. Working together, ORWH and its partners ensure that timely and relevant information is distributed widely 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. 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 use ORWH as a central resource at NIH on women's health and sex and gender research.

NIH widely expanded access to advances resulting from women's health research for the public and scientific community through ORWH monthly podcasts, *Pinn Point on Women's Health*, featuring NIH scientists providing topical updates focused on improving women's health; a new Web portal at the National Library of Medicine (NLM) that provides consumers and researchers with a one-stop resource of publications, ongoing clinical trials and their results, and evidence-based health education materials; and a Seminar Series open to the public on the results and clinical applications of ongoing women's health research, which are made broadly available through archival NIH videocasts.

http://orwh.od.nih.gov/podcast/podcast_archive.html

http://sis.nlm.nih.gov/outreach/whrhome.html

E-Government Approaches to Research Dissemination

NLM–ORWH Web Portal for Women's Health Research

In March 2008, ORWH and the National Library of Medicine announced the launch of an innovative new Web portal on women's health research. This portal, http://sis.nlm.nih.gov/outreach/whrhome.html, uses the *NIH Research Priorities for Women's Health* to identify overarching themes, specific health topics, and research initiatives in women's health. Within each section of the Web site are topics with links to relevant and authoritative resources and research initiatives for women's health. NLM has created specific user-friendly strategies for these topics to ease searching ClinicalTrials.gov and PubMed. Other Web resources used include AIDSinfo, American Indian Health, Arctic Health, Household Products Database, MedlinePlus, and NIHSeniorHealth. Search strategies for major studies related to women's health research have also been created and will be linked between the new Web site and the ORWH Web site. As with the topical search strategies, ClinicalTrials.gov and PubMed searches for each major report are also included.

Women's Health Podcasts

ORWH broadcasts a series of podcasts, *Pinn Point on Women's Health*, hosted by Dr. Vivian W. Pinn, Associate Director for Research on Women's Health and the Director of ORWH. These monthly podcasts discuss the latest news in women's health research referred to as "Hot Flashes," and they include conversations with NIH and other scientists on a variety of subjects.

Conversations with NIH intramural and extramural scientists on a wide variety of subjects were conducted. For easy access to information, the podcasts are posted on the ORWH Web site at http://orwh.od.nih.gov/podcast/podcast_archive.html. The podcasts have brought hundreds of new visitors to the ORWH Web site and won the NIH Plain Language Award for 2008 in recognition of translating scientific information into plain

language. The following topics have been covered, beginning with the most recent:

- ***Pelvic Floor Disorders, October 2008***
  Dr. Linda Brubaker, Professor of Obstetrics/Gynecology and Urology, Loyola University
- ***Domestic Violence, September 2008***
  Dr. Valerie Maholmes, Program Director, Social and Affective Development/Child Maltreatment and Violence Program in the Child Development and Behavior Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- ***Depression, July 2008***
  Dr. Peter Schmidt, Chief, Behavioral Endocrinology Branch, National Institute of Mental Health
- ***Women and Stroke, May 2008***
  Dr. John Lynch, Program Director, Office of Minority Health and Research, National Institute of Neurological Disorders and Stroke
- ***Obesity, March 2008***
  Dr. Susan Yanovsky, Co-Director, Office of Obesity Research, National Institute of Diabetes and Digestive and Kidney Diseases
- ***Irritable Bowel Syndrome, February 2008***
  Dr. Frank Hamilton, Senior Advisor in Gastroenterology, Chief, Digestive Diseases Program Branch, National Institute of Diabetes and Digestive and Kidney Diseases
- ***Women and HIV/AIDS, January 2008***
  Dr. Victoria Cargill, Director of Minority Research and Clinical Studies, Office of AIDS Research
- ***Vulvodynia Awareness, December 2007***
  Dr. Estella Parrott, Program Director of the Reproductive Medicine Gynecology Program in the Center for Population Research at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- ***Bone Health and Osteoporosis, October 2007***
  Dr. Joan McGowan, Director, Division of Musculoskeletal Diseases and Director of the Bone Diseases Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases
- ***Ovarian Cancer, September 2007***
  Dr. Edward L. Trimble, Head, Gynecologic Cancer Therapeutics and Quality of Cancer Care Therapeutics, Clinical Investigation Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute
- ***Eye Diseases in Women, July 2007***
  Dr. Janine Smith, Deputy Clinical Director, National Eye Institute
- ***Update on the Women's Health Initiative, May 2007***
  Dr. Jacques Rossouw; Chief of the Women's Health Initiative Branch; National Heart, Lung, and Blood Institute
- ***Breast Cancer Research Advances, April 2007***
  Dr. Larissa Korde, Staff Clinician, and Dr. Worta McCaskill-Stevens, Program Director and Medical Oncologist, Cancer Prevention Branch, National Cancer Institute
- ***The HPV Vaccine, March 2007***
  Dr. Allan Hildesheim, Senior Investigator, Division of Cancer Epidemiology and Genetics, National Cancer Institute

The Science of Sex and Gender in Human Health Web-Based Course

ORWH is continuing its collaboration with the Food and Drug Administration (FDA) Office of Women's Health (OWH) to provide a free, self-paced, Web-based course on the importance of considering sex and gender in human health to researchers, clinicians, members of academia, students in health professional schools, and others with an interest in women's health or the science of sex and gender in human health.

The first module of this course was designed to offer 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. The module builds upon the Institute of Medicine report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* The module comprises six lessons: definitions of sex and gender, the development and implementation of the Federal research regulations,

cell physiology, developmental biology, pharmacodynamics and pharmacokinetics, and clinical applications of genomics. It is currently available at http://orwh.od.nih.gov and approved for 6 *AMA PRA Category I Credit™*.

From the launch of the course in June 2006 through December 31, 2008, 2,757 registrants signed on to take instruction. They represent, as based on their service providers, government (n = 333), education (n = 688), organizations (n = 178), and others (n = 461). Among those who completed the course, 30 percent of those seeking credit were doctors of medicine. The averaged overall continuing medical education (CME) evaluation score was 4.15 on a 5-point scale and indicated that participants had met their objectives to a considerable degree. In addition, their written comments were quite favorable.

In 2008, the NIH–ORWH and the FDA–OWH initiated and have been engaged in the process of developing a second module that will apply the basic concepts introduced in Module I to specific conditions or organ systems where sex differences may be significant. The topic areas to be covered in Module II include cardiovascular disease, infectious disease, endocrine/autoimmune disorders, bone metabolism and bone diseases, cancer, neurological system and disorders, substance abuse/addictive disorders, substance use and health, and mental health disorders. Chapters will also be included on drug metabolism and biostatistics/clinical trials.

Module II, which is under development, is intended to provide guidance to physicians and other health practitioners and healthcare providers about the importance of sex differences in clinical conditions. Authors were asked to prepare each lesson following the basic structure suggested below, as appropriate to the topic area, while ensuring that known sex and gender differences were highlighted. The importance of setting specific learning goals for each lesson was so that knowledge could be assessed.

I. Introduction that includes definitions and objectives
II. Epidemiology (including genetic, environmental, and sociopsychological risk factors)
III. Pathophysiology
IV. Clinical Presentation and Course
V. Differential Diagnosis and Workup (where appropriate)
VI. Treatment and Management Recommendations (where appropriate)
VII. Public Health Implications or Research Recommendations (as appropriate)

Outreach and Community Partnerships

ORWH Women's Health Seminar Series

The ORWH Women's Health Seminar Series features nationally recognized leaders in women's health research who present the latest information on topics important to women's health. The Seminar Series began in 1990 and its goal is to educate the NIH community and the public at large on issues that affect the health of women. Every seminar focuses on a current women's health issue and showcases recent research related to that theme. The theme for 2007 was The Health of Girls and Women Across the Lifespan. The first seminar was titled, "The Health of Girls and Women Across the Lifespan: Adolescents." Habits of good health are formed early. This seminar focused on physical activity in youth, health risks of obesity, addiction and adolescents, and an update on the National Longitudinal Study of Adolescent Health (Add Health) Research Project. The second seminar in this series was titled, "Accept the Challenge: Stay Healthy! Focus on Nutrition, Exercise, Heart, and Bone Health." Both seminars were well attended and received outstanding evaluations.

In 2008, the Women's Health Seminar Series showcased the research and researchers from the Specialized Centers of Research on Sex and Gender (SCOR) Factors Affecting Women's Health.

Sex and Gender Research in the Urinary Tract

Date: October 16, 2008

Presentations and Presenters

- *E. coli* Biofilms, *Bottlenecks, and Host Responses in Urinary Tract Infections,* Scott Hultgren, Ph.D., Washington University Medical School
- Urinary Incontinence: What We Thought We Knew That Isn't True, John O. L. DeLancey, M.D., University of Michigan Medical School
- *How to SCOR! Urinary Incontinence: Translating Research to Improved Patient Care,* Jeanette S. Brown, M.D., University of California, San Francisco

Sex and Gender Research: Pain

Date: July 17, 2008

Presentations and Presenters

- *Sex Differences in Visceral Pain in Irritable Bowel Syndrome,* Lin Chang, M.D., UCLA Center for Neurobiology of Stress
- *Sex Differences in Brain Responses in Irritable Bowel Syndrome,* Jennifer Labus, Ph.D., UCLA Center for Neurobiology of Stress
- *Sex Differences in Responses of Gastrointestinal Tract to Stress: Implication of CRF-Signaling Pathways,* Muriel Larauche, Ph.D., UCLA Center for Neurobiology of Stress

Sex and Gender Research: Substance Abuse

Date: March 27, 2008

Presentations and Presenters

- *Sex and Gender Influences on Addiction in Adolescents,* Sari Izenwasser, Ph.D., University of Miami Miller School of Medicine
- *Sex Differences in Stress and Cocaine Addiction: Effects on Relapse Outcome,* Rajita Sinha, Ph.D., Yale University School of Medicine
- *Does Gender Matter in Cigarette Smoking Cure-Reactivity and Behavior?,* Himanshu P. Upadhyaya, M.B.B.S., M.S., Medical University of South Carolina

Accept the Challenge: Stay Healthy! Focus on Nutrition, Exercise, Heart, and Bone Health

Date: October 2, 2007

Presentations and Presenters

- *Food: Nature's Prevention Drug of Choice,* Wendy L. Johnson-Taylor, Ph.D., M.P.H., RD, National Institute of Diabetes and Digestive and Kidney Diseases
- *Stop the Silent Thief: Maintain Strong Bones,* Jane A. Cauley, Dr.P.H., University of Pittsburgh
- *How You Can Keep You and Your Heart Healthy: The Facts About Heart Disease in Women,* Ileana L. Piña, M.D., FACC, FAHA, University Hospitals Case Medical Center

The Health of Girls and Women Across the Lifespan: Adolescents

Date: June 5, 2007

Presentations and Presenters

- *Sleep Behaviors and Adolescents,* Ronald Dahl, M.D., University of Pittsburgh
- *Physical Activity in Children and Youth,* Russell Pate, Ph.D., University of South Carolina
- *Obesity and Adolescent Girls: A Slightly Different Perspective,* Dianne Neumark-Sztainer, Ph.D., M.P.H., RD, University of Minnesota
- *Addiction and Adolescents,* Donald R. Vereen, M.D., M.P.H., National Institute on Drug Abuse
- *Update on ADD Health Research Project,* Christine Bachrach, Ph.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Vulvodynia Awareness Campaign

Vulvodynia is a chronic pain disorder that affects as many as 18 percent of women at some point during their lives. This

underdiagnosed and underrecognized disorder adversely impacts quality of life and can profoundly affect women's reproductive choices. To address this women's health issue, ORWH launched a Vulvodynia Awareness Campaign at the National Press Club on October 24, 2007. Participants included 37 Federal and non-Federal partners, members of the ORWH Advisory Committee, ORWH staff, other NIH staff, and members of the media.

Campaign information kits, which include fact sheets, scientific articles, patient vignettes, and Web links to materials from collaborating partners are available on the ORWH Web site at http://orwh.od.nih.gov/health/vulvodynia.html and can be ordered through the NICHD Information Resource Center at http://www.nichd.nih.gov/publications/. As of March 15, 2008, the Resource Center has fulfilled more than 269 requests for campaign information kits and a bulk order of 100 from a health center in Texas. Campaign information kits are also distributed at women's health events, such as the ORWH exhibit at the National Women's Heart Health Fair in Washington, DC, held on February 1, 2008.

The Vulvodynia Awareness Campaign has been mentioned by more than 45 print and electronic media outlets, including ABC News, *The New York Times*, and WebMD. (We have learned through the National Vulvodynia Association that the Oprah Winfrey television talk show has taped a segment on vulvodynia with Mehmet Oz, M.D.) In addition to mentions in news reports, ORWH and many collaborative partners have added extensive content on vulvodynia to their Web sites. For an example, visit the National Women's Health Resource Center vulvodynia Web area at: http://www.healthywomen.org/condition/vulvodynia.

ORWH continues to work with campaign partners to develop other strategies for consumer and professional education and awareness, and to fulfill media requests for information. Below is a list of partners with which ORWH collaborates to provide the public with health information on vulvodynia:

Vulvodynia Awareness Campaign Partners List

U.S. Department of Health and Human Services (HHS), NIH

- Office of Research on Women's Health
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- National Institute of Neurological Disorders and Stroke
- The NIH Pain Consortium
- National Library of Medicine

Additional HHS Partners

- Agency for Healthcare Research and Quality
- Centers for Disease Control and Prevention
- Health Resources and Services Administration
- Office of Disease Prevention and Health Promotion
- Office of Minority Health
- Office of Women's Health
- U.S. Food and Drug Administration

Non-Federal Resources and Partners

- American College of Nurse-Midwives
- American College of Obstetricians and Gynecologists
- American Medical Women's Association
- American Society for Colposcopy and Cervical Pathology
- Association of American Indian Physicians
- Black Women's Health Imperative
- International Society for the Study of Vulvovaginal Disease
- National Alliance for Hispanic Health
- National Black Nurses Association
- National Hispanic Medical Association
- National Medical Association
- National Research Center for Women & Families
- National Vulvodynia Association
- National Women's Health Network
- National Women's Health Resource Center

- North American Menopause Society
- Our Bodies, Ourselves (Boston Women's Health Book Collective)
- Society for Women's Health Research
- The Women's Sexual Health Foundation
- University of Medicine and Dentistry of New Jersey, Women's Health Institute
- University of Michigan Center for Vulvar Diseases
- University of Minnesota, Division of Epidemiology and Community Health
- WebMD
- Women's Health Institute at Howard University
- Women's Health Specialists

A more complete listing of partners, along with information on vulvodynia research, can be found in Appendix I.

Women's Health Week at NIH

ORWH participated in the national efforts for Women's Health Week in May for fiscal years 2007 and 2008. In both years, publications on women's health from all NIH ICs were disseminated at the ORWH exhibit located at the NIH Clinical Center. Over 15,000 publications were distributed in 2008. Additionally in 2008, ORWH participated with the NIH Division of Police for a "Safety Celebration" in recognition of National Police Week and Women's Health Week. ORWH also held a Meet the Cast event in the Clinical Center where previous podcast guests were given time to speak one-on-one with interested NIH staff. In May 2008, ORWH sponsored an NIH Community Forum: Seeking New Dimensions and Strategies for Women's Health Research: Recognizing the Contributions of *Our Bodies, Ourselves*. NIH staff and guests participated in a discussion on the status of women's health research and its future directions. The forum featured special guest speaker Anne S. Kasper, Ph.D., contributing author to the groundbreaking publication, *Our Bodies, Ourselves*, founding member of the U.S. Women's Health Movement, and organizer and chair of the Maryland Women's coalition for Health Care Reform. An enthusiastic audience discussed the future roles of advocacy organizations in setting priorities for women's health research.

Inclusion of Women and Minorities in Clinical Research Outreach Notebook

NIH staff provide outreach to the scientific community to help increase understanding of the revised inclusion policy and U.S. Office of Management and Budget (OMB) requirements. These training and outreach efforts are designed to improve understanding of the sex/gender and minority inclusion policy and 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 Clinical 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 NIH inclusion policy, 1997 OMB requirements for reporting race and ethnicity data, as well as information for application submission, peer review, and funding. Both 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, 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. Additionally, a slide show available electronically and in hard copy, *Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!* was developed for NIH staff to assist them in working with the extramural community.

NIH Summit: The Science of Eliminating Health Disparities

With multiple other ICs, ORWH cosponsored a Summit, principally organized by the NIH Center on Minority Health and Health Disparities, held December 2008 at the Gaylord Conference Center, National Harbor, Maryland. The Summit included highlights of the research progress of NIH on health issues among racial/ethnic minority and medically underserved populations. Other aims were to increase awareness and understanding of disparities in health; showcase best-practice models in research, capacity-building, outreach, and integrated strategies to eliminate health disparities; identify strengths and gaps in health disparities research; and network and dialogue with the Nation's leading experts on minority health and health disparities.

In The Continuum—A Play on HIV/AIDS in the African-American Community

Washington, DC, has the highest rate of persons living with AIDS in a major U.S. city, and African-American women, who are only 58 percent of the District's female population, account for 90 percent of all new female HIV cases. In FY 2008, ORWH provided financial support for an outreach activity to increase awareness of HIV/AIDS within the minority women community, specifically African-American women. This was a collaborative outreach activity between Federal and community partners. As part of the outreach, a play, *In the Continuum*, presented the ramifications for women and their entire constellation of respective networks of HIV/AIDS. The play, written by two black women (1 South African, 1 U.S. resident) was held at the Atlas Theatre in Washington, DC. Open discussions with the actresses, production staff, and production team were held after each showing. Additionally, two mobile HIV/AIDS testing units were parked outside the theatre for rapid testing.

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

Introduction

To demonstrate effective implementation of Public Law 103-43 and implementation of National Institutes of Health (NIH) policies on the tracking and inclusion of women and minorities in clinical research, the Office of Research on Women's Health (ORWH), in collaboration with the Office of Extramural Research (OER) and the Office of Intramural Research (OIR), has led monitoring efforts for compliance, including convening a trans-NIH Tracking and Inclusion Committee. Monitoring efforts have included the documentation of the numbers of males and females by race and ethnicity enrolled in clinical studies funded by NIH, as well as biennial statements from each Institute and Center (IC) Advisory Council to confirm compliance with NIH policies. These and other efforts serve to ensure that NIH procedures comply with the NIH policy on the inclusion of women and minorities in clinical studies.

Data monitoring for the magnitude and diversity of clinical studies funded by NIH is not a simple task. There has been an extensive and dedicated effort to provide accurate and reproducible data. However, transitions in information system software at NIH have introduced the need for modifications for monitoring inclusion and data collection.

The Acting Director of NIH has now established a task force to be co-chaired by the Director of ORWH, the Director of the National Center for Minority Health and Health Disparities (NCMHD), and an IC Director to examine the entire process for evaluating and monitoring the inclusion of women and minorities in clinical research funded by NIH. The results of the deliberations of this task force should be reflected in the next biennial report. However, the fiscal year (FY) 2007 and FY 2008 data in this document reflect the data reporting and current trends of the inclusion of participants in NIH clinical research.

This report would not be possible without the efforts of the members of the NIH Tracking and Inclusion Committee (see Appendix F for a list of members) and the electronic Research Administration (eRA) Population Tracking User Group (ePTUG), who have each provided many hours addressing multiple issues related to data entry, reconciliation of grants, contracts and cooperative agreements, and other related issues or concerns.

Historical Context

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by the National Institutes of Health 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,[1] 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.[2] Later that year, minority and other scientists at NIH recognized the need to address the inclusion of minority populations. Therefore, in a later 1987 version of the NIH guide, a policy *encouraging* the inclusion of minorities in clinical studies was first published.

In order to ensure that the policies for inclusion were firmly implemented by NIH, Congress made what had previously been policy into Public Law, through a section in the NIH Revitalization Act of 1993 (P.L. 103-43)[3] entitled, Women and Minorities as Subjects in Clinical Research. In 1994, NIH revised its inclusion policy to be in compliance with the statutory language. The Revitalization Act essentially reinforced the existing NIH policies, but with four major differences:

- That NIH ensure that women and minorities and their subpopulations be included in all clinical research;

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

Revised inclusion guidelines developed in response to this law were published in the *Federal Register*[4] in March 1994, and they became effective in September 1994. The result was that NIH could not and would not fund any grant, cooperative agreement, or contract or support any intramural project to be conducted or funded in FY 1995 and thereafter that did not comply with this policy.

Strategies to ensure uniform implementation of the revised guidelines across 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 ICs. This trans-NIH committee, convened by ORWH and co-chaired with a senior IC official, meets on a regular basis, focusing on consistent and widespread adherence to the NIH guidelines by all the ICs. Working in collaboration with OER, OIR, and other components of NIH, ORWH coordinates the activity of developing and establishing data collection and reporting methodologies to ensure uniform standards and definitions in the reporting of data on women and minority participants in NIH-funded clinical research.

To ensure NIH-wide adherence to the revised inclusion guidelines, in 1994, NIH conducted extensive training on the revised inclusion guidelines. In June 1994, 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 General Accounting Office (GAO) findings that an earlier policy was inconsistently applied and had not been well communicated or understood within NIH or in the research community. A variety of outreach activities was initiated to explain the revised policy to the scientific research community and to clear up common misunderstandings about the new requirements.

GAO Report, May 2000: Recommendations and Actions Taken

Following a congressional request for an assessment of NIH progress in implementing the1994 guidelines on including women in clinical research, the GAO issued another report in May 2000 entitled, *Women's Health: NIH Has Increased Its Efforts to Include Women in Research*.[5] It concluded that in the past decade, NIH had 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 NIH:

- 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, the NIH Subcommittee Reviewing Inclusion Issues was formed, consisting of representatives from several ICs, ORWH, OER, and OIR to reexamine the NIH system for tracking data on the inclusion of women and minorities in clinical research, recommend any necessary changes to improve its accuracy and performance, and reiterate the NIH policy. Several actions resulted to clarify the requirement for NIH-defined Phase III clinical trials to include women and minority groups, if scientifically appropriate, and for the 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 the following:

- Update of the *NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*[6] and posting it on the ORWH home page, 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;
- Development of a new terms and conditions of award statement for awards made after October 1, 2000, that have NIH-defined Phase III clinical trials;
- Incorporation of language in NIH solicitations for grant applications and contract proposals to clarify the submission requirement for NIH-defined Phase III clinical trials and a description of plans for sex/gender and/or race/ethnicity analysis including subgroups, if applicable, and the reporting of enrollment annually and results of analyses, as appropriate; and
- Development of guidelines and instructions for reviewers and Scientific Review Officers (SROs) to emphasize and clarify the need to review research proposals that are classified as NIH-defined Phase III clinical trials for both inclusion requirements and issues related to analyses by sex/gender and/or race/ethnicity. Instructions were developed for the proper documentation to be included 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 since 2000, including specific topics addressing revisions to the NIH inclusion policy, a grants policy update, and SRO orientation on specific issues related to review meetings and proceedings.

Format Changes for Reporting Race and Ethnicity Data as of FY 2002

Beginning in FY 2002, NIH changed how data are reported based on the 1997 Office of Management and Budget (OMB) revisions to the 1977 Directive 15, "Race and Ethnic Standards for Federal Statistics and Administrative Reporting," which provided minimum standards for maintaining, collecting, and reporting data on race and ethnicity. In October 1997, OMB published *Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity*, and their implementation 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. 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 prior to FY 2002 are completed.

The 1997 OMB reporting format (NEW FORM) and standards do not easily 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 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 originating prior to FY 2002 are difficult, although trends can be approximated.

As demonstrated below, the primary differences are (1) the Hispanic population is considered an ethnic category and reported separately from racial data; (2) there are separate racial categories for Asian population data as distinct from 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 below 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 racial 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. (See Figure 1.)
- Hispanics are defined by country of origin and may be identified as belonging to any one race or more than one racial category.

Continuing Implementation and Monitoring Activities

In FY 2007, two training sessions were collaboratively developed and then sponsored through OER for NIH staff involved in the management or review of clinical research studies. The half-day training sessions were held and were also Web cast throughout the NIH community. While some staff participated in the training via the Web, approximately 300 NIH staff attended each session in person. Participants received a certificate of completion and, if appropriate, extramural scientist administrator credits after completing a short test. The training subcommittee of the NIH Tracking and Inclusion Committee continually updates training documents and methods of training for NIH staff.

The Public Health Service (PHS) 398 Grant Application was significantly revised to provide additional instructions concerning the NIH Women and Minorities Inclusion Policy and the revised form became mandatory as of May 10, 2005. These PHS 398 instructions are also included in the Federal application form SF-424 (R&R) for NIH grants using the Federal Grants.gov system (see http://era.nih.gov/ElectronicReceipt/), including two significant changes in definitions. First, NIH requires use of a revised definition of clinical research that was reported in the 1997 Report of the NIH Director's Panel on Clinical Research and adopted by NIH. Second, NIH adopted the 1997 revisions to OMB Directive 15, "Race and Ethnic Standards for Federal Statistics and Administrative Reporting," and required the revised categories to be used when reporting race and ethnicity data (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html). In addition, 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 interventions being studied affect women or members of minority groups differently than other subjects.

Communication and Outreach Efforts to the Scientific Community

NIH staff provides outreach to the scientific community to help increase understanding of any revised inclusion policies. These training and outreach efforts improve understanding of the sex/gender and minority inclusion policy and 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 Clinical 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 NIH inclusion policy; current OMB requirements for reporting race and ethnicity data; and information for application submission, peer review, and funding. Both the Outreach Notebook and the FAQs are posted on the ORWH Web site, http://orwh.

FIGURE 1

OLD FORM (1977) versus 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	X	
Asian/Pacific Islander	X	
Black or African-American	X	
Hispanic, Not White	X	
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		X
Asian		X
Black or African-American		X
Hawaiian/Pacific Islander		X
White		
More Than One Race		X
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)		X
More Than One Race		
Unknown/Other (Hispanic)		X
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).

od.nih.gov, as well as on the NIH Web site for the inclusion of women and minorities policy implementation, 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. Additionally, a slide show is available electronically and in hard copy entitled, *Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!* The slide show was developed for NIH staff to assist them in working with the extramural community.

Monitoring Compliance: Extramural and Intramural Population Data Analysis

As a way of monitoring compliance with the policy, aggregate data tables compiled from each NIH IC are provided in this chapter. Because the data included in the tables are aggregate data from across NIH, the data tables provide documentation of the monitoring of inclusion with some degree of analysis of data. Caution should be used in interpreting these data. Conclusions that can be reasonably drawn from the data are provided.

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 based upon census data, but rather to conduct biomedical and behavioral research in such a manner that the scientific knowledge acquired will be generalizable to the entire population of the United States. The number of women, men, and/or representatives of racial/ethnic subpopulations included in a particular study depends upon the scientific question addressed in the study and the prevalence among women, men, and/or racial/ethnic subpopulations of the disease, disorder, or condition under investigation.

Scientific Review Groups (SRGs) are instructed to focus on scientific considerations when assessing the planned enrollment for a particular study. The SRG determines if 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 meet the 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 enrollment can be monitored.

NIH has monitored aggregate demographic data for study populations through the evolving NIH computerized tracking system since fiscal year 1994, and monitoring compliance with the NIH inclusion policy is well established in all ICs. Members of the NIH Tracking and Inclusion Committee continually work on ways to refine and improve data collection methods and the quality of the data entered by each IC into the computerized system. In May 2002, the NIH successfully deployed a population tracking system for monitoring inclusion data that was designed to provide easier data entry and project monitoring of investigator data reporting for NIH staff. An ePTUG consisting of representatives from several ICs provides continuous feedback related to procedures to monitor compliance.

Definitions

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

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that use human tissues that cannot be linked to a living individual. Patient-oriented research includes (a) mechanisms of human disease, (b) therapeutic interventions,

(c) clinical trials, and (d) development of new technologies;

(2) Epidemiologic and behavioral studies; and

(3) Outcomes research and health services research.

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, nonpharmacologic, 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 as follows:

- 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 dataset. 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 nonprofit or forprofit organization that is located in the United States or its territories and 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 United States and its territories that is subject to the laws of that country, regardless of the citizenship of the proposed principal investigator (PI).

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 officers introduce and discuss with reviewers the guidelines for reviewing the inclusion of women and minorities in clinical research, as well as the instructions and requirements for designing Phase III clinical trials in order that valid analyses can be conducted for sex/gender and racial/ethnic dif-

ferences. 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.

References

[1]U.S. Public Health Service. Women's health: Report of the Public Health Service Task Force on women's health issues. *Public Health Reports* 100(1):73-106, 1985.

[2]Division of Research Grants. Inclusion of women in study populations. *NIH Guide to Grants and Contracts* 16(3):2, 1987.

[3]Public Law 103-43. National Institutes of Health Revitalization Act of 1993 (42 U.S.C. 289(a)(1)).

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

[5]*Women's Health: NIH Has Increased Its Efforts to Include Women in Research* (GAO/HEHS-00-96, May 2000). Washington, DC: U.S. Government Accountability Office.

[6]NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, NIH Guide for Grants and Contracts, Amended 2001.

For additional information on the implementation of the inclusion policy:

- NIH Office of Extramural Research Inclusion of Women and Minorities Policy Implementation Web site: http://grants.nih.gov/grants/funding/women_min/women_min.htm
- Revitalization Act of 1993, 42 U.S.C. 289 (a)(1): http://grants.nih.gov/grants/guide/notice-files/not94-100.html
- NIH Policy on Reporting Racial and Ethnicity Data: Subjects in Clinical Research, NIH Guide for Grants and Contracts Web page: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html
- Office of Research on Women's Health Web site: http://orwh.od.nih.gov/inclusion.html

Summary Report of NIH Inclusion Data

NIH Aggregate Population Data Reported in FY 2007 and FY 2008

Because new clinical research studies begin each year while other studies may be ending, the inclusion figures will vary from year to year due to the scientific topics under study and the prevalence of those conditions within each individual study. These data help to establish trends on the inclusion of women and minorities as subjects in clinical research. Data on inclusion are tabulated from human subject populations in NIH-defined Phase III clinical trials and other human subject research studies and are based on self-identification by the participants. NIH clinical research studies are determined in accordance with the NIH definition of clinical research to include, for example, nonintervention clinical research, non-Phase III clinical trials, epidemiological studies, behavioral studies, and database studies.

Analysis of aggregate NIH data on inclusion for FY 2007 and FY 2008 documents that substantial numbers of women and men of all ages and minorities have been included as research subjects in NIH clinical trials and other human subject research studies during these fiscal years. However, caution should be used to avoid over-interpreting the figures that are provided. The NIH Tracking and Inclusion Committee has provided for the reader's interest 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, http://orwh.od.nih.gov/inclusion.html.

NIH Clinical Research: Fiscal Years 2007 and 2008

In FY 2007, there were 15,567 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 10,914 protocols reported human

subject participation as noted in this report's trend summary tables (Table 5A). Of these, 95.9 percent were domestic protocols and 4.1 percent were foreign protocols (Table 5E). Approximately 17.4 million participants were enrolled in extramural and intramural research protocols, of which 92.7 percent were domestic participants and 7.3 percent were foreign participants. Of the 17.4 million participants, 58.2 percent were women, 39.5 percent were men, and 2.3 percent were those who did not provide sex identification (Table 5A). Further, 29.9 percent of the total participants and 26.5 percent of the domestic-only participants were reported as minorities following the current OMB categories for race and ethnicity (Table 5F and Table 6C).

Correspondingly, in FY 2008, there were 15,598 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 11,045 protocols reported human subject participation as noted in this report's trend summary tables (Table 5A). Of these, 95.5 percent were domestic protocols and 4.5 percent were foreign protocols (Table 5E). Approximately 15.4 million participants were enrolled in extramural and intramural research protocols, of which 91.7 percent were domestic participants and 8.3 percent were foreign participants. Of the 15.4 million participants, 60.0 percent were women, 38.9 percent were men, and 1.1 percent were those who did not provide sex identification (Table 5A). Further, 28.6 percent of the total participants and 24.9 percent of the domestic-protocol participants were reported as minorities following the current OMB categories for race and ethnicity (Table 5F and Table 7C).

While the number of participants in all extramural and intramural clinical research decreased (17.4 million in FY 2007 and 15.4 million in FY 2008), there was no significant change in the proportion of women and men (58.2 percent females and 39.5 percent males in FY 2007; and 60.0 percent females and 38.9 percent males in FY 2008) (Table 5A).

NIH-Defined Phase III Clinical Research: FY 2007 and FY 2008

In FY 2007, there were 749 extramural and intramural Phase III clinical research protocols, of which 653 protocols reported human subject participation as noted in this report's trend summary tables (Table 9A). Of these, 93.3 percent were domestic protocols and 6.7 percent were foreign protocols. Clinical studies not included in this analysis are those studies that have just begun and have not reported enrollment data or have not begun recruiting patients. There were 591,159 participants enrolled in extramural and intramural Phase III research protocols, of which 72.5 percent were domestic participants and 27.5 percent were foreign participants (Table 8E). Of the 591,159 participants, 54.9 percent were women, 42.2 percent were men, and 2.8 percent were those who did not provide sex identification (Table 8A). Further, 41.4 percent of the total participants and 20.6 percent of domestic-protocol participants in Phase III clinical research were reported as minorities following the current OMB categories for race and ethnicity (Table 9C).

Of the 197 extramural and intramural Phase III research protocols that report following the former OMB standards in FY 2007, minority representation was highest for Blacks (not Hispanic) at 10.3 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Hispanics represented approximately 4.5 percent, Asian/Pacific Islanders 1.9 percent, and Whites (not Hispanic) 81.0 percent of the participants. The categories of Hawaiian/Pacific Islander and More Than One Race were not designations with the former OMB standards (Table 8B).

Moreover, in FY 2007, there were 424 extramural and intramural Phase III research protocols reporting data following the current OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 22.1 percent and lowest for Hawaiian/Pacific Islanders at 0.1 percent. Asians represented 12.4 percent, American Indian/Alaska Natives 2.5 percent, and Whites 34.9 percent of participants. Participants identifying as More Than One Race were 1.1 percent of the total number of participants. In addition, 26.9 percent did not identify a race category (Table 8C). Of the 424 extramural and intramural Phase III research protocols designating an ethnicity in FY 2007, 66.8 percent of total participants identified as "Not Hispanic," 18.8 percent identified as "Hispanic or Latino," and 14.5 percent did not

identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately (Table 8D).

Correspondingly, in FY 2008, there were 726 extramural and intramural Phase III clinical research protocols, of which 639 protocols reported human subject participation as noted in this report's trend summary tables (Table 8A and Table 10A). Of these, 91.5 percent were domestic protocols and 8.5 percent were foreign protocols. Clinical studies not included in this analysis are those studies that have just begun and have not reported enrollment data or have not begun recruiting patients. There were 792,578 participants enrolled in extramural and intramural Phase III research protocols, of which 74.6 percent were domestic participants and 25.4 percent were foreign participants (Table 8E). Of the 792,578 participants, 57.5 percent were women, 40.3 percent were men, and 2.2 percent were those who did not provide sex identification (Table 8A). Further, 38.9 percent of the total participants and 20.2 percent of domestic-only participants in Phase III clinical research were reported as minorities following the current OMB categories for race and ethnicity (Table 10C).

Of the 164 extramural and intramural Phase III research protocols that report following the former OMB standards in FY 2008, minority representation was highest for Blacks (not Hispanic) at 9.7 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Hispanics represented approximately 4.1 percent, Asian/Pacific Islanders 2.0 percent, and Whites (not Hispanic) 82.0 percent of the participants. The categories of Hawaiian/Pacific Islander and More Than One Race were not designations with the former OMB standards (Table 8B).

Moreover, in FY 2008, there were 475 extramural and intramural Phase III research protocols reporting data following the current OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 18.4 percent and lowest for Hawaiian/Pacific Islanders at 0.1 percent. Asians represented 17 percent, American Indian/Alaska Natives 2.7 percent, and Whites 50.2 percent of participants. Participants identifying as More Than One Race were 2.2 percent of the total number of participants. In addition, 9.4 percent did not identify a race category. Of the 475 extramural and intramural Phase III research protocols designating an ethnicity in FY 2008, 82.3 percent of total participants identified as "Not Hispanic," 11.5 percent identified as "Hispanic or Latino," and 6.2 percent did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately (Table 8C).

While the number of participants in Phase III extramural and intramural clinical research increased (591,159 in FY 2007 and 792,578 in FY 2008), there was a slight change in the proportions of women and men (54.9 percent females and 42.2 percent males in FY 2007; and 57.5 percent females and 40.3 percent males in FY 2008) (Table 8A).

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

Extramural Clinical Research: FY 2007 and FY 2008

In FY 2007, there were 13,719 extramural clinical research protocols, including Phase III and other clinical studies, of which 9,362 (8,982 + 380) protocols reported human subject participation. Of these, 82.3 percent were domestic protocols and 3.5 percent were foreign protocols (Table 11A). Approximately 13.9 million participants were enrolled in extramural research protocols, of which 92.8 percent were domestic participants and 7.2 percent were foreign participants (Table 11B). Of the 13.9 million participants, 61.8 percent were women, 35.5 percent were men, and 2.6 percent were those who did not provide sex identification. Further, 31.4 percent of the total participants were reported as minorities following the current OMB categories for race and ethnicity (Table 12A).

Correspondingly, in FY 2008, there were 11,045 extramural clinical research protocols, including Phase III and other clinical studies, of which 9,381 (8,971 + 410) protocols reported human subject participation. Of these, 81.2 percent were domestic protocols and 3.7 percent were foreign protocols (Table 13A). Approximately 12.6 million participants were enrolled in extramural research protocols, of

which 91.7 percent were domestic participants and 8.3 percent were foreign participants (Table 13B). Of the 12.6 million participants, 63.8 percent were women, 35.0 percent were men, and 1.1 percent were those who did not provide sex identification. Further, 29.4 percent of the total participants were reported as minorities following the current OMB categories for race and ethnicity (Table 14A).

While the number of participants in extramural clinical research protocols decreased (13.9 million in FY 2007 and 12.6 million in FY 2008), there was no significant change in the proportions of women and men (61.8 percent females and 35.5 percent males in FY 2007; and 63.8 percent females and 35.0 percent males in FY 2008) (Table 12A and Table 14A). However, when sex-specific studies were excluded, the proportions of women and men in all extramural clinical research reported in FY 2008 were similar to the proportions in the general population reported in FY 2007 (from 46.5 percent to 45.6 percent for females and from 49.8 percent to 52.6 percent for males) (Table 15A and Table 16A).

NIH-Defined Phase III Extramural Clinical Research: FY 2007 and FY 2008

In FY 2007, there were 711 extramural Phase III clinical research protocols, of which 617 (577 + 40) protocols reported human subject participation (Table 17A). There were 547,687 participants enrolled in extramural Phase III research protocols, of which 55.1 percent were women, 41.8 percent were men, and 3.1 percent were those who did not provide sex identification (Table 18A).

In FY 2007, there were 399 extramural Phase III research protocols reporting data following the current OMB standards for reporting race and ethnicity. Minority representation by race was highest for Blacks at 23.21 percent and lowest for Hawaiian/Pacific Islanders at 0.13 percent. Asians represented 13.09 percent, American Indian/Alaska Natives 2.59 percent, and Whites 34.29 percent of participants. Participants identifying as More Than One Race were 1.02 percent of the total number of participants. In addition, 25.67 percent did not identify a race category. Of the 399 extramural Phase III research protocols designating an ethnicity in FY 2007, 67.77 percent of total participants identified as "Not Hispanic," 17.78 percent identified as "Hispanic or Latino," and 14.44 percent did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately (Table 18B).

In FY 2008, there were 696 extramural Phase III clinical research protocols, of which 602 (552 + 50) protocols reported human subject participation (Table 19A). There were 776,034 participants enrolled in extramural Phase III research protocols, of which 57.2 percent were women, 40.6 percent were men, and 2.2 percent were those who did not provide sex identification (Table 20A).

Correspondingly, in FY 2008, there were 452 extramural Phase III research protocols reporting data following the current OMB standards for reporting race and ethnicity. Minority representation by race was highest for Blacks at 18.68 percent and lowest for Hawaiian/Pacific Islanders at 0.12 percent. Asians represented 17.41 percent, American Indian/Alaska Natives 2.74 percent, and Whites 51.22 percent of participants. Participants identifying as More Than One Race were 2.22 percent of the total number of participants. In addition, 7.62 percent did not identify a race category. Of the 452 extramural Phase III research protocols designating an ethnicity in FY 2008, 83.84 percent of total participants identified as "Not Hispanic," 10.38 percent identified as "Hispanic or Latino," and 5.78 percent did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately (Table 20B).

While the number of extramural Phase III clinical research protocols decreased (711 in FY 2007 and 696 in FY 2008) (Table 17A and Table 19A), there was a slight increase in the proportion of women (55.1 percent females and 41.8 percent males in FY 2007; and 57.2 percent females and 40.6 percent males in FY 2008) (Table 18A and Table 20A).

Intramural Clinical Research: FY 2007 and FY 2008

In FY 2007, there were 1,848 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,552 (1,481 + 71) protocols reported human subject

participation (Table 11A). Approximately 3.5 million participants were enrolled in intramural research protocols, of which 43.4 percent were women, 55.4 percent were men, and 1.2 percent were those who did not provide sex identification (Table 21A).

In FY 2007, approximately 3.5 million participants were reported in all intramural research, including Phase III clinical trials and other clinical studies. Of the 449 intramural research protocols that report data following the former OMB standards, minority representation was highest for Blacks (not Hispanic) at 17.59 percent and lowest for American Indian/Alaska Natives at 0.17 percent. Asian/Pacific Islanders represented 3.65 percent, Hispanics 4.31 percent, and Whites (not Hispanic) 73.16 percent of the intramural research study population. The categories of Hawaiian/Pacific Islander and More Than One Race were not designations with the former OMB standards (Table 21C).

For the 1,103 intramural clinical research studies that reported data following the current OMB standards in FY 2007, the largest racial minority group was Blacks at 9.72 percent and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.16 percent. Asians represented 7.66 percent, American Indian/Alaska Natives 0.89 percent, and Whites 69.85 percent of participants in all intramural clinical research. Approximately 0.56 percent of participants reported More Than One Race as their racial category. In addition, 11.16 percent did not identify a race category. Of the 1,103 intramural research protocols following the current OMB standards designating an ethnicity in FY 2007, 85.50 percent of total participants identified as "Not Hispanic," 4.19 percent identified as "Hispanic or Latino," and 10.31 percent did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately (Table 21B).

Correspondingly, in FY 2008, there were 1,873 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,664 (1,577 + 87) protocols reported human subject participation (Table 13A). Approximately 2.8 million participants were enrolled in intramural research protocols, of which 42.82 percent were women, 55.93 percent were men, and 1.25 percent were those who did not provide sex identification (Table 22A).

In FY 2008, approximately 2.8 million participants were reported in all intramural research, including Phase III clinical trials and other clinical studies. Of the 413 intramural research protocols that report data following the former OMB standards, minority representation was highest for Blacks (not Hispanic) at 30.34 percent and lowest for American Indian/Alaska Natives at 0.15 percent. Asian/Pacific Islanders represented 3.38 percent, Hispanics 4.02 percent, and Whites (not Hispanic) 60.73 percent of the intramural research study population. The categories of Hawaiian/Pacific Islander and More Than One Race were not designations with the former OMB standards (Table 22C).

For the 1,251 intramural clinical research studies that reported data following the current OMB standards in FY 2008, the largest racial minority group was Asians at 9.8 percent and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.17 percent. Blacks represented 9.4 percent, American Indian/Alaska Natives 0.81 percent, and Whites 67.92 percent of participants in all intramural clinical research. Approximately 0.61 percent of participants reported More Than One Race as their racial category. In addition, 11.29 percent did not identify a race category. Of the 1,251 intramural research protocols following the current OMB standards designating an ethnicity in FY 2008, 85.30 percent of total participants identified as "Not Hispanic," 4.07 percent identified as "Hispanic or Latino," and 10.62 percent did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately (Table 22B).

While the number of participants specifically in Phase III intramural clinical research protocols significantly decreased (3.5 million in FY 2007 and 2.8 million in FY 2008), there was no substantive change in the proportions of women and men (43.4 percent females and 55.4 percent males in FY 2007; and 42.8 percent females and 55.9 percent males in FY 2008) (Table 21A and Table 22A).

NIH-Defined Phase III Intramural Clinical Research: FY 2007 and FY 2008

In FY 2007, there were 38 intramural Phase III clinical research protocols, of which 36 (32 + 4) protocols reported human subject participation. Of these, 88.8 percent (32/36) were domestic and 11.1 percent (4/36) were foreign (Table 17A). There were 43,472 participants enrolled in intramural Phase III research protocols, of which 77.1 were domestic participants and 22.9 percent were foreign participants (Table 17B). Of the 43,472 participants, 52.8 percent were women, 47.2 percent were men, and 0 percent were those who did not provide sex identification. Further, 27.3 percent of the total participants in Phase III intramural clinical research protocols were reported as minorities following the current OMB categories for race and ethnicity (Table 23A).

Correspondingly, in FY 2008, there were 39 intramural Phase III clinical research protocols, of which 37 (33 + 4) protocols reported human subject participation. Of these, 89.1 percent (33/37) were domestic protocols and 10.8 percent (4/37) were foreign protocols (Table 19A). There were 16,544 participants enrolled in intramural Phase III research protocols, of which 36.7 percent were domestic participants and 63.2 percent were foreign participants (Table 19B). Of the 16,544 participants, 69.7 percent were women, 28.9 percent were men, and 1.4 percent were those who did not provide sex identification. Further, 56.67 percent of the total participants in Phase III clinical research protocols were reported as minorities following the current OMB categories for race and ethnicity (Table 24A).

While the number of participants specifically in Phase III intramural clinical research protocols significantly decreased (43,472 in FY 2007 and 16,544 in FY 2008), there was a substantial increase in the proportions of women (52.8 percent females and 47.2 percent males in FY 2007; and 69.7 percent females and 28.9 percent males in FY 2008) (Table 23A and Table 24A).

Trend Report on NIH Aggregate Population Data: FY 1995 to FY 2008

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.

Table 25 is a 14-year summary report showing a steady increase in the number of protocols and enrollment. The number of protocols with enrollment increased from 3,188 in FY 1995 to 11,045 in FY 2008, a 3.5-fold increase. Reported enrollment increased from approximately 1.0 million (FY 1995) to 15.4 million (FY 2008), a 15.1-fold increase. Minority enrollment increased from approximately 0.4 million (FY 1995) to 4.3 million (FY 2008), an 11.7-fold increase in minority representation in NIH clinical research (Table 25A). The total number of protocols reported with enrollment data has increased such that, since FY 2003, the number has been in excess of 10,000 protocols per year (Table 25B).

With the deployment of an updated population tracking system in 2002 and the OMB requirement to report data using the current format, NIH was able to report domestic and foreign data in a better way. Thus, trend data are available for domestic and foreign protocols and participation beginning in FY 2002. Domestic enrollment increased from 10.2 million (FY 2002) to 14.1 million (FY 2008), a 1.4-fold increase. Foreign enrollment increased from 0.9 million (FY 2002) to 1.3 million (FY 2008), a 1.4-fold increase (Table 25A). Overall, the total enrollment has increased with domestic participation ranging between 75.9 percent and 92.7 percent and foreign participation ranging between 7.3 percent and 24.1 percent. In FY 2008, domestic and foreign enrollment were 91.7 percent and 8.3 percent, respectively (Table 25C).

Table 5 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 ranged between

51.7 percent and 64.2 percent, and male participation in all extramural and intramural research ranged between 34.0 percent and 45.0 percent (Table 5A). Overall minority participation in all extramural and intramural clinical research ranged between 23.3 percent and 44.5 percent (Tables 5B–D). Table 5E provides a comparison of domestic and foreign participation between FY 2002 and FY 2008. The vast majority of protocols are domestic (approximately 94 percent to 96 percent) of the total clinical research protocols. While the number of foreign protocols has increased, they incorporate only about 4 percent to 6 percent of the total clinical research protocols with enrollment. Table 5F shows domestic and foreign enrollment for the 7-year period. Domestic minority enrollment varied between 24.1 percent and 28.9 percent of total domestic participation, while foreign minority enrollment varied between 67.7 percent and 90.9 percent of total foreign participation.

Table 8 is a summary of NIH-funded Phase III extramural and intramural clinical research by sex/gender and minority enrollment following the old and new data reporting formats for domestic and foreign studies. This table demonstrates that female participation in NIH-funded Phase III extramural and intramural clinical research generally ranged between 54.1 percent and 74.8 percent and male participation in NIH-funded Phase III extramural and intramural clinical research ranged between 24.3 percent and 44.6 percent (Table 8A). Overall minority participation in NIH-funded Phase III extramural and intramural clinical research ranged from 20.3 percent to 41.4 percent (Tables 8B–D). Table 8E provides a comparison of domestic and foreign participation between FY 2002 and FY 2008. The vast majority of protocols are domestic, ranging from 75.5 percent to 95.8 percent of the total clinical research protocols. While the number of foreign protocols has decreased, they incorporate only about 4.2 percent to 24.5 percent of the total clinical research protocols with enrollment in the past 7 years. Table 8F shows domestic and foreign enrollment for the 7-year period. Domestic minority enrollment varied between 20.2 percent and 25.4 percent of total domestic participation, while foreign minority enrollment in NIH-funded Phase III clinical research varied between 48.4 percent and 96.2 percent of total foreign participation. In comparing both domestic and foreign Phase III enrollment over the 7-year period, the data show that the small percentage of foreign protocols in FY 2008 account for a significant proportion of the total foreign enrollment.

Tables 26–29 summarize domestic and foreign participation for NIH-funded clinical research and NIH-funded Phase III clinical research. For extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation ranged between 58.1 percent and 67.3 percent while male participation ranged between 31.2 percent and 39.5 percent (Table 26A). For NIH-funded Phase III extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation ranged between 53.3 percent and 64.6 percent while male participation ranged between 34.4 percent and 44.8 percent (Table 27A). For all extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 39.2 percent to 59.5 percent while male participation varied from 39.3 percent to 60.4 percent (Table 28A). For NIH-funded Phase III extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 47.4 percent to 59.2 percent while male participation varied from 40.4 percent to 52.5 percent (Table 29A).

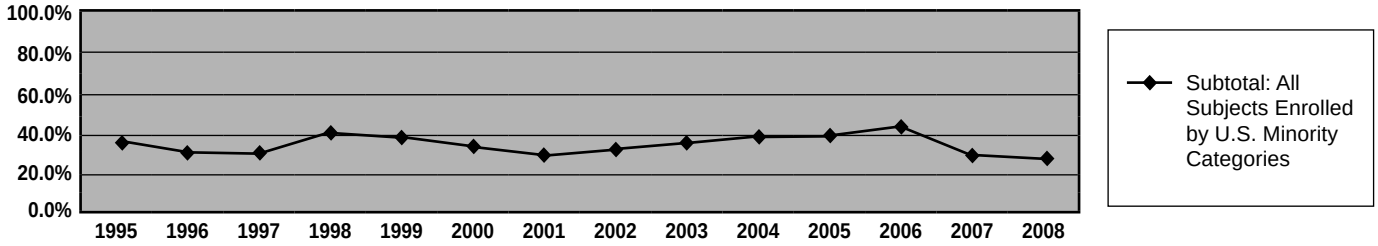
TABLE 5

NIH Fourteen-Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research Reported in FY 1995-2008: Enrollment by Race and Ethnicity

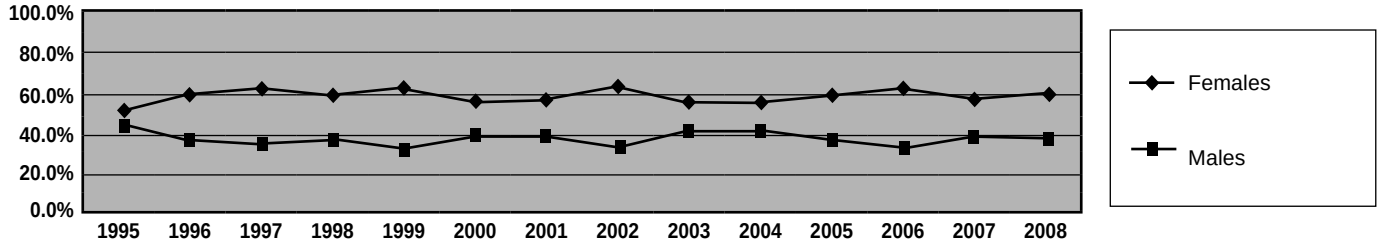
Table 5A. Fourteen-Year Summary Totals: Enrollment by Sex/Gender and Minority Categories in All Protocols (OLD + NEW FORMS)

FY Reported	FY Funded	Form	Females	Males	Unknown	Total All Subjects (OLD + NEW FORMS)	Subtotal: All Subjects Enrolled by US Minority Categories	Number of Protocols with Enrollment data (OLD + NEW FORMS)
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%	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%	
2007	2006	OLD + NEW	10,152,590	6,887,793	408,075	17,448,458	5,216,890	10,914
	%		58.2%	39.5%	2.34%	100.0%	29.9%	
2008	2007	OLD + NEW	9,243,966	5,991,739	176,650	15,412,355	4,412,106	11,045
	%		60.0%	38.9%	1.15%	100.0%	28.6%	

Graph 5A(1). Total Minority Enrollment Reported by Year (FY 1995–2008)



Graph 5A(2). Sex/Gender Enrollment Reported by Year (FY 1995–2008)



Notes for Tables 5B-5D

NOTE 1: The shaded portions of the Tables B, C, and D show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the new 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.

NOTE 2: Data from Tables 5B, 5C, and 5D are combined to provide the summary data in Table 5A.

Table 5B. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards in a Combined Race/ Ethnicity Format

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total	Subtotal Using U.S. Minority Categories (shaded): OLD FORM	Number Protocols with Enrollment data (OLD FORM)
1995	1994	11,221	38,952	234,976	89,284	540,313	106,747	1,021,493	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%	
2007	2006	5,372	51,742	238,004	83,192	1,097,387	48,630	1,524,327	378,310	1,098
	%	0.4%	3.4%	15.6%	5.5%	72.0%	3.2%	100.0%	24.8%	
2008	2007	1,930	16,258	99,164	28,819	460,533	19,715	626,419	146,171	915
	%	0.3%	2.6%	15.8%	4.6%	73.5%	3.1%	100.0%	23.3%	

Orientation to Tables 5C and 5D

1. The NEW FORM consists of Parts A and B (Tables 5C and 5D) for reporting years 2002-2008. This Form is provided as part of the annual progress report.
2. Table 5C displays the NEW FORM Part A for reporting separate race and ethnicity data.
3. Table 5D 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.

Table 5C. NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats

Total of All Subjects by Race										Total of All Subjects by Ethnicity			
FY Reported	FY Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total*	Not Hispanic	Hispanic or Latino**	Unknown/ Not Reported	Total*
2002	2001	77,734	354,049	547,776	21,636	2,651,541	30,955	720,362	4,404,053	3,071,952	292,429	1,039,672	4,404,053
	%	1.8%	8.0%	12.4%	0.5%	60.2%	0.7%	16.4%	100.0%	69.8%	6.6%	23.6%	100.0%
2003	2002	63,544	2,138,002	960,090	37,569	5,415,710	99,462	1,012,622	9,726,999	8,162,259	611,641	953,099	9,726,999
	%	0.7%	22.0%	9.9%	0.4%	55.7%	1.0%	10.4%	100.0%	83.9%	6.3%	9.8%	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	13,168,842	756,339	1,585,131	15,510,312
	%	0.6%	28.0%	8.9%	0.4%	52.0%	1.2%	8.9%	100.0%	84.9%	4.9%	10.2%	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	11,804,164	773,939	1,133,595	13,711,698
	%	2.1%	22.2%	9.9%	0.4%	56.0%	1.3%	8.1%	100.0%	86.1%	5.6%	8.3%	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	11,308,244	1,054,313	1,143,123	13,505,680
	%	1.0%	25.6%	9.3%	0.3%	52.5%	2.4%	8.9%	100.0%	83.7%	7.8%	8.5%	100.0%
2007	2006	145,417	1,356,900	2,012,695	57,149	10,341,483	278,068	1,732,419	15,924,131	13,017,124	1,169,092	1,737,915	15,924,131
	%	0.9%	8.5%	12.6%	0.4%	64.9%	1.7%	10.9%	100.0%	81.7%	7.3%	10.9%	100.0%
2008	2007	134,494	1,168,053	1,835,035	48,560	9,651,267	181,941	1,766,586	14,785,936	11,881,644	1,116,699	1,787,594	14,785,937
	%	0.9%	7.9%	12.4%	0.3%	65.3%	1.2%	11.9%	100.0%	80.4%	7.6%	12.1%	100.0%

Table 5D. NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

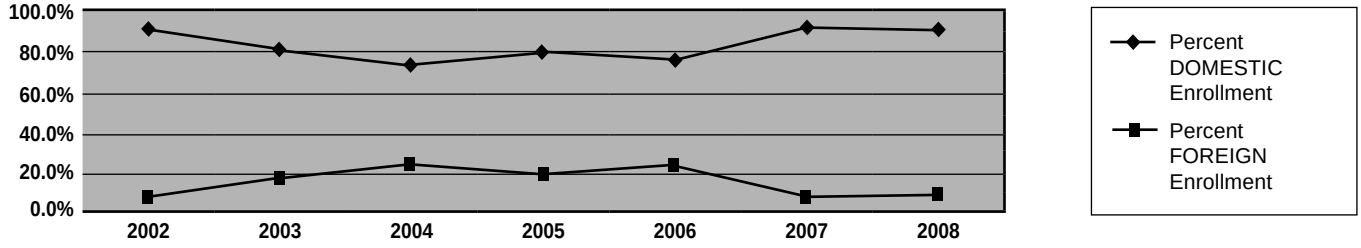
FY Reported	FY Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total Hispanic or Latino**	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Protocols with Enrollment data (NEW FORM)
2002	2001	4,867	1,305	13,066	101	159,252	7390	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%	38.8%	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%	
2007	2006	37,581	7,414	31,239	4,310	538,216	100,197	450,135	1,169,092	4,838,580	9,816
	%	3.2%	0.6%	2.7%	0.4%	46.0%	8.6%	38.5%	100.0%	30.4%	
2008	2007	34,335	31,616	85,548	2,369	518,825	64,979	379,027	1,116,699	4,265,935	10,130
	%	3.1%	2.8%	7.7%	0.2%	46.5%	5.8%	33.9%	100.0%	28.9%	

*These totals must agree
**These totals must agree

Table 5E. Comparison of Domestic and Foreign Enrollment and Protocols With Total Enrollment for the Period FY 2002–2008

Enrollment							Protocols				
FY Reported	FY Funded	Total Enrollment data (OLD + NEW FORMS)	Total DOMESTIC Enrollment	Percent DOMESTIC Enrollment	Total FOREIGN Enrollment	Percent FOREIGN Enrollment	Number of Protocols with Enrollment data (OLD + NEW FORMS)	Number of DOMESTIC Protocols	Percent Domestic Protocols	Number of FOREIGN Protocols	Percent Foreign Protocols
2002	2001	11,138,484	10,192,401	91.5%	946,083	8.5%	8,945	8,463	94.6%	482	5.4%
2003	2002	14,772,254	11,911,357	80.6%	2,860,897	19.4%	10,216	9,578	93.8%	638	6.2%
2004	2003	18,923,920	14,359,793	75.9%	4,564,127	24.1%	10,125	9,760	96.4%	365	3.6%
2005	2004	15,722,752	12,669,858	80.6%	3,052,894	19.4%	10,233	9,862	96.4%	371	3.6%
2006	2005	14,830,930	11,425,701	77.0%	3,405,229	23.0%	10,758	10,294	95.7%	464	4.3%
2007	2006	17,448,458	16,180,588	92.7%	1,267,870	7.3%	10,914	10,463	95.9%	451	4.1%
2008	2007	15,412,355	14,134,627	91.7%	1,277,728	8.3%	11,045	10,548	95.5%	497	4.5%

Graph 5E(1). Percentage of Domestic and Foreign Enrollment (FY 2002–2008)



Graph 5E(2). Percentage of Domestic and Foreign Protocols (FY 2002–2008)

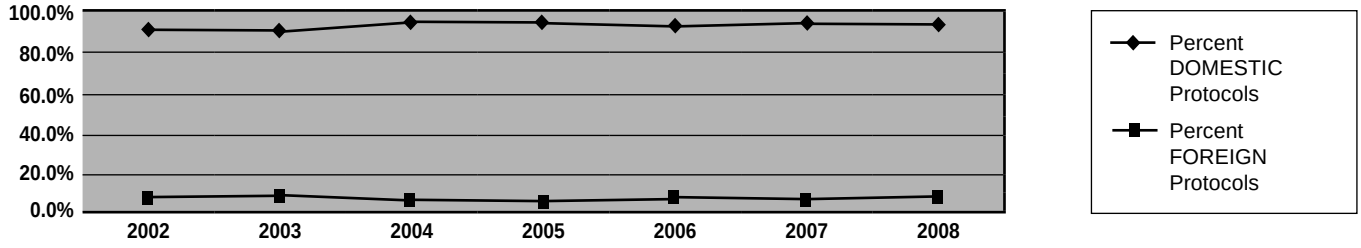


Table 5E Comments

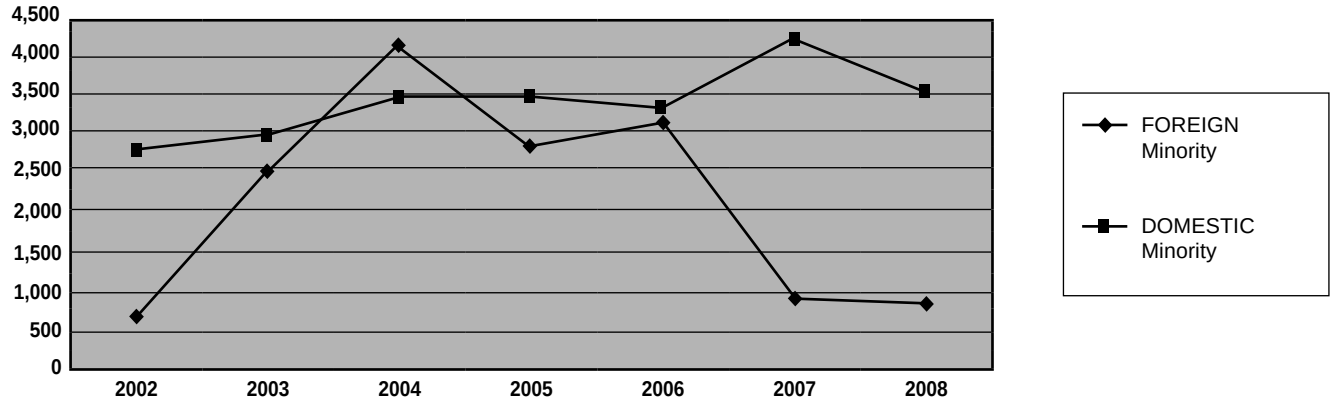
1. The Total Enrollment, Total Domestic, and Total Foreign enrollment increased overall from FY 2002 to FY 2008.
2. The Percent Domestic Enrollment decreased to approximately 91.7%, while the Percent Foreign Enrollment increased to approximately 8.3%.
3. The vast majority of protocols are domestic protocols (approximately 93-96%), while foreign protocols make up approximately 3-6% of total protocols.
4. Foreign enrollment was reported using the same race and ethnicity categories as domestic enrollment.

Table 5F. Comparison of Domestic and Foreign Minority Participation for FY 2002–2008

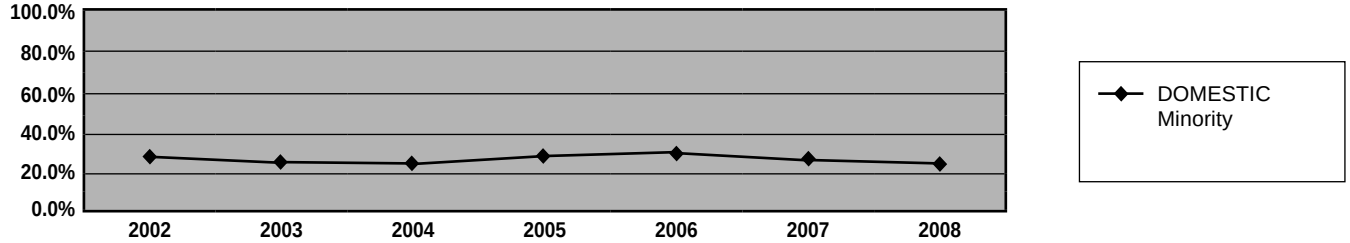
FY Reported	FY Funded	FOREIGN Minority	Foreign Total	DOMESTIC Minority	Domestic Total
2002	2001	777,461	946,083	2,754,820	10,149,869
		82.2%	100.0%	27.1%	100.0%
2003	2002	2,452,329	2,860,897	2,935,363	11,911,357
		85.7%	100.0%	24.6%	100.0%
2004	2003	4,147,255	4,564,127	3,464,356	14,359,793
		90.9%	100.0%	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%
2007	2006	932,686	1,267,870	4,283,738	16,180,588
		73.6%	100.0%	26.5%	100.0%
2008	2007	864,945	1,277,728	3,521,691	14,134,627
		67.7%	100.0%	24.9%	100.0%

1. Domestic Minority Enrollment has varied from 24.1% to 28.9% of Total Domestic Enrollment.
2. Foreign Minority Enrollment has varied from 67.7% 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 2008 was 80.3% Domestic and 19.7% Foreign. The small percentage of foreign protocols acount for a significant proportion (19.7%) of the Total Minority Enrollment, as shown by comparing both domestic and foreign enrollment data.

Graph 5F(1). Number of Minority Participants (FY 2002–2008)



Graph 5F(2). Percentage Comparison of Domestic Minority Enrollment to Total Domestic Enrollment (FY 2002–2008)



Graph 5F(3). Percentage Comparison of Foreign Minority Enrollment to Total Foreign Enrollment (FY 2002–2008)

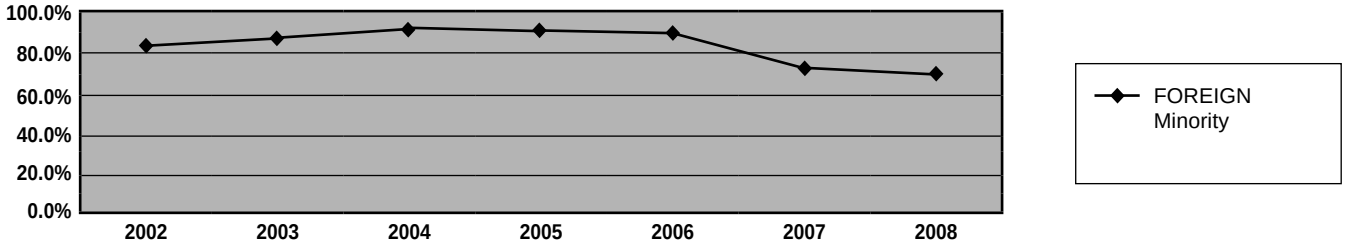


TABLE 6

Summary of NIH Clincal Research Reported in FY 2007: Total Number of Protocols and Enrollment By Sex and Domestic Versus Foreign Protocols

Table 6A. Protocols Reported

	Total All Clincal Studies	Domestic	%	Foreign	%
Protocols with enrollment	10,914	10,463	95.9%	451	4.1%
%	70.1%	70.5%		62.6%	
Protocols with zero enrollment. (Enrollment data has not yet been submitted)	4,653	4,383	94.2%	270	5.8%
%	29.9%	29.5%		37.4%	
Total Number of Protocols	**15,567**	**14,846**	**95.4%**	**721**	**4.6%**
%	100.0%	100.0%		100.0%	

Total Number of Protocols

1. The total number of protocols reported in the NIH database in FY 2007 was 15,567; of these, 10,914 (70.1%) reported subject enrollment. Of these, the remainder are new clinical studies or studies pending enrollment.
2. Subsequent tables reporting “Enrollment Reported” are based on the 10,914 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.”

Total Domestic Protocols

4. Domestic protocols made up the vast majority of protocols (14,846; 95.4%); of these, 10,463 (70.5%) reported domestic subject enrollment.
5. Clinical research involving both domestic and foreign sites are reported as separate domestic and foreign protocols in subsequent tables.

Total Foreign Protocols

6. Foreign protocols account for only a small percentage of protocols 721 (4.6%); of these, 451 (62.6%) reported foreign subject enrollment.

Table 6B. Enrollment Reported

	Total All Clincal Studies	Domestic	%	Foreign	%
Females Enrolled	10,152,589	9,397,957	92.6%	754,632	7.4%
%	58.2%	58.1%		59.5%	
Males Enrolled	6,887,791	6,389,817	92.8%	497,974	7.2%
%	39.5%	39.5%		39.3%	
Sex of Subjects is Unknown	408,078	392,814	96.3%	15,264	3.7%
%	2.3%	2.4%		1.2%	
Total Subjects Enrolled	**17,448,458**	**16,180,588**	**92.7%**	**1,267,870**	**7.3%**
%	100.0%	100.0%		100.0%	

Total Enrollment Reported

1. The total "Enrollment Reported" in the NIH database in FY 2007 was 17,448,458 subjects in 10,914 protocols with enrollment.
2. Females made up 58.2% (10.2M) of total subjects enrolled, while males made up 39.5% (6.9M), with 2.3% unknown.
3. Total Enrollment Reported increased by 18% in the past year (14,830,930 in FY 2006; 17,448,458 in FY 2007).

Total Domestic Enrollment Reported

4. The total Domestic Enrollment reported was 16,180,588 (92.7%).
5. Females made up 58.1% (9.4M) of the domestic subjects enrolled, while Males made up 39.5% (6.4M) with 2.4% (0.4M) unknown.

Total Foreign Enrollment

6. The total Foreign Enrollment reported was 1,267,870 (7.3%).
7. Females made up 59.5% (0.75M) of the foreign subjects enrolled, while males made up 39.3% (0.50M) with 1.2% unknown (0.015M).

Table 6C. Minority Enrollment Reported

	Total All Clinical Studies*	Domestic	%	Foreign	%
Minority Total	5,216,434	4,283,738	82.1%	932,696	17.9%
% Minority Enrollment	29.9%	26.5%		73.6%	

1. Minorities made up 29.9% (5.2M) of the total subjects enrolled.
2. Minorities made up 26.5% (4.3M) of the total Domestic Enrollment.
3. Minority Enrollment Reported decreased 18% in the past year (6,388,316 in FY 2006; 5,216,434 in FY 2007). The small percentage of foreign protocols (4.1%) account for 17.9% of minority enrollment.

* Clinical research studies include nonintervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total All Clinical Studies" includes NIH Defined Phase III Clinical Trials.

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

TABLE 7

Summary of NIH Clinical Research Reported in FY 2008: Total Number of Protocols and Enrollment By Sex and Domestic Versus Foreign Protocols

Table 7A. Protocols Reported

	Total All Clincal Studies	Domestic	%	Foreign	%
Protocols with enrollment	11,045	10,548	95.5%	497	4.5%
%	70.8%	70.9%		68.7%	
Protocols with zero enrollment. (Enrollment data has not yet been submitted)	4,553	4,327	95.0%	226	5.0%
	29.2%	29.1%		31.3%	
Total Number of Protocols	**15,598**	**14,875**	**95.4%**	**723**	**4.6%**
%	100.0%	100.0%		100.0%	

Total Number of Protocols

1. The total number of protocols reported in the NIH database in FY 2008 was 15,598; of these, 11,045 (70.8%) reported subject enrollment.
2. Subsequent tables reporting “Enrollment Reported” are based on the 11,045 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.”

Total Domestic Protocols

4. Domestic protocols made up the vast majority of protocols (14,875; 95.4%); of these, 10,548 (70.9%) reported domestic subject enrollment.
5. Clinical research involving both domestic and foreign sites are reported as separate domestic and foreign protocols in subsequent tables.

Total Foreign Protocols

6. Foreign protocols account for only a small percentage of protocols (723; 4.6%); of these, 497 (68.7%) reported foreign subject enrollment.

Table 7B. Enrollment Reported

	Total All Clincal Studies	Domestic	%	Foreign	%
Females Enrolled	9,243,966	8,514,768	92.1%	729,198	7.9%
%	60.0%	60.2%		57.1%	
Males Enrolled	5,991,739	5,451,624	91.0%	540,115	9.0%
%	38.9%	38.6%		42.3%	
Sex of Subjects is Unknown	176,650	168,235	95.2%	8,415	4.8%
%	1.1%	1.2%		0.7%	
Total Subjects Enrolled	**15,412,355**	**14,134,627**	**91.7%**	**1,277,728**	**8.3%**
%	100.0%	100.0%		100.0%	

Total Enrollment Reported

1. The total "Enrollment Reported" in the NIH database in FY 2008 was 15,412,355 subjects in 11,045 protocols with enrollment.
2. Females made up 60.0% (9.2M) of total subjects enrolled, while males made up 38.9% (6.0M), with 1.1% unknown.
3. Total Enrollment Reported decreased by 11.7% in the past year (17,448,458 in FY2007; 15,412,355 in FY 2008).

Total Domestic Enrollment Reported

4. The total Domestic Enrollment reported was 14,134,627 (91.7%).
5. Females made up 60.2% (8.5M) of the domestic subjects enrolled, while males made up 38.6% (5.5M) with 1.2% (0.2M) unknown.

Total Foreign Enrollment

6. The total Foreign Enrollment reported was 1,277,728 (8.3%).
7. Females made up 57.1% (0.73M) of the foreign subjects enrolled, while males made up 42.3% (0.54M) with 0.7% unknown (0.008M).

Table 7C. Minority Enrollment Reported

	Total All Clinical Studies*	Domestic	%	Foreign	%
Minority Total	4,386,636	3,521,691	80.3%	864,945	19.7%
% Minority Enrollment	28.5%	24.9%		67.7%	

1. Minorities made up 28.5% (4.4M) of the total subjects enrolled.
2. Minorities made up 24.9% (3.5M) of the total Domestic Enrollment.
3. Minority Enrollment Reported decreased 16% in the past year (5,216,434 in FY 2007; 4,386,636 in FY 2008). The small percentage of foreign protocols (4.5%) account for 19.7% of minority enrollment.

* Clinical research studies include nonintervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total All Clinical Studies" includes NIH Defined Phase III Clinical Trials.

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

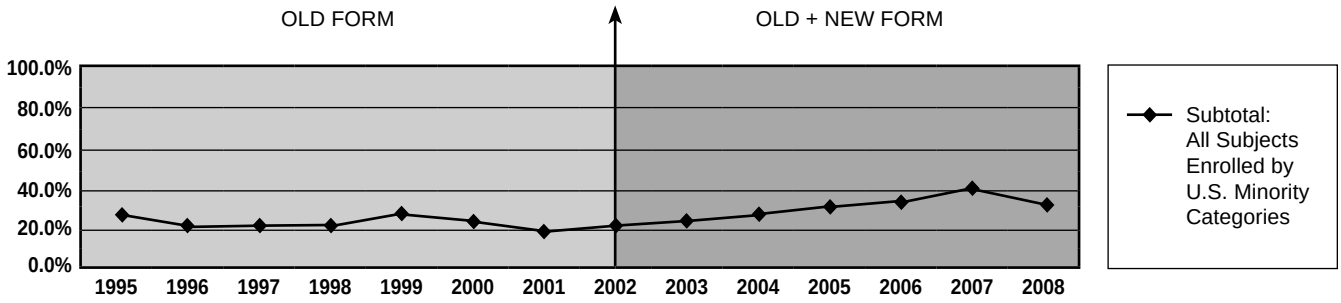
TABLE 8

Fourteen-Year Minority Trend Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY 1995–2008: Enrollment by Race and Ethnicity

Table 8A. Phase III Fourteen-Year Summary Totals: Enrollment by Sex/Gender in All Protocols (OLD + NEW FORMS)

FY Reported	FY Funded	Females	Males	Unknown	Total All Subjects (OLD + NEW FORMS)	Subtotal: All Subjects Enrolled by US Minority Categories	Number of Protocols with Enrollment data (OLD + NEW FORMS)
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%	
2007	2006	324,694	249,633	16,832	591,159	244,932	621
	%	54.9%	42.2%	2.8%	100.0%	41.4%	
2008	2007	455,612	319,732	17,234	792,578	270,899	639
	%	57.5%	40.3%	2.2%	100.0%	34.2%	

Graph 8A(1). Percentage of Total Minority Enrollment by Year Reported (FY 1995-2008)



Graph 8A(2). Percentage of Sex/Gender Enrollment by Year Reported (FY 1995-2008)

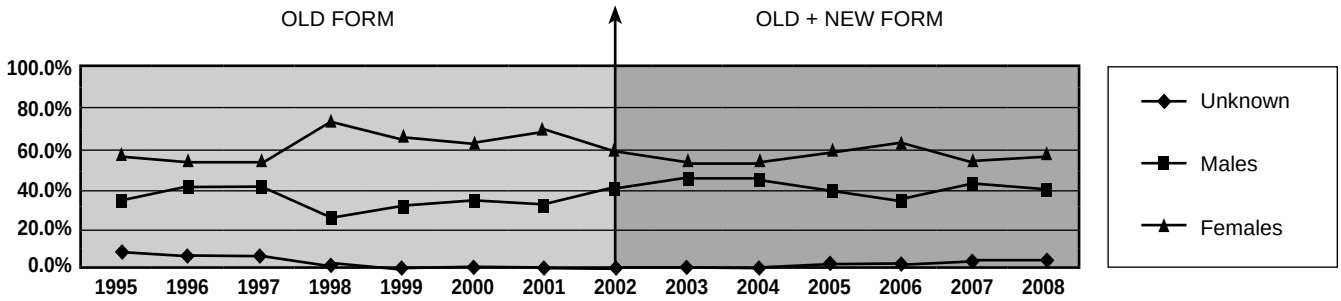


Table 8A Comments

1. Table 8A summarizes enrollment by sex/gender and minority race/ethnicity categories for the 14-year reporting period (1995-2008). The data are compiled from Tables 8B, 8C, and 8D below, which provide the detailed distributions by sex/gender and race/ethnicity using the Old Enrollment Form (Table 8B) and the New Enrollment Form (Tables 8C and 8D).
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).

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; (3) and the subtraction of studies that are no longer reported.

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

NOTE 1: The shaded portions of the Tables B, C, and D show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the new 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.

NOTE 2: Data from Tables 8B, 8C, and 8D are combined to provide the summary data in Table 8A.

Table 8B. Phase III OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM	Number Protocols with Enrollment data (OLD FORM)
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%	72.7%	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
	%	0.38%	4.8%	12.0%	6.9%	73.1%	2.8%	100.00%	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%	
2007	2006	751	3,943	21,582	9,333	169,789	4,259	209,657	35,609	197
	%	0.4%	1.9%	10.3%	4.5%	81.0%	2.0%	100.0%	17.0%	
2008	2007	900	4,542	22,445	9,642	190,753	4,262	232,544	37,529	164
	%	0.4%	2.0%	9.7%	4.1%	82.0%	1.8%	100.0%	16.1%	

Orientation to Tables 8C and 8D

1. The NEW FORM consists of Parts A and B (Tables 8C and 8D) for reporting years 2002-2008. This form is provided as part of the annual progress report.
2. Table 8C displays the NEW FORM Part A for reporting separate race and ethnicity data.
3. Table 8D 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.

Table 8C. Phase II NEW FORM: Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity

		Total of All Subjects by Race								Total of All Subjects by Ethnicity			
FY Reported	**FY Funded**	**American Indian/ Alaska Native**	**Asian**	**Black or African American**	**Hawaiian/ Pacific Islander**	**White**	**More Than One Race**	**Unknown/ Other**	**Total**	**Not Hispanic**	**Hispanic or Latino**	**Unknown/ Not Reported**	**Total**
2002	2001	159	799	4,647	52	34,654	560	2,273	43,144	36,224	1,629	5,291	43,144
	%	0.37%	1.85%	10.77%	0.12%	80.32%	1.30%	5.27%	100.00%	83.96%	3.78%	12.26%	100.00%
2003	2002	484	2,609	21,641	220	47,869	989	8,138	81,950	64,295	7,831	9,824	81,950
	%	0.6%	3.2%	26.4%	0.3%	58.4%	1.2%	9.9%	100.0%	78.5%	9.6%	12.0%	100.0%
2004	2003	1,396	4,385	43,721	611	106,793	4,419	5,657	166,982	145,742	13,435	7,805	166,982
	%	0.8%	2.6%	26.2%	0.4%	64.0%	2.6%	3.4%	100.0%	87.3%	8.0%	4.7%	100.0%
2005	2004	2,164	9,192	50,338	462	101,238	3,063	10,254	176,711	156,650	10,397	9,664	176,711
	%	1.2%	5.2%	28.5%	0.3%	57.3%	1.7%	5.8%	100.0%	88.6%	5.9%	5.5%	100.0%
2006	2005	4,630	32,360	50,780	535	126,670	4,246	50,446	269,667	202,358	31,034	36,275	269,667
	%	1.7%	12.0%	18.8%	0.2%	47.0%	1.6%	18.7%	100.0%	75.0%	11.5%	13.5%	100.0%
2007	2006	9,351	47,364	84,468	555	133,002	4,145	102,617	381,502	254,692	71,622	55,188	381,502
	%	2.5%	12.4%	22.1%	0.1%	34.9%	1.1%	26.9%	100.0%	66.8%	18.8%	14.5%	100.0%
2008	2007	15,006	95,296	103,166	716	281,344	12,136	52,370	560,034	460,862	64,351	34,821	560,034
	%	2.7%	17.0%	18.4%	0.1%	50.2%	2.2%	9.4%	100.0%	82.3%	11.5%	6.2%	100.0%

Table 8D. Phase III Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

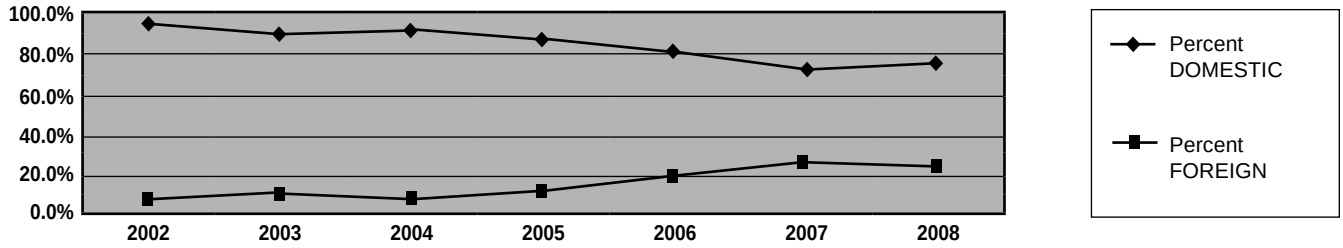
FY Reported	**FY Funded**	**American Indian/ Alaska Native**	**Asian**	**Black or African American**	**Hawaiian/ Pacific Islander**	**White**	**More Than One Race**	**Unknown/ Other**	**Total**	**Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B**	**Number of Protocols with Enrollment data (NEW FORM)**
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%	
2007	2006	7,333	45	458	24	7,430	322	56,010	71,622	209,323	424
	%	10.2%	0.1%	0.6%	0.0%	10.4%	0.4%	78.2%	100.0%	54.9%	
2008	2007	13,060	229	717	122	22,293	5,654	22,276	64,351	270,889	475
	%	20.3%	0.4%	1.1%	0.2%	34.6%	8.8%	34.6%	100.0%	48.4%	

* These totals must agree.
** These totals must agree.

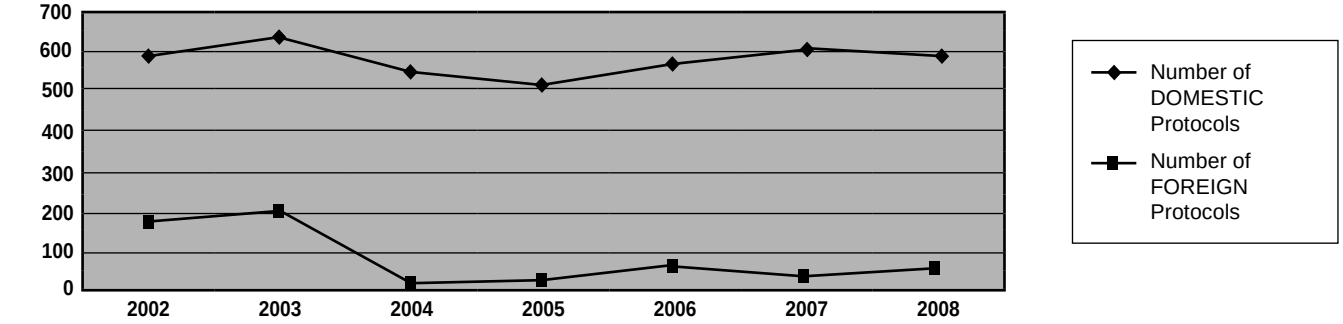
Table 8E. Comparison of Domestic and Foreign Phase III Enrollment and Protocols With Enrollment for the Period FY 2002–2008

		Enrollment					Protocols				
FY Reported	FY Funded	Total Enrollment data (OLD + NEW FORMS)	Total DOMESTIC	Percent DOMESTIC	Total FOREIGN	Percent FOREIGN	Number of Protocols with Enrollment data (OLD + NEW FORMS)	Number of DOMESTIC Protocols	Percent Domestic Protocols	Number of FOREIGN Protocols	Percent Foreign Protocols
2002	2001	474,747	444,436	93.6%	30,311	6.4%	754	582	77.2%	172	22.8%
2003	2002	536,267	486,857	90.8%	49,410	9.2%	852	643	75.5%	209	24.5%
2004	2003	545,367	496,241	91.0%	49,126	9.0%	573	549	95.8%	24	4.2%
2005	2004	493,000	437,902	88.8%	55,098	11.2%	547	517	94.5%	30	5.5%
2006	2005	499,430	400,297	80.2%	99,133	19.8%	624	564	90.4%	60	9.6%
2007	2006	591,159	428,440	72.5%	162,719	27.5%	653	609	93.3%	44	6.7%
2008	2007	792,578	591,105	74.6%	201,473	25.4%	639	585	91.5%	54	8.5%

Graph 8E(1). Percentage of Phase III Domestic and Foreign Enrollment



Graph 8E(2). Number of Phase III Domestic and Foreign Enrollment

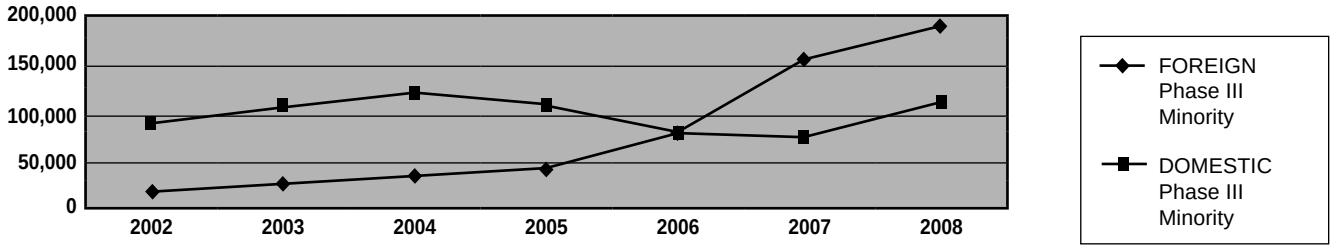


1. The Total Enrollment, Total Domestic, and Total Foreign enrollment increased overall from FY 2002–2008.
2. The Percent Domestic enrollment increased to approximately 74.6%, while Foreign enrollment decreased to approximately 25.4% in 2008.
3. The vast majority of protocols in FY 2004–2008 are domestic protocols.

Table 8F. Phase III Foreign and Domestic Minority Comparison for FY 2002–2008

FY Reported	FY 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%
2007	2006	156,533	162,713	79,769	383,050
	%	96.2%	100.0%	20.8%	100.0%
2008	2007	188,851	201,473	119,582	591,105
	%	93.7%	100.0%	20.2%	100.0%

Graph 8F(1). Number of Minority Participants in Phase III Clinical Studies (FY 2002-2008)



1. The Total Phase III Minority Foreign Participants increased from 60.4% in 2002 to 93.7% in 2008.
2. The Total Phase III Minority Domestic Participants varied from 20.2% to 25.4% between 2002 and 2008.
3. The Total Minority Enrollment reported in FY 2008 was 80.3% Domestic and 19.7% Foreign (see Table 1). The small percentage of foreign protocols (4.5%) account for a significant proportion (19.7%) of the Total Minority Enrollment, as shown by comparing both domestic and foreign enrollment data.

TABLE 9

Summary of NIH Phase III Clinical Research Reported in FY 2007: Total Number of Protocols and Enrollment by Sex and Domestic Versus Foreign Protocols

Table 9A. Protocols Reported

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
Protocols with enrollment	653	609	93.3%	44	6.7%
%	87.2%	87.6%		81.5%	
Protocols with zero enrollment. (Enrollment data has not yet been submitted.)%	96	86	89.6%	10	10.4%
	12.8%	12.4%		18.5%	
Total Number of Protocols	**749**	**695**	**92.8%**	**54**	**7.2%**
%	100.0%	100.0%		100.0%	

Total Number of Protocols

1. The total number of NIH defined Phase III Clinical Protocols reported in the NIH database in FY 2007 was 749; of these, 653 (87.2%) reported subject enrollment. Of these, the remainder are new clinical studies or studies pending enrollment.
2. Subsequent tables reporting "Enrollment Reported" are based on the 653 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."

Total Domestic Protocols

4. Domestic protocols made up the majority of protocols with a total of 695 (92.8%); of these, 609 (87.6%) reported domestic subject enrollment.
5. Clinical Research involving both domestic and foreign sites are reported as separate domestic and foreign protocols in subsequent tables.

Total Foreign Protocols

6. Total Foreign Protocols accounted for only a small percentage of protocols 54 (7.2%). Of these, 44 (6.7%) reported foreign enrollment.

Table 9B. Enrollment Reported

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
Females Enrolled	324,694	228,289	70.3%	96,405	29.7%
%	54.9%	53.3%		59.2%	
Males Enrolled	249,633	183,878	73.7%	65,755	26.3%
%	42.2%	42.9%		40.4%	
Sex of Subjects is Unknown	16,832	16,273	96.7%	559	0.0%
%	2.8%	3.8%		0.3%	
Total Subjects Enrolled	**591,159**	**428,440**	**72.5%**	**162,719**	**27.5%**
%	100.0%	100.0%		100.0%	

Total Enrollment Reported

1. The total "Enrollment Reported" in NIH Defined Phase III Protocols in the NIH database in FY 2007 was 591,159 subjects in 653 protocols.
2. Females 324,649 made up (54.9%) of the total subjects enrolled, while males 249,633 made up (42.2%) with unknowns 16,832 making up (2.8%).
3. Minorities 244,932 made up (41.4%) of the total subjects enrolled 591,159.

Total Domestic Enrollment Reported

4. The total Domestic Enrollment reported was 428,440 (72.5%).
5. Females 228,289 made up (53.3%) of the Domestic subjects enrolled, while males 183,878 made up 42.9% with unknowns 16,273 making up (3.8%).

Total Foreign Enrollment Reported

6. The total Foreign Enrollment Reported was 162,719 (27.5%).
7. Females 96,405 made up (59.2%) of the foreign subjects enrolled, while males 65,755 made up (40.4%), with unknowns 559 making up (0.3%).
8. Total Foreign Enrollment increased by 64% from 99,133 in FY 2006 to 162,719 in FY 2007

Table 9C. Minority Enrollment Reported

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
Minority Total for All Phase III Studies	244,932	88,339	36.1%	156,593	63.9%
% Minority Enrollment	41.4%	20.6%		96.2%	

1. Total Minority Enrollment was 41.4% (244,932) of Total Enrollment Reported 591,159.
2. Minorities 88,339 made up (20.6%) of the Total Domestic Enrollment 428,440.
3. Minorities 156,593 made up (96.2%) of the Total Foreign Enrollment 162,719.
4. Total Minority Enrollment 88,339 was (36.1%) Domestic 156,593 and (63.9%) Foreign.

* 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.

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

TABLE 10

Summary of NIH Phase III Clinical Research Reported in FY 2008: Total Number of Protocols and Enrollment by Sex and Domestic Versus Foreign Protocols

Table 10A. Protocols Reported

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
Protocols with enrollment	639	585	91.5%	54	8.5%
%	88.0%	88.1%		87.1%	
Protocols with zero enrollment. Enrollment data has not yet been submitted.	87	79	90.8%	8	9.2%
	12.0%	11.9%		12.9%	
Total Number of Protocols	**726**	**664**	**91.5%**	**62**	**8.5%**
%	100.0%	100.0%		100.0%	

Total Number of Protocols

1. The total number of NIH Defined Phase III Clinical Protocols reported in the NIH database in FY 2008 was 726; of these, 639 (88.0%) reported subject enrollment.
2. Subsequent tables reporting "Enrollment Reported" are based on the 639 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."

Total Domestic Protocols

4. Domestic protocols made up the majority of protocols with a total of 664 (91.5%); of these, 585 (91.5%) reported domestic subject enrollment.
5. Clinical Research involving both domestic and foreign sites are reported as separate domestic and foreign protocols in subsequent tables.

Total Foreign Protocols

6. Total Foreign Protocols increased from 44 in FY 2007 to 54 in FY 2008.

Table 10B. Enrollment Reported

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
Females Enrolled	455,590	347,982	76.4%	107,608	23.6%
%	57.5%	58.9%		53.4%	
Males Enrolled	319,754	226,266	70.8%	93,488	29.2%
%	40.3%	38.3%		46.4%	
Sex of Subjects is Unknown	17,234	16,857	97.8%	377	0.0%
%	2.2%	2.9%		0.2%	
Total Subjects Enrolled	**792,578**	**591,105**	**74.6%**	**201,473**	**25.4%**
%	100.0%	100.0%		100.0%	

Total Enrollment Reported

1. The total "Enrollment Reported" in NIH Defined Phase III Protocols in the NIH database in FY 2008 was 792,578 subjects in 639 protocols.
2. Females made up 57.5% (455,590) of the total subjects enrolled, while males made up 40.3% (319,754), with 2.2% (17,234) unknown.
3. Minorities made up 38.9% (308,433) of the total subjects enrolled (792,578).

Total Domestic Enrollment Reported

4. The total Domestic Enrollment reported was 591,105 (74.6%).
5. Females made up 58.9% (347,982) of the domestic subjects enrolled, while males made up 38.3% (226,266), with 2.9% (16,857) unknown.

Total Foreign Enrollment Reported

6. The total Foreign Enrollment Reported was 201,473 (25.4%).
7. Females made up 53.4% (107,608) of the foreign subjects enrolled, while males made up 46.4% (93,488), with 0.2% (377) unknown.
8. Total Foreign Enrollment increased by 24% (162,719 in FY 2007; 201,473 in FY 2008).

Table 10C. Minority Enrollment Reported

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
Minority Total for All Phase III Studies	308,433	119,582	38.8%	188,851	61.2%
% Minority Enrollment	38.9%	20.2%		93.7%	

1. Total Minority Enrollment was 38.9% (308,433) of Total Enrollment Reported (792,578).
2. Minorities made up 20.2% (119,582) of the Total Domestic Enrollment (591,105).
3. Minorities made up 93.7% (188,851) - the vast majority - of the Total Foreign Enrollment (201,473).
4. Total Minority Enrollment was 38.86% Domestic and 61.2% Foreign.

* 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.

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

TABLE 11

Overview of NIH Extramural and Intramural Clinical Research Reported in FY2007: Number of Sex-Specific Protocols and Domestic versus Foreign Protocols

Table 11A. Protocols Reported

		Domestic				Foreign			
	Total All Clinical Studies	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Number of protocols reporting females only	1,340	1,161	86.6%	127	9.5%	46	3.4%	6	0.4%
%	8.6%	8.9%		7.2%		7.3%		6.9%	
Number of protocols reporting males only	517	470	90.9%	27	5.2%	15	2.9%	5	1.0%
%	3.3%	3.6%		1.5%		2.4%		5.7%	
Number of protocols with both female and male enrollment (excluding sex-specific protocols)	9,057	7,351	81.2%	1,327	14.7%	319	3.5%	60	0.7%
%	58.2%	56.2%		75.4%		50.3%		69.0%	
Total Number of Protocols With Enrollment	**10,914**	**8,982**	**82.3%**	**1,481**	**13.6%**	**380**	**3.5%**	**71**	**0.7%**
%	70.1%	69%		84.1%		59.9%		81.6%	
Number of protocols with zero enrollment. Enrollment data has not yet been submitted.	4,653	4,103	88.2%	280	6.0%	254	5.5%	16	0.3%
%	29.9%	31.4%		15.9%		40.1%		18.4%	
Total Number of Protocols	**15,567**	**13,085**	**84.1%**	**1,761**	**11.3%**	**634**	**4.1%**	**87**	**0.6%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Number of Protocols With Enrollment

1. Female-Only Protocols: There were 1,340 protocols reporting females only, representing 12.3% (1,340/10,914) of protocols with enrollment.
   1,207 (90.1%) were Extramural Protocols; 132 (9.9%) were NIH Intramural Protocols.

   1,288 (96.1%) were Domestic Protocols; 52 (3.9%) were Foreign Protocols.

2. Male-Only Protocols: There were 517 protocols reporting males only, representing 4.7% (516/10,914) of protocols with enrollment.
   485 (93.8%) were Extramural Protocols; 32 (6.2%) were NIH Intramural Protocols.

   497 (96.1%) were Domestic Protocols; 20 (3.9%) were Foreign Protocols.

3. Protocols Reporting Both Females and Males (excluding sex-specific protocols): There were 9,057 protocols reporting both female and male participants representing 83.0 % (9,057/10,914) of protocols with enrollment.
   7,760 (84.7%) were Extramural Protocols; 1,384 (15.3%) were NIH Intramural Protocols.

   8,678 (95.8%) were Domestic Protocols; 379 (4.2%) were Foreign Protocols.

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

Table 11B. Enrollment Reported

		Domestic				Foreign			
	Total All Clinical Studies	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
In protocols reporting females only	9,000,648	6,830,795	75.9%	1,884,141	20.9%	142,737	1.6%	142,975	1.6%
%	51.6%	52.2%		60.8%		15.7%		40.1%	
In protocols reporting males only	377,803	335,655	88.8%	3,203	0.8%	11,998	3.2%	26,947	7.1%
%	2.2%	2.6%		0.1%		1.3%		7.5%	
In protocols excluding female-only and male-only enrollment protocols	8,070,007	5,913,901	73.3%	1,212,893	15.0%	756,196	9.4%	187,017	2.3%
%	46.3%	45.2%		39.1%		83.0%		52.4%	
Enrollment Totals for All Studies	**17,448,458**	**13,080,351**	**75.0%**	**3,100,237**	**17.8%**	**910,931**	**5.2%**	**356,939**	**2.0%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Enrollment Reported

1. In Female-Only Protocols: There were approximately 9.0 M females, representing 51.6% of total enrollment.
   7.0M (77.5%) were in Extramural Protocols; 2.03 (22.5%) were in NIH Intramural Protocols.

   8.7M (96.8%) were Domestic Protocols, 0.28 (3.2%) were Foreign Protocols.

2. In Male-Only Protocols: There were approximately 377,803 males, representing 2.2% of total enrollment.
   0.35M (92.0%) were in Extramural Protocols; 0.3 (8.0%) were in NIH Intramural Protocols.

   0.34M (89.7%) were Domestic Protocols; 0.38M (10.3%) were Foreign Protocols.

3. In Protocols reporting Both Females and Males (excluding sex-specific studies): There were approximately 8.1M subjects, representing 46.3% of total enrollment.
   6.6M (82.7%) were in Extramural Protocols; 1.4M (17.3%) were in NIH Intramural Protocols.

   7.13M (88.3%) were Domestic Protocols, 0.94M (11.7%) were Foreign Protocols.

Table 11C. Minority Enrollment Reported

		Domestic				Foreign			
		Extramural	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Minority Totals for All Studies	5,216,434	3,651,722	70.0%	632,016	12.1%	746,278	14.3%	186,418	3.6%
% Minority Enrollment	29.9%	27.9%		20.4%		81.9%		52.2%	

Total Minority Enrollment: 29.9% of Total Enrollment (5.2M/17.4M)

Total Domestic Minority Enrollment: 4.3M (82.1%) of Total Minority Enrollment (4,283,738/5,216,434).

Total Foreign Minority Enrollment: 0.93M (17.9%) of Total Minority Enrollment (932,696/5,216,434).

Total Domestic Minority Enrollment (Extramural + Intramural): 4.3M (24.6%) of Total Enrollment (4,283,738/17,448,458).

Total Foreign Minority Enrollment (Extramural + Intramural): 0.93M (5.3%) of Total Enrollment (932,696/17,448,458).

Total Minority Enrollment in all Extramural protocols (Domestic + Foreign): 4.4M (25.2%) of Total Enrollment (4,398,000/17,448,458).

Total Minority Enrollment in all Intramural protocols (Domestic + Foreign): 0.82M (4.7%) of Total Enrollment (818,434/17,448,458).

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

TABLE 12

Aggregate Enrollment Data for Extramural Research Protocols Funded in FY 2006 and Reported in FY 2007: Percent Analysis

Table 12A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 9,362

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	8,652,645	2,716,478		31.39%
%	61.84%	61.76%		
Males	4,971,895	1,663,177		33.45%
%	35.54%	37.81%		
Unknown	366,742	18,789		5.12%
%	2.62%	0.43%		
TOTAL	**13,991,282**	**4,398,444**	**31.44%**	
Total %	100%	100.00%		

Table 12B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 8,713

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	86,249	799,997	996,531	30,436	5,456,346	160,305	847,000	8,376,864	6,917,630	683,000	776,234	8,376,864
	0.64%	**5.93%**	**7.39%**	**0.23%**	**40.46%**	**1.19%**	**6.28%**	**62.12%**	**51.30%**	**5.07%**	**5.76%**	**62.12%**
	1.03%	*9.55%*	*11.90%*	*0.36%*	*65.14%*	*1.91%*	*10.11%*	*100.00%*	*82.58%*	*8.15%*	*9.27%*	*100.00%*
	69.75%	68.38%	56.12%	57.28%	63.17%	60.63%	58.00%	62.12%	63.28%	64.02%	52.22%	62.12%
Male	36,876	368,138	771,181	22,345	3,157,379	102,084	291,234	4,749,237	3,985,057	378,293	385,887	4,749,237
	0.27%	**2.73%**	**5.72%**	**0.17%**	**23.41%**	**0.76%**	**2.16%**	**35.22%**	**29.55%**	**2.81%**	**2.86%**	**35.22%**
	0.78%	*7.75%*	*16.24%*	*0.47%*	*66.48%*	*2.15%*	*6.13%*	*100.00%*	*83.91%*	*7.97%*	*8.13%*	*100.00%*
	29.82%	31.46%	43.43%	42.05%	36.55%	38.61%	19.94%	35.22%	36.46%	35.46%	25.96%	35.22%
Unknown	526	1,863	7,854	355	23,725	2,003	322,015	358,341	28,501	5,547	324,293	358,341
	0.00%	**0.01%**	**0.06%**	**0.00%**	**0.18%**	**0.01%**	**2.39%**	**2.66%**	**0.21%**	**0.04%**	**2.40%**	**2.66%**
	0.15%	*0.52%*	*2.19%*	*0.10%*	*6.62%*	*0.56%*	*89.86%*	*100.00%*	*7.95%*	*1.55%*	*90.50%*	*100.00%*
	0.43%	0.16%	0.44%	0.67%	0.27%	0.76%	22.05%	2.66%	0.26%	0.52%	21.82%	2.66%
Total	123,651	1,169,998	1,775,566	53,136	8,637,450	264,392	1,460,249	13,484,442	10,931,188	1,066,840	1,486,414	13,484,442
	0.92%	**8.68%**	**13.17%**	**0.39%**	**64.05%**	**1.96%**	**10.83%**	**100.00%**	**81.07%**	**7.91%**	**11.02%**	**100.00%**
	0.92%	*8.68%*	*13.17%*	*0.39%*	*64.05%*	*1.96%*	*10.83%*	*100.00%*	*81.07%*	*7.91%*	*11.02%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 12B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	19,600	5,562	17,069	2,574	328,520	55,722	253,953	683,000	2,655,991
	1.84%	**0.52%**	**1.60%**	**0.24%**	**30.79%**	**5.22%**	**23.80%**	**64.02%**	**19.70%**
	2.87%	*0.81%*	*2.50%*	*0.38%*	*48.10%*	*8.16%*	*37.18%*	*100.00%*	*31.71%*
	55.79%	75.35%	60.43%	60.52%	68.30%	57.60%	61.33%	64.02%	62.03%
Male	15,372	1,784	11,091	1665	151,846	40,563	155,972	378,293	1,608,442
	1.44%	**0.17%**	**1.04%**	**0.16%**	**14.23%**	**3.80%**	**14.62%**	**35.46%**	**11.93%**
	4.06%	*0.47%*	*2.93%*	*0.44%*	*40.14%*	*10.72%*	*41.23%*	*100.00%*	*33.87%*
	43.76%	24.17%	39.26%	39.15%	31.57%	41.93%	37.67%	35.46%	37.56%
Unknown	159	36	88	14	652	452	4,146	5,547	17,399
	0.01%	**0.00%**	**0.01%**	**0.00%**	**0.06%**	**0.04%**	**0.39%**	**0.52%**	**0.13%**
	2.87%	*0.65%*	*1.59%*	*0.25%*	*11.75%*	*8.15%*	*74.74%*	*100.00%*	*4.86%*
	0.45%	0.49%	0.31%	0.33%	0.14%	0.47%	1.00%	0.52%	0.41%
Total	35,131	7,382	28,248	4,253	481,018	96,737	414,071	1,066,840	4,281,832
	3.29%	**0.69%**	**2.65%**	**0.40%**	**45.09%**	**9.07%**	**38.81%**	**100.00%**	**31.75%**
	3.29%	*0.69%*	*2.65%*	*0.40%*	*45.09%*	*9.07%*	*38.81%*	*100.00%*	*31.75%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 12C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 649

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	1,804	7,845	30,985	19,853	198,153	17,141	275,781	60,487
	0.36%	**1.55%**	**6.11%**	**3.92%**	**39.10%**	**3.38%**	**54.41%**	**11.93%**
	0.65%	*2.84%*	*11.24%*	*7.20%*	*71.85%*	*6.22%*	*100.00%*	*21.93%*
	49.10%	53.55%	52.52%	50.52%	56.14%	45.98%	54.41%	51.87%
Male	1,727	6,638	27,428	18,942	153,077	14,846	222,658	54,735
	0.34%	**1.31%**	**5.41%**	**3.74%**	**30.20%**	**2.93%**	**43.93%**	**10.80%**
	0.78%	*2.98%*	*12.32%*	*8.51%*	*68.75%*	*6.67%*	*100.00%*	*24.58%*
	47.01%	45.31%	46.50%	48.20%	43.37%	39.82%	43.93%	46.94%
Unknown	143	168	578	501	1,717	5,294	8,401	1390
	0.028%	**0.03%**	**0.11%**	**0.10%**	**0.34%**	**1.04%**	**1.66%**	**0.27%**
	1.70%	*2.00%*	*6.88%*	*5.96%*	*20.44%*	*63.02%*	*100.00%*	*16.55%*
	3.89%	1.15%	0.98%	1.27%	0.49%	14.20%	1.66%	1.19%
Total	3,674	14,651	58,991	39,296	352,947	37,281	506,840	116,612
	0.72%	**2.89%**	**11.64%**	**7.75%**	**69.64%**	**7.36%**	**100.00%**	**23.01%**
	0.72%	*2.89%*	*11.64%*	*7.75%*	*69.64%*	*7.36%*	*100.00%*	*23.01%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 12 Comments

Sex/Gender

In FY 2007 more females (8,652,645; 61.84%) than males (4,971,895; 35.54%) were enrolled in aggregate extramural research protocols.

More minority females (2,716,478; 61.76%) than minority males (1,663,177; 37.81%) were enrolled in aggregate extramural research protocols.

Race

Approximately 31.44% (4,398,444) of participants in aggregate extramural research (16,979,004 total) were classified as U.S. minorities.

Largest identified racial group was White at 69.64% following the 1977 OMB standards and 64.05% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 11.64% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 13.17% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.72%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.39%.

Ethnicity

7.91% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was White at 45.09% (2nd largest category is Unknown/Other at 38.81%).

Smallest identified racial group was Hawaiian/Pacific Islanders at 0.40% .

Of the 1,066,840 participants, 64.02% were women and 35.46% were men.

7.75% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 13

Overview of NIH Extramural and Intramural Clinical Research Reported in FY 2008: Number of Sex-Specific Protocols, and Domestic versus Foreign Protocols

Table 13A. Protocols Reported

		Domestic				Foreign			
	Total All Clinical Studies	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Number of protocols reporting females only	1,272	1,104	86.8%	121	9.5%	40	3.1%	7	0.6%
%	8.2%	8.4%		6.8%		6.4%		7.2%	
Number of protocols reporting males only	529	480	90.7%	26	4.9%	18	3.4%	5	0.9%
%	3.4%	3.7%		1.5%		2.9%		5.2%	
Number of protocols with both female and male enrollment (excluding sex-specific protocols)	9,244	7,387	79.9%	1,430	15.5%	352	3.8%	75	0.8%
%	59.3%	56.4%		80.5%		56.2%		77.3%	
Total Number of Protocols With Enrollment	**11,045**	**8,971**	**81.2%**	**1,577**	**14.3%**	**410**	**3.7%**	**87**	**0.8%**
%	70.8%	68%		88.8%		65.5%		89.7%	
Number of protocols with zero enrollment. Enrollment data has not yet been submitted.	4,553	4,128	90.7%	199	4.4%	216	4.7%	10	0.2%
%	29.2%	31.5%		11.2%		34.5%		10.3%	
Total Number of Protocols	**15,598**	**13,099**	**84.0%**	**1,776**	**11.4%**	**626**	**4.0%**	**97**	**0.6%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Number of Protocols with Enrollment

1. Female-Only protocols: There were 1,272 protocols reporting females only, representing 11.5% (1,272/11,045) of protocols with enrollment.

   89.9% were Extramural Protocols (1,104+40); 10.1% were NIH Intramural Protocols (121+7).

   96.3% were Domestic Protocols (1,104+121); 3.7% were Foreign Protocols (40+7).

2. Male-Only protocols: There were 529 protocols reporting males only, representing 4.8% (529/11,045) of protocols with enrollment.

   94.1% were Extramural Protocols (480+18); 5.9% were NIH Intramural Protocols (26+5).

   95.7% were Domestic Protocols (480+26) ; 4.3% were Foreign Protocols (18+5).

3. Protocols Reporting Both Females and Males (excluding sex-specific Protocols): There were 9,244 protocols reporting both female and male participants representing 83.7% (9,244/11,045) of Protocols with enrollment.

   83.7% were Extramural Protocols (7,387+352); 16.3% were NIH Intramural Protocols (1,430+75).

   95.4% were Domestic Protocols (7,387+1,430); 4.6% were Foreign Protocols (352+75).

Table 13B. Enrollment Reported

		Domestic				Foreign			
	Total All Clinical Studies	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
In protocols reporting females only	7,507,149	6,805,570	90.7%	401,336	5.3%	142,737	1.9%	157,506	2.1%
%	48.7%	57.7%		17.2%		18.3%		31.6%	
In protocols reporting males only	361,434	314,494	87.0%	7,670	2.1%	12,319	3.4%	26,951	7.5%
%	2.3%	2.7%		0.3%		1.6%		5.4%	
In protocols excluding female-only and male-only enrollment protocols	7,543,772	4,677,541	62.0%	1,928,016	25.6%	624,208	8.3%	314,007	4.2%
%	48.9%	39.6%		82.5%		80.1%		63.0%	
Enrollment Totals for All Studies	**15,412,355**	**11,797,605**	**76.5%**	**2,337,022**	**15.2%**	**779,264**	**5.1%**	**498,464**	**3.2%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Enrollment Reported

1. In Female-Only Protocols: There were approximately 7.5M females, representing 48.7% of total enrollment
   92.6% were in Extramural Protocols; 7.4% were in NIH Intramural Protocols

   96.0% were Domestic Protocols, 4.0% were Foreign Protocols

2. In Male-Only Protocols: There were approximately 361,434 males, representing 2.3% of total enrollment
   90.4% were in Extramural Protocols; 9.6% were in NIH Intramural Protocols

   89.1% were Domestic Protocols; 10.9% were Foreign Protocols

3. In Protocols reporting Both Females and Males (excluding sex-specific studies): There were approximately 7.5M subjects, representing 48.9% of total enrollment
   70.3% were in Extramural Protocols; 29.7% were in NIH Intramural Protocols

   87.6% were Domestic Protocols; 12.4% were Foreign Protocols

Table 13C. Minority Enrollment Reported

		Domestic				Foreign			
		Extramural	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Minority Totals for All Studies	**4,416,770**	**3,092,465**	**70.0%**	**459,360**	**10.4%**	**603,124**	**13.7%**	**261,821**	**5.9%**
% Minority Enrollment	28.7%	26.2%		19.7%		77.4%		52.5%	

Total Minority Enrollment: 28.7% of Total Enrollment (4.4M/15.4M)

Total Domestic Minority Enrollment: 80.4% of Minority Enrollment (3,551,825/4,416,770)

Total Foreign Minority Enrollment: 19.6% of Minority Enrollment (864,945/4,416,770)

Total Domestic Minority Enrollment (Extramural + Intramural): 23.0% of Total Enrollment (3,551,825/15,412,355)

Total Foreign Minority Enrollment (Extramural + Intramural): 5.6% of Total Enrollment (864,945/15,412,355)

Total Minority Enrollment in all Extramural projects (Domestic + Foreign): 24.0% of Total Enrollment (3,695,589/15,412,355)

Total Minority Enrollment in all Intramural projects (Domestic + Foreign): 4.7% of Total Enrollment (721,181/15,412,355)

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

TABLE 14

Aggregate Enrollment Data for Extramural Research Protocols Funded in FY 2007 and Reported in FY 2008: Percent Analysis

Table 14A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 9,381

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	8,029,181	2,263,551		28.19%
%	63.84%	61.25%		
Males	4,406,583	1,414,608		32.10%
%	35.04%	38.28%		
Unknown	141,104	17,429		12.35%
%	1.12%	0.47%		
TOTAL	**12,576,868**	**3,695,588**	**29.38%**	
Total %	100%	100.00%		

Table 14B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 8,879

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	78,464	618,320	867,547	26,282	4,932,495	100,278	1,097,714	7,721,100	6,099,147	620,632	1,001,322	7,721,101
	0.65%	**5.09%**	**7.14%**	**0.22%**	**40.60%**	**0.83%**	**9.04%**	**63.55%**	**50.20%**	**5.11%**	**8.24%**	**63.55%**
	1.02%	*8.01%*	*11.24%*	*0.34%*	*63.88%*	*1.30%*	*14.22%*	*100.00%*	*78.99%*	*8.04%*	*12.97%*	*100.00%*
	69.79%	67.98%	54.55%	59.72%	62.75%	60.49%	74.91%	63.55%	63.30%	61.49%	66.58%	63.55%
Male	33,452	289,799	715,125	17,520	2,920,167	64,052	246,846	4,286,961	3,521,042	382,036	383,883	4,286,961
	0.28%	**2.39%**	**5.89%**	**0.14%**	**24.04%**	**0.53%**	**2.03%**	**35.29%**	**28.98%**	**3.14%**	**3.16%**	**35.29%**
	0.78%	*6.76%*	*16.68%*	*0.41%*	*68.12%*	*1.49%*	*5.76%*	*100.00%*	*82.13%*	*8.91%*	*8.95%*	*100.00%*
	29.75%	31.86%	44.96%	39.81%	37.15%	38.64%	16.85%	35.29%	36.54%	37.85%	25.53%	35.29%
Unknown	517	1,479	7,813	204	8,468	1,435	120,805	140,721	15,345	6,668	118,708	140,721
	0.00%	**0.01%**	**0.06%**	**0.00%**	**0.07%**	**0.01%**	**0.99%**	**1.16%**	**0.13%**	**0.05%**	**0.98%**	**1.16%**
	0.37%	*1.05%*	*5.55%*	*0.14%*	*6.02%*	*1.02%*	*85.85%*	*100.00%*	*10.90%*	*4.74%*	*84.36%*	*100.00%*
	0.46%	0.16%	0.49%	0.46%	0.11%	0.87%	8.24%	1.16%	0.16%	0.66%	7.89%	1.16%
Total	112,433	909,598	1,590,485	44,006	7,861,130	165,765	1,465,365	12,148,782	9,635,534	1,009,336	1,503,913	12,148,783
	0.93%	**7.49%**	**13.09%**	**0.36%**	**64.71%**	**1.36%**	**12.06%**	**100.00%**	**79.31%**	**8.31%**	**12.38%**	**100.00%**
	0.93%	*7.49%*	*13.09%*	*0.36%*	*64.71%*	*1.36%*	*12.06%*	*100.00%*	*79.31%*	*8.31%*	*12.38%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 14B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	18,647	17,212	27,081	1,360	316,968	31,241	208,123	620,632	2,215,982
	1.85%	**1.71%**	**2.68%**	**0.13%**	**31.40%**	**3.10%**	**20.62%**	**61.49%**	**18.24%**
	3.00%	*2.77%*	*4.36%*	*0.22%*	*51.07%*	*5.03%*	*33.53%*	*100.00%*	*28.70%*
	54.51%	54.50%	32.96%	58.17%	68.95%	54.97%	60.77%	61.49%	61.14%
Male	15,384	14,252	54,818	941	141,977	25,477	129,187	382,036	1,391,112
	1.52%	**1.41%**	**5.43%**	**0.09%**	**14.07%**	**2.52%**	**12.80%**	**37.85%**	**11.45%**
	4.03%	*3.73%*	*14.35%*	*0.25%*	*37.16%*	*6.67%*	*33.82%*	*100.00%*	*32.45%*
	44.97%	45.13%	66.72%	40.25%	30.88%	44.83%	37.72%	37.85%	38.38%
Unknown	179	116	260	37	778	114	5,184	6,668	17,410
	0.02%	**0.01%**	**0.03%**	**0.00%**	**0.08%**	**0.01%**	**0.51%**	**0.66%**	**0.14%**
	2.68%	*1.74%*	*3.90%*	*0.55%*	*11.67%*	*1.71%*	*77.74%*	*100.00%*	*12.37%*
	0.52%	0.37%	0.32%	1.58%	0.17%	0.20%	1.51%	0.66%	0.48%
Total	34,210	31,580	82,159	2,338	459,723	56,832	342,494	1,009,336	3,624,504
	3.39%	**3.13%**	**8.14%**	**0.23%**	**45.55%**	**5.63%**	**33.93%**	**100.00%**	**29.83%**
	3.39%	*3.13%*	*8.14%*	*0.23%*	*45.55%*	*5.63%*	*33.93%*	*100.00%*	*29.83%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 14C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 502

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	1,243	7,330	26,019	12,977	250,613	9,899	308,081	47,569
	0.29%	**1.71%**	**6.08%**	**3.03%**	**58.54%**	**2.31%**	**71.97%**	**11.11%**
	0.40%	*2.38%*	*8.45%*	*4.21%*	*81.35%*	*3.21%*	*100.00%*	*15.44%*
	76.49%	77.00%	66.54%	62.28%	73.69%	58.47%	71.97%	66.92%
Male	382	2,176	13,082	7,856	89,286	6,840	119,622	23,496
	0.09%	**0.51%**	**3.06%**	**1.84%**	**20.86%**	**1.60%**	**27.94%**	**5.49%**
	0.32%	*1.82%*	*10.94%*	*6.57%*	*74.64%*	*5.72%*	*100.00%*	*19.64%*
	23.51%	22.86%	33.45%	37.71%	26.25%	40.40%	27.94%	33.05%
Unknown	0	13	4	2	174	190	383	19
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.04%**	**0.04%**	**0.09%**	**0.00%**
	0.00%	*3.39%*	*1.04%*	*0.52%*	*45.43%*	*49.61%*	*100.00%*	*4.96%*
	0.00%	0.14%	0.01%	0.01%	0.05%	1.12%	0.09%	0.03%
Total	1,625	9,519	39,105	20,835	340,073	16,929	428,086	71,084
	0.38%	**2.22%**	**9.13%**	**4.87%**	**79.44%**	**3.95%**	**100.00%**	**16.61%**
	0.38%	*2.22%*	*9.13%*	*4.87%*	*79.44%*	*3.95%*	*100.00%*	*16.61%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 14 Comments

Sex/Gender

In FY 2008 more females (8,029,181; 63.84%) than males (4,406,583; 35.04%) were enrolled in aggregate extramural research protocols.

More minority females (2,263,551; 61.25%) than minority males (1,414,608; 38.28%) were enrolled in aggregate extramural research protocols.

Race

Approximately 29.38% (3,695,588) of participants in aggregate extramural research (12,576,868 total) were classified as U.S. minorities.

Largest identified racial group was White at 79.44% following the 1977 OMB standards and 64.71% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 9.13% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 13.10% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.38%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.36%.

Ethnicity

8.31% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was White at 45.55% (2nd largest category is Unknown/Other at 33.93%).

Smallest identified racial group was Hawaiian/Pacific Islanders at 0.23% .

Of the 1,009,336 participants, 61.49% were women and 37.85% were men.

4.87% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 15

Aggregate Enrollment Data for Extramural Research Protocols Excluding Male-Only and Female-Only Protocols Funded in FY 2006 and Reported in FY 2007: Percent Analysis

Table 15A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 7,651

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	4,435,292	1,645,545		37.10%
%	46.45%	50.36%		
Males	4,761,326	1,606,976		33.75%
%	49.87%	49.18%		
Unknown	350,892	14,743		4.20%
%	3.68%	0.45%		
TOTAL	**9,547,510**	**3,267,264**	**34.22%**	
Total %	100%	100.00%		

Table 15B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 7,158

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	43,409	408,811	666,263	28,253	2,635,011	134,098	338,551	4,254,396	3,523,627	395,681	335,088	4,254,396
	0.47%	**4.45%**	**7.26%**	**0.31%**	**28.71%**	**1.46%**	**3.69%**	**46.36%**	**38.39%**	**4.31%**	**3.65%**	**46.36%**
	1.02%	*9.61%*	*15.66%*	*0.66%*	*61.94%*	*3.15%*	*7.96%*	*100.00%*	*82.82%*	*9.30%*	*7.88%*	*100.00%*
	54.07%	53.12%	47.06%	55.61%	46.35%	57.38%	35.94%	46.36%	47.43%	51.37%	34.26%	46.36%
Male	36,344	359,148	744,527	22,194	3,034,321	98,583	285,602	4,580,719	3,883,627	369,165	327,927	4,580,719
	0.40%	**3.91%**	**8.11%**	**0.24%**	**33.06%**	**1.07%**	**3.11%**	**49.91%**	**42.32%**	**4.02%**	**3.57%**	**49.91%**
	0.79%	*7.84%*	*16.25%*	*0.48%*	*66.24%*	*2.15%*	*6.23%*	*100.00%*	*84.78%*	*8.06%*	*7.16%*	*100.00%*
	45.27%	46.67%	52.59%	43.69%	53.37%	42.18%	30.32%	49.91%	52.27%	47.92%	33.53%	49.91%
Unknown	526	1,648	5,062	355	15,996	1,028	317,876	342,491	22,055	5,483	314,953	342,491
	0.01%	**0.02%**	**0.06%**	**0.00%**	**0.17%**	**0.01%**	**3.46%**	**3.73%**	**0.24%**	**0.06%**	**3.43%**	**3.73%**
	0.15%	*0.48%*	*1.48%*	*0.10%*	*4.67%*	*0.30%*	*92.81%*	*100.00%*	*6.44%*	*1.60%*	*91.96%*	*100.00%*
	0.66%	0.21%	0.36%	0.70%	0.28%	0.44%	33.74%	3.73%	0.30%	0.71%	32.20%	3.73%
Total	80,279	769,607	1,415,852	50,802	5,685,328	233,709	942,029	9,177,606	7,429,309	770,329	977,968	9,177,606
	0.87%	**8.39%**	**15.43%**	**0.55%**	**61.95%**	**2.55%**	**10.26%**	**100.00%**	**80.95%**	**8.39%**	**10.66%**	**100.00%**
	0.87%	*8.39%*	*15.43%*	*0.55%*	*61.95%*	*2.55%*	*10.26%*	*100.00%*	*80.95%*	*8.39%*	*10.66%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 15B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	14,546	1,914	12,613	2019	166,532	46,927	151,130	395,681	1,598,496
	1.89%	**0.25%**	**1.64%**	**0.26%**	**21.62%**	**6.09%**	**19.62%**	**51.37%**	**17.42%**
	3.68%	*0.48%*	*3.19%*	*0.51%*	*42.09%*	*11.86%*	*38.19%*	*100.00%*	*37.57%*
	48.65%	51.48%	53.75%	54.76%	52.98%	54.58%	48.87%	51.37%	50.37%
Male	15,195	1,768	10,764	1654	147,159	38,607	154,018	369,165	1,561,973
	1.97%	**0.23%**	**1.40%**	**0.21%**	**19.10%**	**5.01%**	**19.99%**	**47.92%**	**17.02%**
	4.12%	*0.48%*	*2.92%*	*0.45%*	*39.86%*	*10.46%*	*41.72%*	*100.00%*	*34.10%*
	50.82%	47.55%	45.87%	44.86%	46.81%	44.90%	49.81%	47.92%	49.21%
Unknown	159	36	88	14	652	452	4,082	5,483	13,353
	0.02%	**0.00%**	**0.01%**	**0.00%**	**0.08%**	**0.06%**	**0.53%**	**0.71%**	**0.15%**
	2.90%	*0.66%*	*1.60%*	*0.26%*	*11.89%*	*8.24%*	*74.45%*	*100.00%*	*3.90%*
	0.53%	0.97%	0.38%	0.38%	0.21%	0.53%	1.32%	0.71%	0.42%
Total	29,900	3,718	23,465	3,687	314,343	85,986	309,230	770,329	3,173,822
	3.88%	**0.48%**	**3.05%**	**0.48%**	**40.81%**	**11.16%**	**40.14%**	**100.00%**	**34.58%**
	3.88%	*0.48%*	*3.05%*	*0.48%*	*40.81%*	*11.16%*	*40.14%*	*100.00%*	*34.58%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 15C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 493

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	1,426	6,160	22,464	16,999	118,059	15,788	180,896	47,049
	0.39%	**1.67%**	**6.07%**	**4.60%**	**31.92%**	**4.27%**	**48.90%**	**12.72%**
	0.79%	*3.41%*	*12.42%*	*9.40%*	*65.26%*	*8.73%*	*100.00%*	*26.01%*
	45.30%	49.49%	51.10%	50.16%	48.92%	44.94%	48.90%	50.35%
Male	1,579	6,119	20,917	16,388	121,551	14,053	180,607	45,003
	0.43%	**1.65%**	**5.65%**	**4.43%**	**32.86%**	**3.80%**	**48.83%**	**12.17%**
	0.87%	*3.39%*	*11.58%*	*9.07%*	*67.30%*	*7.78%*	*100.00%*	*24.92%*
	50.16%	49.16%	47.58%	48.36%	50.37%	40.00%	48.83%	48.16%
Unknown	143	168	578	501	1,717	5,294	8,401	1390
	0.039%	**0.05%**	**0.16%**	**0.14%**	**0.46%**	**1.43%**	**2.27%**	**0.38%**
	1.70%	*2.00%*	*6.88%*	*5.96%*	*20.44%*	*63.02%*	*100.00%*	*16.55%*
	4.54%	1.35%	1.31%	1.48%	0.71%	15.07%	2.27%	1.49%
Total	3,148	12,447	43,959	33,888	241,327	35,135	369,904	93,442
	0.85%	**3.36%**	**11.88%**	**9.16%**	**65.24%**	**9.50%**	**100.00%**	**25.26%**
	0.85%	*3.36%*	*11.88%*	*9.16%*	*65.24%*	*9.50%*	*100.00%*	*25.26%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 15 Comments

Sex/Gender

Excluding sex-specific studies, the number of males (4,761,326 or 49.87%) exceeded the number of females (4,435,292 or 46.45%) enrolled in Extramural Research Protocols.

Excluding sex-specific studies, the number of minority females (1,645,545 or 50.36%) exceeded the number of minority males (1,606,976 or 49.18%) enrolled in Extramural Research Protocols.

Race

Approximately 34.22% (3,267,264) of participants in aggregate extramural research (9,547,510 total) were classified as U.S. minorities.

Largest identified racial group was White at 65.24% following the 1977 OMB standards and 61.95% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 11.88% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 15.43% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.85%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.55%.

Ethnicity

8.39% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was White at 40.81% (2nd largest category is Unknown/Other at 40.14%).

Smallest identified racial group was Hawaiian/Pacific Islanders at 0.48%.

Of the 770,329 participants, 51.37% were women and 47.92% were men.

9.16% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 16

Aggregate Enrollment Data for Extramural Research Protocols Excluding Male-Only and Female-Only Protocols Funded in FY 2007 and Reported in FY 2008: Percent Analysis

Table 16A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 7,736

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	3,596,589	1,313,179		36.51%
%	45.61%	48.81%		
Males	4,147,836	1,359,572		32.78%
%	52.60%	50.54%		
Unknown	141,240	17,453		12.36%
%	1.79%	0.65%		
TOTAL	**7,885,665**	**2,690,204**	**34.12%**	
Total %	100%	100.00%		

Table 16B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 7,361

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	35,360	314,994	558,191	23,664	2,239,935	73,443	278,062	3,523,649	2,930,462	373,580	219,608	3,523,650
	0.46%	**4.07%**	**7.22%**	**0.31%**	**28.96%**	**0.95%**	**3.60%**	**45.56%**	**37.89%**	**4.83%**	**2.84%**	**45.56%**
	1.00%	*8.94%*	*15.84%*	*0.67%*	*63.57%*	*2.08%*	*7.89%*	*100.00%*	*83.17%*	*10.60%*	*6.23%*	*100.00%*
	51.40%	52.75%	44.55%	57.43%	44.81%	54.25%	43.49%	45.56%	46.03%	49.56%	35.80%	45.56%
Male	32,920	280,625	686,904	17,335	2,750,884	60,495	240,319	4,069,482	3,420,952	373,562	274,968	4,069,482
	0.43%	**3.63%**	**8.88%**	**0.22%**	**35.57%**	**0.78%**	**3.11%**	**52.62%**	**44.23%**	**4.83%**	**3.56%**	**52.62%**
	0.81%	*6.90%*	*16.88%*	*0.43%*	*67.60%*	*1.49%*	*5.91%*	*100.00%*	*84.06%*	*9.18%*	*6.76%*	*100.00%*
	47.85%	47.00%	54.82%	42.07%	55.03%	44.69%	37.59%	52.62%	53.73%	49.56%	44.83%	52.62%
Unknown	517	1,479	7,828	204	8,472	1,435	120,922	140,857	15,360	6,669	118,828	140,857
	0.01%	**0.02%**	**0.10%**	**0.00%**	**0.11%**	**0.02%**	**1.56%**	**1.82%**	**0.20%**	**0.09%**	**1.54%**	**1.82%**
	0.37%	*1.05%*	*5.56%*	*0.14%*	*6.01%*	*1.02%*	*85.85%*	*100.00%*	*10.90%*	*4.73%*	*84.36%*	*100.00%*
	0.75%	0.25%	0.62%	0.50%	0.17%	1.06%	18.91%	1.82%	0.24%	0.88%	19.37%	1.82%
Total	68,797	597,098	1,252,923	41,203	4,999,291	135,373	639,303	7,733,988	6,366,774	753,811	613,404	7,733,989
	0.89%	**7.72%**	**16.20%**	**0.53%**	**64.64%**	**1.75%**	**8.27%**	**100.00%**	**82.32%**	**9.75%**	**7.93%**	**100.00%**
	0.89%	*7.72%*	*16.20%*	*0.53%*	*64.64%*	*1.75%*	*8.27%*	*100.00%*	*82.32%*	*9.75%*	*7.93%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 16B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	14,926	14,360	22,744	1,020	155,074	26,040	139,416	373,580	1,300,142
	1.98%	**1.90%**	**3.02%**	**0.14%**	**20.57%**	**3.45%**	**18.49%**	**49.56%**	**16.81%**
	4.00%	*3.84%*	*6.09%*	*0.27%*	*41.51%*	*6.97%*	*37.32%*	*100.00%*	*36.90%*
	49.29%	50.07%	29.29%	51.26%	52.32%	54.91%	51.37%	49.56%	48.82%
Male	15,188	14,201	54,648	933	140,538	21,269	126,785	373,562	1,345,602
	2.01%	**1.88%**	**7.25%**	**0.12%**	**18.64%**	**2.82%**	**16.82%**	**49.56%**	**17.40%**
	4.07%	*3.80%*	*14.63%*	*0.25%*	*37.62%*	*5.69%*	*33.94%*	*100.00%*	*33.07%*
	50.15%	49.52%	70.38%	46.88%	47.42%	44.85%	46.72%	49.56%	50.53%
Unknown	171	116	260	37	778	114	5,193	6,669	17,434
	0.02%	**0.02%**	**0.03%**	**0.00%**	**0.10%**	**0.02%**	**0.69%**	**0.88%**	**0.23%**
	2.56%	*1.74%*	*3.90%*	*0.55%*	*11.67%*	*1.71%*	*77.87%*	*100.00%*	*12.38%*
	0.56%	0.40%	0.33%	1.86%	0.26%	0.24%	1.91%	0.88%	0.65%
Total	30,285	28,677	77,652	1,990	296,390	47,423	271,394	753,811	2,663,178
	4.02%	**3.80%**	**10.30%**	**0.26%**	**39.32%**	**6.29%**	**36.00%**	**100.00%**	**34.43%**
	4.02%	*3.80%*	*10.30%*	*0.26%*	*39.32%*	*6.29%*	*36.00%*	*100.00%*	*34.43%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 16C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 375

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	237	1,679	6,568	4,553	53,370	6,533	72,940	13,037
	0.16%	**1.11%**	**4.33%**	**3.00%**	**35.19%**	**4.31%**	**48.09%**	**8.60%**
	0.32%	*2.30%*	*9.00%*	*6.24%*	*73.17%*	*8.96%*	*100.00%*	*17.87%*
	50.21%	49.50%	49.51%	46.01%	47.71%	51.06%	48.09%	48.24%
Male	235	1,700	6,694	5,341	58,312	6,072	78,354	13,970
	0.15%	**1.12%**	**4.41%**	**3.52%**	**38.44%**	**4.00%**	**51.66%**	**9.21%**
	0.30%	*2.17%*	*8.54%*	*6.82%*	*74.42%*	*7.75%*	*100.00%*	*17.83%*
	49.79%	50.12%	50.46%	53.97%	52.13%	47.46%	51.66%	51.69%
Unknown	0	13	4	2	174	190	383	19
	0.000%	**0.01%**	**0.00%**	**0.00%**	**0.11%**	**0.13%**	**0.25%**	**0.01%**
	0.00%	*3.39%*	*1.04%*	*0.52%*	*45.43%*	*49.61%*	*100.00%*	*4.96%*
	0.00%	0.38%	0.03%	0.02%	0.16%	1.48%	0.25%	0.07%
Total	472	3,392	13,266	9,896	111,856	12,795	151,677	27,026
	0.31%	**2.24%**	**8.75%**	**6.52%**	**73.75%**	**8.44%**	**100.00%**	**17.82%**
	0.31%	*2.24%*	*8.75%*	*6.52%*	*73.75%*	*8.44%*	*100.00%*	*17.82%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 16 Comments

Sex/Gender

Excluding sex-specific studies, the number of males (4,147,836 or 52.60%) exceeded the number of females (3,596,589 or 46.61%) enrolled in Extramural Research Protocols.

Excluding sex-specific studies, the number of minority females (1,359,572 or 50.54%) exceeded the number of minority males (1,313,179 or 48.81%) enrolled in Extramural Research Protocols.

Race

Approximately 34.12% (2,690,204) of participants in aggregate extramural research (7,885,665 total) were classified as U.S. minorities.

Largest identified racial group was White at 73.75% following the 1977 OMB standards and 64.64% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 8.75% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 16.20% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.31%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.53%.

Ethnicity

9.75% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was White at 39.32% (2nd largest category is Unknown/Other at 36.00%).

Smallest identified racial group was Hawaiian/Pacific Islanders at 0.26% .

Of the 753,811 participants, 49.56% were women and 49.56% were men.

6.52% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 17

Overview of NIH Phase III Extramural and Intramural Clinical Research Reported In FY 2007: Number of Sex-Specific Protocols and Enrollment and Domestic versus Foreign Protocols

Table 17A. Protocols Reported

		Domestic				Foreign			
	Total of Phase III Clinical Trials*	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Protocols reporting female only	121	111	91.7%	4	3.3%	5	4.1%	1	0.8%
%	16.2%	16.8%		11.8%		10.0%		25.0%	
Protocols reporting male only	41	40	97.6%	0	0.0%	1	2.4%	0	0.0%
%	5.5%	6.1%		0.0%		2.0%		0.0%	
Protocols with both female and male enrollment (excluding sex-specific protocols)	491	426	86.8%	28	5.7%	34	6.9%	3	0.6%
%	65.6%	64.4%		82.4%		68.0%		75.0%	
Total Number of Protocols With Enrollment	**653**	**577**	**88.4%**	**32**	**4.9%**	**40**	**6.1%**	**4**	**0.6%**
%	87.2%	87%		94.1%		80.0%		100.0%	
Phase III protocols with zero enrollment. (Enrollment data has not yet been submitted.)	96	84	87.5%	2	2.1%	10	10.4%	0	0.0%
%	12.8%	12.7%		5.9%		20.0%		0.0%	
Total Number of Phase III Protocols	**749**	**661**	**88.3%**	**34**	**4.5%**	**50**	**6.7%**	**4**	**0.5%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Number of Protocols with Enrollment

1. Female-Only Protocols: There were 121 protocols reporting females only, representing 18.5% of protocols with enrollment.
   116 (95.8%) were Extramural Protocols; 5 (3.4%) were NIH Intramural Protocols.

   40 (97.6%) were Domestic Protocols; 1 (2.4%) were Foreign Protocols.

2. Male-Only Protocols: There were 41 protocols reporting males only, representing 0.6% of protocols with enrollment.
   41 (100%) were Extramural Protocols; there were no NIH Intramural Protocols.

   40 (97.6%) were Domestic Protocols; 1 (2.4%) were Foreign Protocols.

3. Protocols Reporting Both Females and Males (excluding sex-specific protocols): There were 491 protocols reporting both female and male participants representing 75.2% of protocols with enrollment.
   460 (93.7%) were Extramural protocols; 31 (6.3%) were NIH Intramural protocols.

   454 (92.5%) were Domestic Protocols; 36 (7.5%) were Foreign Protocols.

Table 17B. Enrollment Reported

		Domestic				Foreign			
	Total of Phase III Trials*	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Protocols reporting female only	181,625	144,902	79.8%	7	0.0%	29,707	16.4%	7,009	3.9%
%	30.7%	36.7%		0.0%		19.4%		70.3%	
Protocols reporting male only	79,434	76,650	96.5%	0	0.0%	2,784	3.5%	0	0.0%
%	13.4%	19.4%		0.0%		1.8%		0.0%	
Protocols excluding female-only and male-only enrollment protocols	330,100	173,384	52.5%	33,497	10.1%	120,260	36.4%	2,959	0.9%
%	55.8%	43.9%		100.0%		78.7%		29.7%	
Total Subjects Enrolled	**591,159**	**394,936**	**66.8%**	**33,504**	**5.67%**	**152,751**	**25.84%**	**9,968**	**1.7%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Enrollment Reported

1. In Female-Only Protocols: There were approximately 181,625 females, representing 30.7% of total enrollment.
   174,609 (96.2%) were in Extramural Protocols; 7,016 (3.9%) were in NIH Intramural Protocols.

   144,909 (79.8%) were Domestic Protocols, 36,716 (20.3%) were Foreign Protocols.

2. In Male-Only Protocols: There were approximately 377,803 males, representing 2.2% of total enrollment.
   79,434 (100%) were in Extramural Protocols; there were no NIH Intramural Protocols.

   76,650 (96.5%) were Domestic Protocols; 2,784 (3.5%) were Foreign Protocols.

3. In Protocols reporting Both Females and Males (excluding sex-specific studies): There were approximately 330,100 subjects, representing 5.1% of total enrollment.
   293,644 (88.9%) were in Extramural Protocols; 36,456 (11%) were in NIH Intramural Protocols.

   206,881 (62.6%) were Domestic Protocols, 123,219 (36.4%) were Foreign Protocols.

Table 17C. Minority Enrollment Reported

		Domestic				Foreign			
	Total of Phase III Clinical Trials*	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Minority Totals for All Phase III Studies	244,932	83,634	34.1%	4,705	1.9%	149,424	61.0%	7,169	2.9%
% Minority Enrollment	41.4%	21.2%		14.0%		97.8%		71.9%	

Total Minority Enrollment: 41% of Total Enrollment (244,932/591,159)

Total Domestic Minority Enrollment: 36% of Minority Enrollment (88,339/244,932).

Total Foreign Minority Enrollment: 63% of Minority Enrollment (156,593/244,932).

Total Domestic Minority Enrollment (Extramural + Intramural): 15% of Total Enrollment (88,339/591,159).

Total Foreign Minority Enrollment (Extramural + Intramural): 26% of Total Enrollment (156,593/591,159).

Total Minority Enrollment in all Extramural projects (Domestic + Foreign): 39% of Total Enrollment (233,058/591,159).

Total Minority Enrollment in all Intramural projects (Domestic + Foreign): 2% of Total Enrollment (11,874/591,159).

*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.

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

TABLE 18

Aggregate Enrollment Data for Extramural Phase III Research Protocols Funded in FY 2006 and Reported in FY 2007: Percent Analysis

Table 18A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 585

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	301,735	134,342		44.52%
%	55.10%	57.64%		
Males	229,062	97,934		42.75%
%	41.83%	42.02%		
Unknown	16,830	794		4.72%
%	3.07%	0.34%		
TOTAL	**547,627**	**233,070**	**42.56%**	
Total %	100%	100.00%		

Table18B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 399

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	5,069	22,153	45,059	263	64,693	1,822	55,182	194,241	125,448	47,629	21,164	194,241
	1.41%	**6.15%**	**12.51%**	**0.07%**	**17.96%**	**0.51%**	**15.32%**	**53.91%**	**34.82%**	**13.22%**	**5.87%**	**53.91%**
	2.61%	*11.40%*	*23.20%*	*0.14%*	*33.31%*	*0.94%*	*28.41%*	*100.00%*	*64.58%*	*24.52%*	*10.90%*	*100.00%*
	54.34%	46.98%	53.88%	54.45%	52.36%	49.70%	59.67%	53.91%	51.37%	74.34%	40.66%	53.91%
Male	4,213	24,969	38,165	218	58,552	1,772	21,366	149,255	117,914	16,176	15,165	149,255
	1.17%	**6.93%**	**10.59%**	**0.06%**	**16.25%**	**0.49%**	**5.93%**	**41.42%**	**32.73%**	**4.49%**	**4.21%**	**41.42%**
	2.82%	*16.73%*	*25.57%*	*0.15%*	*39.23%*	*1.19%*	*14.32%*	*100.00%*	*79.00%*	*10.84%*	*10.16%*	*100.00%*
	45.17%	52.95%	45.64%	45.13%	47.39%	48.34%	23.10%	41.42%	48.29%	25.25%	29.14%	41.42%
Unknown	46	35	405	2	319	72	15,930	16,809	825	267	15,717	16,809
	0.01%	**0.01%**	**0.11%**	**0.00%**	**0.09%**	**0.02%**	**4.42%**	**4.67%**	**0.23%**	**0.07%**	**4.36%**	**4.67%**
	0.27%	*0.21%*	*2.41%*	*0.01%*	*1.90%*	*0.43%*	*94.77%*	*100.00%*	*4.91%*	*1.59%*	*93.50%*	*100.00%*
	0.49%	0.07%	0.48%	0.41%	0.26%	1.96%	17.23%	4.67%	0.34%	0.42%	30.20%	4.67%
Total	9,328	47,157	83,629	483	123,564	3,666	92,478	360,305	244,187	64,072	52,046	360,305
	2.59%	**13.09%**	**23.21%**	**0.13%**	**34.29%**	**1.02%**	**25.67%**	**100.00%**	**67.77%**	**17.78%**	**14.44%**	**100.00%**
	2.59%	*13.09%*	*23.21%*	*0.13%*	*34.29%*	*1.02%*	*25.67%*	*100.00%*	*67.77%*	*17.78%*	*14.44%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 18B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	3,847	21	234	16	4,492	174	38,845	47,629	117,703
	6.00%	**0.03%**	**0.37%**	**0.02%**	**7.01%**	**0.27%**	**60.63%**	**74.34%**	**32.67%**
	8.08%	*0.04%*	*0.49%*	*0.03%*	*9.43%*	*0.37%*	*81.56%*	*100.00%*	*60.60%*
	52.60%	50.00%	56.93%	76.19%	64.41%	54.21%	79.29%	74.34%	58.78%
Male	3433	21	177	5	2,482	146	9,912	16,176	81,731
	5.36%	**0.03%**	**0.28%**	**0.01%**	**3.87%**	**0.23%**	**15.47%**	**25.25%**	**22.68%**
	21.22%	*0.13%*	*1.09%*	*0.03%*	*15.34%*	*0.90%*	*61.28%*	*100.00%*	*54.76%*
	46.94%	50.00%	43.07%	23.81%	35.59%	45.48%	20.23%	25.25%	40.82%
Unknown	33	0	0	0	0	1	233	267	793
	0.05%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.36%**	**0.42%**	**0.22%**
	12.36%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.37%*	*87.27%*	*100.00%*	*4.72%*
	0.45%	0.00%	0.00%	0.00%	0.00%	0.31%	0.48%	0.42%	0.40%
Total	7,313	42	411	21	6,974	321	48,990	64,072	200,227
	11.41%	**0.07%**	**0.64%**	**0.03%**	**10.88%**	**0.50%**	**76.46%**	**100.00%**	**55.57%**
	11.41%	*0.07%*	*0.64%*	*0.03%*	*10.88%*	*0.50%*	*76.46%*	*100.00%*	*55.57%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 18C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 186

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	415	2,190	10,067	3,967	88,698	2,157	107,494	16,639
	0.22%	**1.17%**	**5.37%**	**2.12%**	**47.35%**	**1.15%**	**57.38%**	**8.88%**
	0.39%	*2.04%*	*9.37%*	*3.69%*	*82.51%*	*2.01%*	*100.00%*	*15.48%*
	57.24%	62.64%	50.83%	44.99%	59.01%	51.80%	57.38%	50.66%
Male	310	1,306	9,736	4,851	61,601	2,003	79,807	16,203
	0.17%	**0.70%**	**5.20%**	**2.59%**	**32.89%**	**1.07%**	**42.60%**	**8.65%**
	0.39%	*1.64%*	*12.20%*	*6.08%*	*77.19%*	*2.51%*	*100.00%*	*20.30%*
	42.76%	37.36%	49.16%	55.01%	40.98%	48.10%	42.60%	49.33%
Unknown	0	0	1	0	16	4	21	1
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	**0.01%**	**0.00%**
	0.00%	*0.00%*	*4.76%*	*0.00%*	*76.19%*	*19.05%*	*100.00%*	*4.76%*
	0.00%	0.00%	0.01%	0.00%	0.01%	0.10%	0.01%	0.00%
Total	725	3,496	19,804	8,818	150,315	4,164	187,322	32,843
	0.39%	**1.87%**	**10.57%**	**4.71%**	**80.24%**	**2.22%**	**100.00%**	**17.53%**
	0.39%	*1.87%*	*10.57%*	*4.71%*	*80.24%*	*2.22%*	*100.00%*	*17.53%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 18 Comments

Sex/Gender

More females (301,735 or 55.10%) than males (229,062 or 41.83%) were enrolled in aggregate Phase III Extramural Research Protocols.

More minority females (134,342 or 57.64%) than males (97,934 or 42.02%) were enrolled in aggregate Phase III Extramural Research Protocols.

Race

Approximately 42.56% (233,070) of participants in aggregate Phase III Extramural Research (547,627 total) were classified as U.S. minorities.

Largest identified racial group was White at 80.24% following the 1977 OMB standards and 32.99% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 10.57% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 23.21% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.39%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.13%.

Ethnicity

About 17.78% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was Unknown/Other at 76.46% (2nd largest category was American Indian/Alaska Native at 11.41%)

Smallest identified racial group was Hawaiian/Pacific Islander at 0.07%.

Of the 187,322 participants, 57.38% were women and 42.60% were men.

About 4.71% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 19

Overview of NIH Phase III Extramural and Intramural Clinical Research Reported in FY 2008: Number of Sex-Specific Protocols and Enrollment and Domestic versus Foreign Protocols

Table 19A. Protocols Reported

		Domestic				Foreign			
	Total of Phase III Clinical Trials*	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Protocols reporting female only	126	111	88.1%	4	3.2%	10	7.9%	1	0.8%
%	17.1%	17.5%		11.4%		16.7%		25.0%	
Protocols reporting male only	42	40	95.2%	0	0.0%	2	4.8%	0	0.0%
%	5.7%	6.3%		0.0%		3.3%		0.0%	
Protocols with both female and male enrollment (excluding sex-specific protocols)	471	401	85.1%	29	6.2%	38	8.1%	3	0.6%
%	64.1%	63.1%		82.9%		63.3%		75.0%	
Total Number of Protocols With Enrollment	**639**	**552**	**86.4%**	**33**	**5.2%**	**50**	**7.8%**	**4**	**0.6%**
%	86.9%	87%		94.3%		83.3%		100.0%	
Phase III protocols with zero enrollment. (Enrollment data has not yet been submitted.)	96	84	87.5%	2	2.1%	10	10.4%	0	0.0%
%	13.1%	13.2%		5.7%		16.7%		0.0%	
Total Number of Phase III Protocols	**735**	**636**	**86.5%**	**35**	**4.8%**	**60**	**8.2%**	**4**	**0.5%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Number of Protocols

1. Female-Only: There were 126 protocols reporting females only, representing 19.7% of protocols with enrollment and 17.1% of the Total Number of Protocols.

   96% were Extramural Protocols (121); 4% were NIH Intramural Protocols (5).

   91% were Domestic Protocols (115); 9% were Foreign Protocols (11).

2. Male-Only Protocols: There were 42 protocols reporting males only, representing 6.6% (42/639) of protocols with enrollment and 5.7% of Total Number of Protocols.

   100% were Extramural Protocols (42); 0% were NIH Intramural Protocols (0).

   95% were Domestic Protocols (40); 5% were Foreign Protocols (2).

3. Protocols Reporting Both Females and Males (excluding sex-specific protocols): There were 471 protocols reporting both males and females representing 64% of the total number of protocols.

   93% were Extramural Protocols (439); 7% were NIH Intramural Protocols (32).

   91% were Domestic Protocols (430); 9% were Foreign Protocols (41).

Table 19B. Enrollment Reported

		Domestic				Foreign			
	Total of Phase III Clinical Trials*	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Protocols reporting female only	219,673	199,371	90.8%	9	0.0%	12,827	5.8%	7,466	3.4%
%	27.7%	34.1%		0.1%		6.7%		71.4%	
Protocols reporting male only	79,613	76,378	95.9%	159	0.2%	3,076	3.9%	0	0.0%
%	10.0%	13.1%		2.6%		1.6%		0.0%	
Protocols excluding female-only and male-only enrollment protocols	493,292	309,274	62.7%	5,914	1.2%	175,108	35.5%	2,996	0.6%
%	62.2%	52.9%		97.2%		91.7%		28.6%	
Total Subjects Enrolled	**792,578**	**585,023**	**73.8%**	**6,082**	**0.77%**	**191,011**	**24.10%**	**10,462**	**1.3%**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

Total Enrollment Reported

1. In Female-Only Protocols: There were approximately 219,673 females, representing 27.7% of total enrollment.
   96.6% (212,198) were in Extramural Protocols; 3.4% (7,475) were in NIH Intramural Protocols.

   90.8% (199,380) were in Domestic Protocols; 9.2% (20,193) were in Foreign Protocols.

2. In Male-Only Protocols: There were approximately 79,613 males, representing 10.0% of total enrollment.
   99.8% (79,454) were in Extramural Protocols; 0.2% (159) were in NIH Intramural Protocols.

   96.1% (76,537) were in Domestic Protocols; 3.9% (3,076) were in Foreign Protocols.

3. In Protocols reporting Both Females and Males (excluding sex-specific studies): There were approximately 493,292 subjects, representing 62.2% of total enrollment.
   98.2% (484,382) were in Extramural Protocols; 1.8% (8,910) were in NIH Intramural Protocols.

   63.9% (315,188) were in Domestic Protocols; 36.1% (178,104) were in Foreign Protocols.

Table 19C. Minority Enrollment Reported

		Domestic				Foreign			
	Total of Phase III Clinical Trials*	**Extramural**	**%**	**Intramural**	**%**	**Extramural**	**%**	**Intramural**	**%**
Minority Totals for all Phase III studies	308,433	117,869	38.2%	1,713	0.6%	181,188	58.7%	7,663	2.5%
% Minority Enrollment	38.9%	20.1%		28.2%		94.9%		73.2%	

1. Total Minority Enrollment: 38.9% (308,433) of Total Enrollment (792,578)
   Total Minority Enrollment, Extramural projects (299,057) was 37.7% of Total Enrollment (792,578) and 97.0% of Total Minority Enrollment (308,433).

   Total Minority Enrollment, Intramural projects (9,376), was 1.2% of Total Enrollment (792,578) and 3.0% of Total Minority Enrollment (308,433).

2. Total Minority Enrollment, Domestic Only (119,582), was 20.2% of total Domestic Enrollment (591,105) and 38.8% of Total Minority Enrollment (308,433).
3. Total Minority Enrollment, Foreign Only (188,851), was 93.7% of total Foreign Enrollment (201,473) and 61.2% of Total Minority Enrollment (308,433).

* 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.

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

TABLE 20

Aggregate Enrollment Data for Extramural Phase III Research Protocols Funded in FY 2007 and Reported in FY 2008: Percent Analysis

Table 20A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 605

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	444,079	161,091		36.28%
%	57.22%	53.87%		
Males	314,948	137,069		43.52%
%	40.58%	45.84%		
Unknown	17,007	882		5.19%
%	2.19%	0.29%		
TOTAL	**776,034**	**299,042**	**38.53%**	
Total %	100%	100.00%		

Table 20B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 452

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	7,618	49,108	54,738	336	151,809	6,536	13,129	283,274	243,922	29,653	9,699	283,274
	1.39%	**8.98%**	**10.01%**	**0.06%**	**27.77%**	**1.20%**	**2.40%**	**51.82%**	**44.62%**	**5.42%**	**1.77%**	**51.82%**
	2.69%	*17.34%*	*19.32%*	*0.12%*	*53.59%*	*2.31%*	*4.63%*	*100.00%*	*86.11%*	*10.47%*	*3.42%*	*100.00%*
	50.79%	51.60%	53.61%	52.58%	54.22%	53.87%	31.52%	51.82%	53.22%	52.25%	30.68%	51.82%
Male	7,328	45,963	47,069	299	126,943	5,472	13,366	246,440	212,880	26,676	6,884	246,440
	1.34%	**8.41%**	**8.61%**	**0.05%**	**23.22%**	**1.00%**	**2.44%**	**45.08%**	**38.94%**	**4.88%**	**1.26%**	**45.08%**
	2.97%	*18.65%*	*19.10%*	*0.12%*	*51.51%*	*2.22%*	*5.42%*	*100.00%*	*86.38%*	*10.82%*	*2.79%*	*100.00%*
	48.86%	48.29%	46.10%	46.79%	45.34%	45.10%	32.09%	45.08%	46.45%	47.00%	21.78%	45.08%
Unknown	53	103	294	4	1,257	124	15,152	16,987	1,536	425	15,026	16,987
	0.01%	**0.02%**	**0.05%**	**0.00%**	**0.23%**	**0.02%**	**2.77%**	**3.11%**	**0.28%**	**0.08%**	**2.75%**	**3.11%**
	0.31%	*0.61%*	*1.73%*	*0.02%*	*7.40%*	*0.73%*	*89.20%*	*100.00%*	*9.04%*	*2.50%*	*88.46%*	*100.00%*
	0.35%	0.11%	0.29%	0.63%	0.45%	1.02%	36.38%	3.11%	0.34%	0.75%	47.54%	3.11%
Total	14,999	95,174	102,101	639	280,009	12,132	41,647	546,701	458,338	56,754	31,609	546,701
	2.74%	**17.41%**	**18.68%**	**0.12%**	**51.22%**	**2.22%**	**7.62%**	**100.00%**	**83.84%**	**10.38%**	**5.78%**	**100.00%**
	2.74%	*17.41%*	*18.68%*	*0.12%*	*51.22%*	*2.22%*	*7.62%*	*100.00%*	*83.84%*	*10.38%*	*5.78%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 20B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	6,524	95	337	65	12,607	3,170	6,855	29,653	137,798
	11.50%	**0.17%**	**0.59%**	**0.11%**	**22.21%**	**5.59%**	**12.08%**	**52.25%**	**25.21%**
	22.00%	*0.32%*	*1.14%*	*0.22%*	*42.52%*	*10.69%*	*23.12%*	*100.00%*	*48.64%*
	49.97%	41.67%	47.13%	53.28%	56.32%	56.01%	46.98%	52.25%	52.59%
Male	6,489	126	370	54	9,665	2428	7544	26,676	123,340
	11.43%	**0.22%**	**0.65%**	**0.10%**	**17.03%**	**4.28%**	**13.29%**	**47.00%**	**22.56%**
	24.33%	*0.47%*	*1.39%*	*0.20%*	*36.23%*	*9.10%*	*28.28%*	*100.00%*	*50.05%*
	49.71%	55.26%	51.75%	44.26%	43.18%	42.90%	51.70%	47.00%	47.07%
Unknown	42	7	8	3	111	62	192	425	881
	0.07%	**0.01%**	**0.01%**	**0.01%**	**0.20%**	**0.11%**	**0.34%**	**0.75%**	**0.16%**
	9.88%	*1.65%*	*1.88%*	*0.71%*	*26.12%*	*14.59%*	*45.18%*	*100.00%*	*5.19%*
	0.32%	3.07%	1.12%	2.46%	0.50%	1.10%	1.32%	0.75%	0.34%
Total	13,055	228	715	122	22,383	5,660	14,591	56,754	262,019
	23.00%	**0.40%**	**1.26%**	**0.21%**	**39.44%**	**9.97%**	**25.71%**	**100.00%**	**47.93%**
	23.00%	*0.40%*	*1.26%*	*0.21%*	*39.44%*	*9.97%*	*25.71%*	*100.00%*	*47.93%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 20C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 153

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	652	3,449	13,516	5,676	134,866	2,646	160,805	23,293
	0.28%	**1.50%**	**5.89%**	**2.48%**	**58.81%**	**1.15%**	**70.12%**	**10.16%**
	0.41%	*2.14%*	*8.41%*	*3.53%*	*83.87%*	*1.65%*	*100.00%*	*14.49%*
	72.85%	77.02%	61.21%	59.33%	71.71%	62.35%	70.12%	62.91%
Male	243	1,029	8,566	3,891	53,192	1,587	68,508	13,729
	0.11%	**0.45%**	**3.74%**	**1.70%**	**23.19%**	**0.69%**	**29.87%**	**5.99%**
	0.35%	*1.50%*	*12.50%*	*5.68%*	*77.64%*	*2.32%*	*100.00%*	*20.04%*
	27.15%	22.98%	38.79%	40.67%	28.28%	37.39%	29.87%	37.08%
Unknown	0	0	1	0	8	11	20	1
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**
	0.00%	*0.00%*	*5.00%*	*0.00%*	*40.00%*	*55.00%*	*100.00%*	*5.00%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.26%	0.01%	0.00%
Total	895	4,478	22,083	9,567	188,066	4,244	229,333	37,023
	0.39%	**1.95%**	**9.63%**	**4.17%**	**82.01%**	**1.85%**	**100.00%**	**16.14%**
	0.39%	*1.95%*	*9.63%*	*4.17%*	*82.01%*	*1.85%*	*100.00%*	*16.14%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 20 Comments

Sex/Gender

More females (444,079 or 57.22%) than males (314,948 or 40.58%) were enrolled in aggregate Phase III Extramural Research Protocols.

More minority females (161,091 or 53.87%) than males (137,069 or 45.84%) were enrolled in aggregate Phase III Extramural Research Protocols.

Race

Approximately 38.53% (299,042) of participants in aggregate Phase III Extramural Research (776,034 total) were classified as U.S. minorities.

Largest identified racial group was White at 82.01% following the 1977 OMB standards and 51.22% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 9.63% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 18.68% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.39%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.12%.

Ethnicity

About 10.38% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was White at 39.44%; (2nd largest category was Unknown/ Other at 25.71%).

Smallest identified racial group was Hawaiian/Pacific Islander at 0.21%.

Of the 56,754 participants, 52.25% were women and 47.00% were men.

About 4.17% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 21

Aggregate Enrollment Data for Intramural Research Protocols Funded in FY 2006 and Reported in FY 2007: Percent Analysis

Table 21A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 1,552

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	1,499,945	395,722		26.38%
%	43.39%	48.34%		
Males	1,915,898	421,306		21.99%
%	55.42%	51.47%		
Unknown	41,333	1,518		3.67%
%	1.20%	0.19%		
TOTAL	**3,457,176**	**818,546**	**23.68%**	
Total %	100%	100.00%		

Table 21B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 1,103

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	10,730	124,260	55,037	3,467	716,439	9,823	65,286	985,042	888,411	56,223	40,408	985,042
	0.44%	**5.09%**	**2.26%**	**0.14%**	**29.37%**	**0.40%**	**2.68%**	**40.38%**	**36.41%**	**2.30%**	**1.66%**	**40.38%**
	1.09%	*12.61%*	*5.59%*	*0.35%*	*72.73%*	*1.00%*	*6.63%*	*100.00%*	*90.19%*	*5.71%*	*4.10%*	*100.00%*
	49.30%	66.48%	23.21%	86.39%	42.04%	71.83%	23.99%	40.38%	42.59%	54.98%	16.07%	40.38%
Male	11,014	61,936	182,077	546	984,999	3,084	169,715	1,413,371	1,194,236	46,009	173,126	1,413,371
	0.45%	**2.54%**	**7.46%**	**0.02%**	**40.37%**	**0.13%**	**6.96%**	**57.93%**	**48.95%**	**1.89%**	**7.10%**	**57.93%**
	0.78%	*4.38%*	*12.88%*	*0.04%*	*69.69%*	*0.22%*	*12.01%*	*100.00%*	*84.50%*	*3.26%*	*12.25%*	*100.00%*
	50.60%	33.14%	76.78%	13.61%	57.80%	22.55%	62.36%	57.93%	57.25%	45.00%	68.84%	57.93%
Unknown	22	706	15	0	2,595	769	37,169	41,276	3289	20	37,967	41,276
	0.00%	**0.03%**	**0.00%**	**0.00%**	**0.11%**	**0.03%**	**1.52%**	**1.69%**	**0.13%**	**0.00%**	**1.56%**	**1.69%**
	0.05%	*1.71%*	*0.04%*	*0.00%*	*6.29%*	*1.86%*	*90.05%*	*100.00%*	*7.97%*	*0.05%*	*91.98%*	*100.00%*
	0.10%	0.38%	0.01%	0.00%	0.15%	5.62%	13.66%	1.69%	0.16%	0.02%	15.10%	1.69%
Total	21,766	186,902	237,129	4,013	1,704,033	13,676	272,170	2,439,689	2,085,936	102,252	251,501	2,439,689
	0.89%	**7.66%**	**9.72%**	**0.16%**	**69.85%**	**0.56%**	**11.16%**	**100.00%**	**85.50%**	**4.19%**	**10.31%**	**100.00%**
	0.89%	*7.66%*	*9.72%*	*0.16%*	*69.85%*	*0.56%*	*11.16%*	*100.00%*	*85.50%*	*4.19%*	*10.31%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 21B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	1200	14	332	40	25,628	1,875	27,134	56,223	256,079
	1.17%	**0.01%**	**0.32%**	**0.04%**	**25.06%**	**1.83%**	**26.54%**	**54.98%**	**10.50%**
	2.13%	*0.02%*	*0.59%*	*0.07%*	*45.58%*	*3.33%*	*48.26%*	*100.00%*	*26.00%*
	48.98%	43.75%	11.48%	70.18%	44.81%	54.19%	75.03%	54.98%	45.99%
Male	1234	18	2559	17	31,570	1,585	9,026	46,009	299,253
	1.21%	**0.02%**	**2.50%**	**0.02%**	**30.87%**	**1.55%**	**8.83%**	**45.00%**	**12.27%**
	2.68%	*0.04%*	*5.56%*	*0.04%*	*68.62%*	*3.44%*	*19.62%*	*100.00%*	*21.17%*
	50.37%	56.25%	88.52%	29.82%	55.19%	45.81%	24.96%	45.00%	53.74%
Unknown	16	0	0	0	0	0	4	20	1,516
	0.02%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.02%**	**0.06%**
	80.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*20.00%*	*100.00%*	*3.67%*
	0.65%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%	0.02%	0.27%
Total	2,450	32	2,891	57	57,198	3,460	36,164	102,252	556,848
	2.40%	**0.03%**	**2.83%**	**0.06%**	**55.94%**	**3.38%**	**35.37%**	**100.00%**	**22.82%**
	2.40%	*0.03%*	*2.83%*	*0.06%*	*55.94%*	*3.38%*	*35.37%*	*100.00%*	*22.82%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 21C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 449

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	876	19,092	96,523	23,152	369,148	6,112	514,903	139,643
	0.09%	**1.88%**	**9.49%**	**2.28%**	**36.28%**	**0.60%**	**50.61%**	**13.72%**
	0.17%	*3.71%*	*18.75%*	*4.50%*	*71.69%*	*1.19%*	*100.00%*	*27.12%*
	0.00%	51.47%	53.92%	52.74%	49.59%	53.85%	50.61%	53.36%
Male	822	17,999	82,489	20,743	375,273	5,201	502,527	122,053
	0.08%	**1.77%**	**8.11%**	**2.04%**	**36.88%**	**0.51%**	**49.39%**	**12.00%**
	0.16%	*3.58%*	*16.41%*	*4.13%*	*74.68%*	*1.03%*	*100.00%*	*24.29%*
	0.00%	48.53%	46.08%	47.25%	50.41%	45.83%	49.39%	46.64%
Unknown	0	0	1	1	19	36	57	2
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**
	0.00%	*0.00%*	*1.75%*	*1.75%*	*33.33%*	*63.16%*	*100.00%*	*3.51%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.32%	0.01%	0.00%
Total	1,698	37,091	179,013	43,896	744,440	11,349	1,017,487	261,698
	0.17%	**3.65%**	**17.59%**	**4.31%**	**73.16%**	**1.12%**	**100.00%**	**25.72%**
	0.17%	*3.65%*	*17.59%*	*4.31%*	*73.16%*	*1.12%*	*100.00%*	*25.72%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 21 Comments

Sex/Gender

More males (1,915,298 or 55.42%) than females (1,499,945 or 43.39%) were enrolled in aggregate Intramural Research Protocols.

More minority males (421,306 or 51.47%) than females (395,722 or 48.34%) were enrolled in aggregate Intramural Research Protocols.

Race

Approximately 23.68% (818,546) of participants in aggregate Intramural Research (3,457,176 total) were classified as U.S. minorities.

Largest identified racial group was White at 73.16% following the 1977 OMB standards and 69.85% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 17.59% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 9.72% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.17%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.16%.

Ethnicity

4.19% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was White at 55.94% (2nd largest category Unknown/Other at 35.37%).

Smallest identified racial group was Asian at 0.03%.

Of the 102,252 participants, 54.98% were women and 45.00% were men.

4.31% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 22

Aggregate Enrollment Data for Intramural Research Protocols Funded in FY 2007 and Reported in FY 2008: Percent Analysis

Table 22A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 1,664

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	1,214,079	349,293		28.77%
%	42.82%	48.43%		
Males	1,585,861	371,373		23.42%
%	55.93%	51.50%		
Unknown	35,546	515		1.45%
%	1.25%	0.07%		
TOTAL	**2,835,486**	**721,181**	**25.43%**	
Total %	100%	100.00%		

Table 22B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 1,251

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	10,523	166,051	61,501	3,985	775,883	11,344	84,101	1,113,388	989,883	60,344	63,161	1,113,388
	0.40%	**6.30%**	**2.33%**	**0.15%**	**29.42%**	**0.43%**	**3.19%**	**42.21%**	**37.53%**	**2.29%**	**2.39%**	**42.21%**
	0.95%	*14.91%*	*5.52%*	*0.36%*	*69.69%*	*1.02%*	*7.55%*	*100.00%*	*88.91%*	*5.42%*	*5.67%*	*100.00%*
	49.31%	64.25%	24.81%	87.43%	43.31%	70.13%	28.24%	42.21%	44.00%	56.20%	22.54%	42.21%
Male	10,786	91,976	186,322	573	1,012,698	4,832	181,472	1,488,659	1,256,314	47,010	185,335	1,488,659
	0.41%	**3.49%**	**7.06%**	**0.02%**	**38.40%**	**0.18%**	**6.88%**	**56.44%**	**47.63%**	**1.78%**	**7.03%**	**56.44%**
	0.72%	*6.18%*	*12.52%*	*0.04%*	*68.03%*	*0.32%*	*12.19%*	*100.00%*	*84.39%*	*3.16%*	*12.45%*	*100.00%*
	50.55%	35.59%	75.17%	12.57%	56.53%	29.87%	60.94%	56.44%	55.84%	43.78%	66.14%	56.44%
Unknown	30	428	48	0	2,800	0	32,217	35,523	3768	17	31,738	35,523
	0.00%	**0.02%**	**0.00%**	**0.00%**	**0.11%**	**0.00%**	**1.22%**	**1.35%**	**0.14%**	**0.00%**	**1.20%**	**1.35%**
	0.08%	*1.20%*	*0.14%*	*0.00%*	*7.88%*	*0.00%*	*90.69%*	*100.00%*	*10.61%*	*0.05%*	*89.34%*	*100.00%*
	0.14%	0.17%	0.02%	0.00%	0.16%	0.00%	10.82%	1.35%	0.17%	0.02%	11.33%	1.35%
Total	21,339	258,455	247,871	4,558	1,791,381	16,176	297,790	2,637,570	2,249,965	107,371	280,234	2,637,570
	0.81%	**9.80%**	**9.40%**	**0.17%**	**67.92%**	**0.61%**	**11.29%**	**100.00%**	**85.30%**	**4.07%**	**10.62%**	**100.00%**
	0.81%	*9.80%*	*9.40%*	*0.17%*	*67.92%*	*0.61%*	*11.29%*	*100.00%*	*85.30%*	*4.07%*	*10.62%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 22B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	86	22	455	50	27,870	3,137	28,724	60,344	309,998
	0.08%	**0.02%**	**0.42%**	**0.05%**	**25.96%**	**2.92%**	**26.75%**	**56.20%**	**11.75%**
	0.14%	*0.04%*	*0.75%*	*0.08%*	*46.19%*	*5.20%*	*47.60%*	*100.00%*	*27.84%*
	58.90%	45.83%	14.45%	65.79%	47.41%	51.19%	73.59%	56.20%	47.97%
Male	52	26	2694	26	30,919	2,991	10,302	47,010	335,710
	0.05%	**0.02%**	**2.51%**	**0.02%**	**28.80%**	**2.79%**	**9.59%**	**43.78%**	**12.73%**
	0.11%	*0.06%*	*5.73%*	*0.06%*	*65.77%*	*6.36%*	*21.91%*	*100.00%*	*22.55%*
	35.62%	54.17%	85.55%	34.21%	52.59%	48.81%	26.39%	43.78%	51.95%
Unknown	8	0	0	0	0	0	9	17	515
	0.01%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.02%**	**0.02%**
	47.06%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*52.94%*	*100.00%*	*1.45%*
	5.48%	0.00%	0.00%	0.00%	0.00%	0.00%	0.02%	0.02%	0.08%
Total	146	48	3,149	76	58,789	6,128	39,035	107,371	646,223
	0.14%	**0.04%**	**2.93%**	**0.07%**	**54.75%**	**5.71%**	**36.36%**	**100.00%**	**24.50%**
	0.14%	*0.04%*	*2.93%*	*0.07%*	*54.75%*	*5.71%*	*36.36%*	*100.00%*	*24.50%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 22C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 413

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	150	3,531	31,362	4,252	59,909	1,487	100,691	39,295
	0.08%	**1.78%**	**15.85%**	**2.15%**	**30.27%**	**0.75%**	**50.88%**	**19.85%**
	0.15%	*3.51%*	*31.15%*	*4.22%*	*59.50%*	*1.48%*	*100.00%*	*39.03%*
	0.00%	52.85%	52.24%	53.50%	49.84%	53.94%	50.88%	52.42%
Male	141	3,150	28,676	3,696	60,287	1,252	97,202	35,663
	0.07%	**1.59%**	**14.49%**	**1.87%**	**30.46%**	**0.63%**	**49.11%**	**18.02%**
	0.15%	*3.24%*	*29.50%*	*3.80%*	*62.02%*	*1.29%*	*100.00%*	*36.69%*
	0.00%	47.15%	47.76%	46.50%	50.16%	45.41%	49.11%	47.58%
Unknown	0	0	0	0	5	18	23	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.01%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*21.74%*	*78.26%*	*100.00%*	*0.00%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.65%	0.01%	0.00%
Total	291	6,681	60,038	7,948	120,201	2,757	197,916	74,958
	0.15%	**3.38%**	**30.34%**	**4.02%**	**60.73%**	**1.39%**	**100.00%**	**37.87%**
	0.15%	*3.38%*	*30.34%*	*4.02%*	*60.73%*	*1.39%*	*100.00%*	*37.87%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 22 Comments

Sex/Gender

More males (1,585,861 or 55.93%) than females (1,214,079 or 42.82%) were enrolled in aggregate Intramural Research Protocols.

More minority males (371,373 or 51.50%) than females (349,293 or 48.43%) were enrolled in aggregate Intramural Research Protocols.

Race

Approximately 25.43% (721,181) of participants in aggregate Intramural Research (2,835,486 total) were classified as U.S. minorities.

Largest identified racial group was White at 60.73% following the 1977 OMB standards and 67.92% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 30.34% following the 1977 OMB standards.

Largest identified racial minority group was Asian at 9.80% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.15%.

According to the 1997 OMB standards, the smallest identified racial minority was Hawaiian/Pacific Islander at 0.17%.

Ethnicity

4.07% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was White at 54.75% (2nd largest category Unknown/Other at 36.36%).

Smallest identified racial group was Asian at 0.04%.

Of the 107,371 participants, 56.20% were women and 43.78% were men.

4.02% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 23

Aggregate Enrollment Data for Intramural Phase III Research Protocols Funded in FY 2006 and Reported in FY 2007: Percent Analysis

Table 23A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 36

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	22,959	9,212		40.12%
%	52.81%	77.58%		
Males	20,511	2,662		12.98%
%	47.18%	22.42%		
Unknown	2	0		0.00%
%	0.00%	0.00%		
TOTAL	**43,472**	**11,874**	**27.31%**	
Total %	100%	100.00%		

Table 23B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 25

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	11	95	544	72	5,366	266	8,523	14,877	6,016	7,307	1,554	14,877
	0.05%	**0.45%**	**2.57%**	**0.34%**	**25.31%**	**1.25%**	**40.21%**	**70.18%**	**28.38%**	**34.47%**	**7.33%**	**70.18%**
	0.07%	*0.64%*	*3.66%*	*0.48%*	*36.07%*	*1.79%*	*57.29%*	*100.00%*	*40.44%*	*49.12%*	*10.45%*	*100.00%*
	47.83%	45.89%	64.84%	100.00%	56.86%	55.53%	84.06%	70.18%	57.27%	96.78%	49.46%	70.18%
Male	12	112	295	0	4,072	213	1,614	6,318	4,489	243	1,586	6,318
	0.06%	**0.53%**	**1.39%**	**0.00%**	**19.21%**	**1.00%**	**7.61%**	**29.81%**	**21.18%**	**1.15%**	**7.48%**	**29.81%**
	0.19%	*1.77%*	*4.67%*	*0.00%*	*64.45%*	*3.37%*	*25.55%*	*100.00%*	*71.05%*	*3.85%*	*25.10%*	*100.00%*
	52.17%	54.11%	35.16%	0.00%	43.14%	44.47%	15.92%	29.81%	42.73%	3.22%	50.48%	29.81%
Unknown	0	0	0	0	0	0	2	2	0	0	2	2
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	**0.00%**	**0.01%**	**0.01%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.02%	0.01%	0.00%	0.00%	0.06%	0.01%
Total	23	207	839	72	9,438	479	10,139	21,197	10,505	7,550	3,142	21,197
	0.11%	**0.98%**	**3.96%**	**0.34%**	**44.53%**	**2.26%**	**47.83%**	**100.00%**	**49.56%**	**35.62%**	**14.82%**	**100.00%**
	0.11%	*0.98%*	*3.96%*	*0.34%*	*44.53%*	*2.26%*	*47.83%*	*100.00%*	*49.56%*	*35.62%*	*14.82%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 23B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	1	0	0	0	2	1	7,303	7,307	8,293
	0.01%	**0.00%**	**0.00%**	**0.00%**	**0.03%**	**0.01%**	**96.73%**	**96.78%**	**39.12%**
	0.01%	*0.00%*	*0.00%*	*0.00%*	*0.03%*	*0.01%*	*99.95%*	*100.00%*	*55.74%*
	100.00%	0.00%	0.00%	0.00%	66.67%	100.00%	96.79%	96.78%	90.46%
Male	0	0	0	0	1	0	242	243	875
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	**3.21%**	**3.22%**	**4.13%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.41%*	*0.00%*	*99.59%*	*100.00%*	*13.85%*
	0.00%	0.00%	0.00%	0.00%	33.33%	0.00%	3.21%	3.22%	9.54%
Unknown	0	0	0	0	0	0	0	0	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Total	1	0	0	0	3	1	7,545	7,550	9,168
	0.01%	**0.00%**	**0.00%**	**0.00%**	**0.04%**	**0.01%**	**99.93%**	**100.00%**	**43.25%**
	0.01%	*0.00%*	*0.00%*	*0.00%*	*0.04%*	*0.01%*	*99.93%*	*100.00%*	*43.25%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%	100.00%	100.00%

Table 23C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 11

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	6	169	570	174	7,132	31	8,082	919
	0.03%	**0.76%**	**2.56%**	**0.78%**	**32.02%**	**0.14%**	**36.28%**	**4.13%**
	0.07%	*2.09%*	*7.05%*	*2.15%*	*88.25%*	*0.38%*	*100.00%*	*11.37%*
	0.00%	37.81%	33.18%	33.79%	36.62%	32.63%	36.28%	33.96%
Male	20	278	1,148	341	12,342	64	14,193	1,787
	0.09%	**1.25%**	**5.15%**	**1.53%**	**55.41%**	**0.29%**	**63.72%**	**8.02%**
	0.14%	*1.96%*	*8.09%*	*2.40%*	*86.96%*	*0.45%*	*100.00%*	*12.59%*
	0.00%	62.19%	66.82%	66.21%	63.38%	67.37%	63.72%	66.04%
Unknown	0	0	0	0	0	0	0	0
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*0.00%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Total	26	447	1,718	515	19,474	95	22,275	2,706
	0.12%	**2.01%**	**7.71%**	**2.31%**	**87.43%**	**0.43%**	**100.00%**	**12.15%**
	0.12%	*2.01%*	*7.71%*	*2.31%*	*87.43%*	*0.43%*	*100.00%*	*12.15%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 23 Comments

Sex/Gender

More females (22,959 or 52.81%) than males (20,511 or 47.18%) were enrolled in aggregate Intramural Phase III Research Protocols.

More minority females (9,212 or 77.58%) than males (2,662 or 22.42%) are enrolled in aggregate Intramural Phase III Research Protocols.

Compared to FY 2006, minority female enrollment decreased by 1.16% and minority male enrollment increased by 1.15%.

Race

Approximately 27.31% (11,874) of participants in aggregate Intramural Phase III Research (43,472 total) were classified as U.S. minorities.

Largest identified racial group was White at 87.43% following the 1977 OMB standards and 44.53% following the 1997 OMB standards.

This is a significant change from FY 2006 when, according to the 1977 OMB standards, Asian/Pacific Islander was the largest identified racial group at 78.7%.

Largest identified racial minority group was Black or African American at 7.71% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 3.96% following the 1997 OMB standards.

According to the 1997 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.11%.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.12%.

Ethnicity

35.62% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was Unknown/Other at 99.93% (2nd largest category is White at 0.04%).

Asian, Black or African American and Hawaiian/Pacific Islander all had 0.0%.

Of the 7,550 participants, 96.78% were women and 3.22% were men.

2.31% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 24

Aggregate Enrollment Data for Intramural Phase III Research Protocols Funded in FY 2007 and Reported in FY 2008: Percent Analysis

Table 24A. Summary Totals: OLD FORM + NEW FORM

Total Number of Protocols with Enrollment Data: 37

Sex /Gender	Total Enrollment	Minority Enrollment	Total % Minority	% Minority by Sex
Females	11,533	8,448		73.25%
%	69.71%	90.10%		
Males	4,784	915		19.13%
%	28.92%	9.76%		
Unknown	227	13		0.00%
%	1.37%	0.14%		
TOTAL	**16,544**	**9,376**	**56.67%**	
Total %	100%	100.00%		

Table 24B(1). NEW FORM (Part A): Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 26

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	6	36	629	77	695	2	8,933	10,378	1,361	7,527	1,490	10,378
	0.05%	**0.27%**	**4.72%**	**0.58%**	**5.21%**	**0.02%**	**67.00%**	**77.84%**	**10.21%**	**56.45%**	**11.18%**	**77.84%**
	0.06%	*0.35%*	*6.06%*	*0.74%*	*6.70%*	*0.02%*	*86.08%*	*100.00%*	*13.11%*	*72.53%*	*14.36%*	*100.00%*
	85.71%	29.51%	59.06%	100.00%	52.06%	50.00%	83.31%	77.84%	53.92%	99.08%	46.39%	77.84%
Male	1	86	423	0	640	2	1,576	2,728	1,150	70	1,508	2,728
	0.01%	**0.65%**	**3.17%**	**0.00%**	**4.80%**	**0.02%**	**11.82%**	**20.46%**	**8.63%**	**0.53%**	**11.31%**	**20.46%**
	0.04%	*3.15%*	*15.51%*	*0.00%*	*23.46%*	*0.07%*	*57.77%*	*100.00%*	*42.16%*	*2.57%*	*55.28%*	*100.00%*
	14.29%	70.49%	39.72%	0.00%	47.94%	50.00%	14.70%	20.46%	45.56%	0.92%	46.95%	20.46%
Unknown	0	0	13	0	0	0	214	227	13	0	214	227
	0.00%	**0.00%**	**0.10%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**1.70%**	**0.10%**	**0.00%**	**1.61%**	**1.70%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	0.00%	1.22%	0.00%	0.00%	0.00%	2.00%	1.70%	0.52%	0.00%	6.66%	1.70%
Total	7	122	1,065	77	1,335	4	10,723	13,333	2,524	7,597	3,212	13,333
	0.05%	**0.92%**	**7.99%**	**0.58%**	**10.01%**	**0.03%**	**80.42%**	**100.00%**	**18.93%**	**56.98%**	**24.09%**	**100.00%**
	0.05%	*0.92%*	*7.99%*	*0.58%*	*10.01%*	*0.03%*	*80.42%*	*100.00%*	*18.93%*	*56.98%*	*24.09%*	*100.00%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 24B(2). NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

	Total of Subjects by Race								
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B
Female	1	0	0	0	2	1	7,523	7,527	8,275
	0.01%	**0.00%**	**0.00%**	**0.00%**	**0.03%**	**0.01%**	**99.03%**	**99.08%**	**62.06%**
	0.01%	*0.00%*	*0.00%*	*0.00%*	*0.03%*	*0.01%*	*99.95%*	*100.00%*	*79.74%*
	100.00%	0.00%	0.00%	0.00%	66.67%	100.00%	99.09%	99.08%	93.29%
Male	0	0	0	0	1	0	69	70	582
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	**0.91%**	**0.92%**	**4.37%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*1.43%*	*0.00%*	*98.57%*	*100.00%*	*21.33%*
	0.00%	0.00%	0.00%	0.00%	33.33%	0.00%	0.91%	0.92%	6.56%
Unknown	0	0	0	0	0	0	0	0	13
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.10%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.15%
Total	1	0	0	0	3	1	7,592	7,597	8,870
	0.01%	**0.00%**	**0.00%**	**0.00%**	**0.04%**	**0.01%**	**99.93%**	**100.00%**	**66.53%**
	0.01%	*0.00%*	*0.00%*	*0.00%*	*0.04%*	*0.01%*	*99.93%*	*100.00%*	*66.53%*
	100.00%	0.00%	0.00%	0.00%	100.00%	0.00%	100.00%	100.00%	100.00%

Table 24C. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards

Number of Protocols with Enrollment Data: 11

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM
Female	2	23	121	27	977	5	1,155	173
	0.06%	**0.72%**	**3.77%**	**0.84%**	**30.43%**	**0.16%**	**35.97%**	**5.39%**
	0.17%	*1.99%*	*10.48%*	*2.34%*	*84.59%*	*0.43%*	*100.00%*	*14.98%*
	0.00%	35.94%	33.43%	36.00%	36.36%	27.78%	35.97%	34.19%
Male	3	41	241	48	1,710	13	2,056	333
	0.09%	**1.28%**	**7.51%**	**1.49%**	**53.25%**	**0.40%**	**64.03%**	**10.37%**
	0.15%	*1.99%*	*11.72%*	*2.33%*	*83.17%*	*0.63%*	*100.00%*	*16.20%*
	0.00%	64.06%	66.57%	64.00%	63.64%	72.22%	64.03%	65.81%
Unknown	0	0	0	0	0	0	0	0
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*0.00%*
	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Total	5	64	362	75	2,687	18	3,211	506
	0.16%	**1.99%**	**11.27%**	**2.34%**	**83.68%**	**0.56%**	**100.00%**	**15.76%**
	0.16%	*1.99%*	*11.27%*	*2.34%*	*83.68%*	*0.56%*	*100.00%*	*15.76%*
	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Legend for Data Tables

Bold: Percentage of Total No. of Participants in Research Protocols (OLD or NEW FORM)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Typeface: Percentage of Total No. of Participants Sorted by Race/Ethnicity (Column Total)

Table 24 Comments

Sex/Gender

More females (11,533 or 69.71%) than males (4,784 or 28.92%) were enrolled in aggregate Intramural Phase III Research Protocols.

More minority females (8,448 or 90.10%) than males (915 or 9.76%) are enrolled in aggregate Intramural Phase III Research Protocols.

Race

Approximately 56.67% (9,376) of participants in aggregate Intramural Phase III Research (16,544 total) were classified as U.S. minorities.

Largest identified racial group was White at 83.68% following the 1977 OMB standards and Unknown/Other at 80.42% following the 1997 OMB standards.

Largest identified racial minority group was Black or African American at 11.27% following the 1977 OMB standards.

Largest identified racial minority group was Black or African American at 7.99% following the 1997 OMB standards.

According to the 1997 OMB standards, the smallest identified racial minority was More Than One Race at 0.03%.

According to the 1977 OMB standards, the smallest identified racial minority was American Indian/Alaska Native at 0.16%.

Ethnicity

56.98% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards.

For participants reporting ethnicity as Hispanic/Latino:

Largest identified racial group was Unknown/Other at 99.93% (2nd largest category is White at 0.04%).

Asian, Black or African American and Hawaiian/Pacific Islander all had 0.0%.

Of the 7,597 participants, 99.08% were women and 0.92% were men.

2.34% of participants identified their ethnicity as Hispanic according to the 1977 OMB standards.

TABLE 25

*NIH Fourteen-Year Trends for Protocol and Enrollment Data: 1995-2008**

Table 25A.

Part I. Fourteen-Year Increases in Protocols and Enrollment Data

FY Reported	1995	2008	Relative Increase, 2007 / 1995
Total Protocols With Enrollment	3,188	11,045	3.5
Total Enrollment	1,021,493	15,412,355	15.1
Total Minorities	374,433	4,386,636	11.7
% of Minority	36.7%	28.5%	0.8

Part II. Seven-Year Increases in Protocols and Enrollment Data: Foreign and Domestic

FY Reported	2002	2008	Relative Increase, 2007 / 1995
Total DOMESTIC	10,192,401	14,134,627	1.4
Total FOREIGN Enrollment	946,083	1,277,728	1.4

1. There was a 3.5-fold increase in protocols with enrollment reported from 1995 to 2008, from 3,188 protocols to 11,045 protocols.
2. There was a 15.1-fold increase in enrollment reported from 1995 to 2008, from approximately 1M to 15M.
3. There was a 11.7-fold increase in minority enrollment from 1995 to 2008, from approximately 0.4 M to 4M.
4. Domestic and foreign data were reported for FY 2002–2008, and showed 1.4-fold increase in domestic enrollment (from 10.2M to 14.12M) and a 1.4 fold increase in foreign enrollment (from 0.95M to 1.3M).

Table 25B. Fourteen-Year Summary of Total Number of Protocols Reported: FY 1995-2008

FY Reported	FY Funded	Number of Protocols with Enrollment data (OLD + NEW FORMS)	Number of DOMESTIC Protocols with Enrollment data	Number of FOREIGN Protocols with Enrollment data	Percent Domestic Protocols	Protocol Form*
1995	**1994**	3,188				OLD
1996	**1995**	6,036				
1997	**1996**	5,692				
1998	**1997**	7,602				
1999	**1998**	8,285				
2000	**1999**	9,390				
2001	**2000**	10,212				
2002	**2001**	8,945	8,463	482	94.6%	OLD + NEW
2003	**2002**	10,216	9,578	638	93.8%	
2004	**2003**	10,125	9,760	365	96.4%	
2005	**2004**	10,233	9,862	371	96.4%	
2006	**2005**	10,758	10,294	464	95.7%	
2007	**2006**	10,914	10,463	451	95.9%	
2008	**2007**	11,045	10,548	497	95.5%	

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.

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

Graph 25B. Total Protocols by Year Reported (FY 1995–2008)

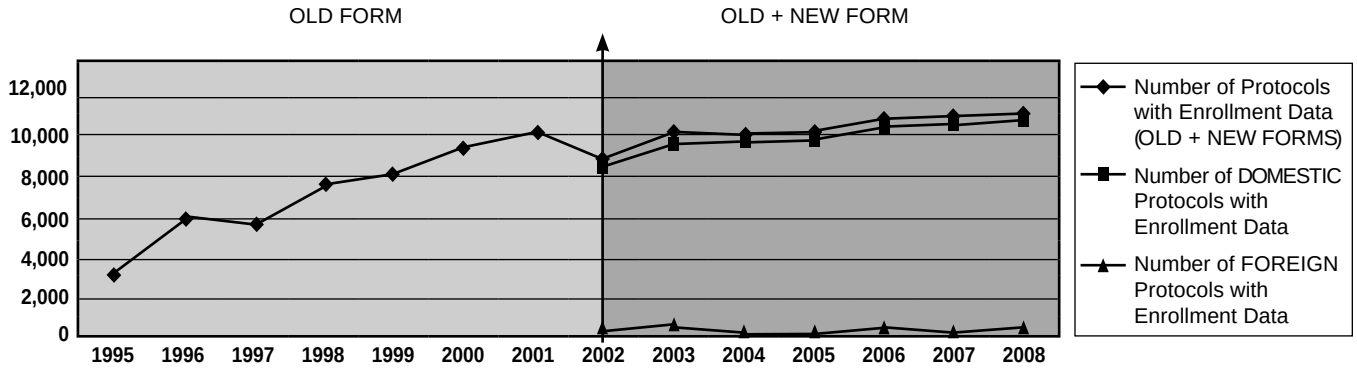


Table 25B Comments

1. Table 25B and 25B Graph provide the number of OLD and NEW protocols year by year (1995-2008) and the distribution between domestic and foreign protocols for years 2002-2008.
2. The total number of protocols reported with enrollment have leveled off between 10,000 and 11,000 over the last 4 years.
3. The vast majority of protocols were for domestic studies for 2002-2008, ranging from 93.8% to 96.4% of protocols.

* 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 2002-2008, data have been reported using both OLD and NEW FORMS.

Table 25C. Comparison of Domestic and Foreign Enrollment Reported in FY 2002–2008

FY Reported	FY Funded	Total Enrollment data (OLD + NEW FORMS)	Total DOMESTIC Enrollment data	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%
2007	**2006**	17,448,458	16,180,588	92.7%	1,267,870	7.3%
2008	**2007**	15,412,355	14,134,627	91.7%	1,277,728	8.3%

Graph 25C. Percent Comparison of Domestic and Foreign Enrollment (FY2002–2008)

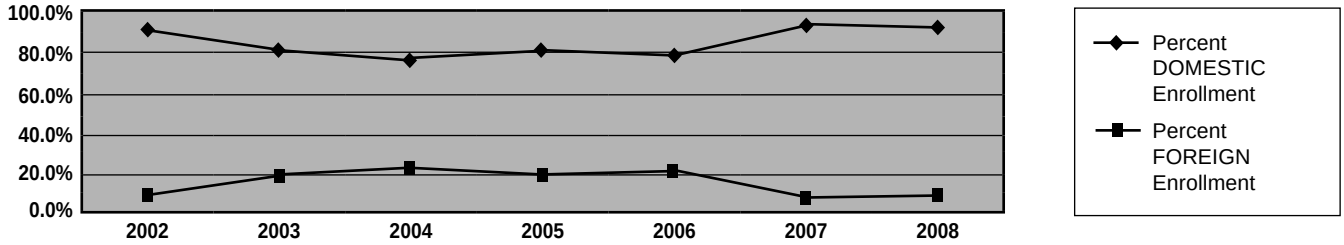


Table 25C Comments

1. Overall total enrollment has increased, as well as total domestic and foreign enrollment during the last 7 years. The percentage of foreign enrollment has decreased from 23.0% in FY 2006 to approximately 8.3% in FY 2008 as domestic enrollment increased.

TABLE 26

Domestic Protocols: Summary of NIH Extramural and Intramural Clinical Research Reported: FY 2002–2008: Enrollment Using U.S. Race/Ethnicity Categories

Table 26A. Seven-Year Summary Totals: Domestic Subjects in Domestic Protocols (OLD + NEW FORMS)

FY Reported	FY Funded	Females	Males	Unknown	Total Domestic Subjects (OLD + NEW FORMS)	Subtotal: Domestic Subjects Enrolled by US Minority Categories	Number of Domestic Protocols with Enrollment data (OLD + NEW FORMS)
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	14,359,793	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%	
2007	2006	9,397,957	6,389,817	392,814	16,180,588	4,283,738	10,463
	%	58.1%	39.5%	2.4%	100.0%	26.5%	
2008	2007	8,514,768	5,451,624	168,235	14,134,627	3,409,896	10,548
	%	60.2%	38.6%	1.2%	100.0%	24.1%	

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

1. There were approximately an average of 62.4% females, 36.1% males and 1.5% of unknown sex enrolled in domestic protocols from 2002-2008.
2. There were approximately an average of 26.1% domestic minority subjects enrolled in domestic protocols from 2002-2008.
3. Total domestic enrollment ranged from 10.1M to 16.2M during the past 7 years.
4. The number of domestic protocols increased from 8,425 to 10,548 in 7 years.

NOTE on 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).

NOTE on 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).

NOTE on 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).

NOTE on 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).

NOTE on 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).

NOTE of FY 2007 Reported Data:

One domestic study had an enrollment of 1,817,915 subjects (NEW FORM).

One domestic study had an enrollment of 1,879,841 subjects (NEW FORM).

One domestic study had an enrollment of 2,024,369 subjects (NEW FORM).

NOTE 1: The shaded portions of the Tables B, C, and D show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the new 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.

NOTE 2: Data from Tables 26B, 26C, and 26D are combined to provide the summary data in Table 26A.

Table 26B. OLD FORM: Total of All Domestic Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total Domestic Enrollment (OLD FORM)	Domestic Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Domestic Protocols with Enrollment data (OLD FORM)
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%	
2007	2006	5,372	51,740	238,003	81,677	1,095,702	48,625	1,521,119	376,792	1,092
	%	0.4%	3.4%	15.6%	5.4%	72.0%	3.2%	100.0%	24.8%	
2008	2007	12,505	11,366	62,753	25,171	350,300	160,259	622,354	111,795	909
	%	2.0%	1.8%	10.1%	4.0%	56.3%	25.8%	100.0%	18.0%	

Table 26C. NEW FORM (Part A): Inclusion Enrollment Report: Total of All Domestic Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats (Cumulative)

		Total of All Subjects by Race								Total of All Subjects by Ethnicity			
FY Reported	FY Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	*Total of All Subjects by Racial Categories (NEW FORM)	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	*Total of All Subjects by Ethnic Category
2002	2001	74,593	174,215	473,699	7,623	2,626,547	30,200	716,640	4,103,517	2,785,590	285,921	1,032,006	4,103,517
	%	1.8%	4.2%	11.5%	0.2%	64.0%	0.7%	17.5%	100.0%	67.9%	7.0%	25.1%	100.0%
2003	2002	61,526	295,061	897,518	23,068	5,161,965	94,138	1,005,604	7,538,880	6,003,326	602,018	933,536	7,538,880
	%	0.8%	3.9%	11.9%	0.3%	68.5%	1.2%	13.3%	100.0%	79.6%	8.0%	12.4%	100.0%
2004	2003	97,854	485,137	1,280,129	42,945	7,772,927	172,185	1,335,093	11,186,270	8,893,158	720,551	1,572,561	11,186,270
	%	0.9%	4.3%	11.4%	0.4%	69.5%	1.5%	11.9%	100.0%	79.5%	6.4%	14.1%	100.0%
2005	2004	291,044	655,959	1,232,957	42,993	7,485,193	164,096	1,010,730	10,882,972	9,120,293	721,138	1,041,541	10,882,972
	%	2.7%	6.0%	11.3%	0.4%	68.8%	1.5%	9.3%	100.0%	83.8%	6.6%	9.6%	100.0%
2006	2005	111,048	946,613	1,032,199	35,142	6,844,960	178,275	1,055,436	10,203,673	8,384,360	796,556	1,022,757	10,203,673
	%	1.1%	9.3%	10.1%	0.3%	67.1%	1.7%	10.3%	100.0%	82.2%	7.8%	10.0%	100.0%
2007	2006	129,830	892,410	1,719,631	46,569	10,028,992	270,005	1,572,032	14,659,469	11,991,388	1,002,302	1,665,779	14,659,469
	%	0.9%	6.1%	11.7%	0.3%	68.4%	1.8%	10.7%	100.0%	81.8%	6.8%	11.4%	100.0%
2008	2007	111,668	719,287	1,582,616	41,780	9,256,041	168,750	1,632,131	13,512,273	10,871,618	945,603	1,695,053	13,512,274
	%	0.8%	5.3%	11.7%	0.3%	68.5%	1.2%	12.1%	100.0%	80.5%	7.0%	12.5%	100.0%

Table 26D. NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	Domestic Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Domestic Protocols with Enrollment data (NEW FORM)
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%	
2007	2006	20,932	6,875	28,078	3,199	493,196	94,717	355,305	1,002,302	3,906,946	9,371
	%	2.1%	0.7%	2.8%	0.3%	49.2%	9.4%	35.4%	100.0%	26.7%	
2008	2007	14,528	7,086	84,215	2,361	468,176	51,618	317,619	945,603	3,409,896	9,578
	%	1.5%	0.7%	8.9%	0.2%	49.5%	5.5%	33.6%	100.0%	25.2%	

* These totals must agree.

** These totals must agree.

TABLE 27

Domestic Protocols: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY 2002-2008: Enrollment Using U.S. Race/Ethnicity Categories

Table 27A. Phase III Seven-Year Summary Totals: Domestic Subjects in Domestic Protocols (OLD + NEW FORMS)

FY Reported	FY Funded	Females	Males	Unknown	Total Domestic Subjects (OLD + NEW FORMS)	Subtotal: Domestic Subjects Enrolled by US Minority Categories	Number of Domestic Protocols with Enrollment data (OLD + NEW FORMS)
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%	
2007	2006	228,289	183,878	16,273	428,440	88,339	609
	%	53.3%	42.9%	3.8%	100.0%	20.6%	
2008	2007	347,982	226,266	16,857	591,105	119,582	585
	%	58.9%	38.3%	2.9%	100.0%	20.2%	

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

1. There were approximately an average of 58.1% females, 40.6% males, and 1.3% of unknown sex enrolled in Phase III domestic protocols from 2002-2008.
2. There were approximately an average of 22.2% domestic minority subjects enrolled in domestic Phase III protocols from 2002-2008.
3. Total domestic Phase III enrollment ranged from 400,297 to 591,105 during these 7 years.
4. The number of domestic Phase III protocols ranged from 517 to 643 between Fiscal Years 2002 and 2008.

NOTE 1: The shaded portions of the Tables B, C, and D show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the new 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.

NOTE 2: Data from Tables 27B, 27C, and 27D are combined to provide the summary data in Table 27A.

Table 27B. OLD FORM: Total of All Domestic Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total Domestic Enrollment (OLD FORM)	Domestic Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Domestic Protocols with Enrollment data (OLD FORM)
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%	
2007	2006	751	3,941	21,581	9,331	168,127	4,254	207,985	35,604	204
	%	0.4%	1.9%	10.4%	4.5%	80.8%	2.0%	100.0%	17.1%	
2008	2007	885	4,506	22,431	9,636	187,719	4,171	229,348	37,458	162
	%	0.4%	2.0%	9.8%	4.2%	81.8%	1.8%	100.0%	16.3%	

Table 27C. NEW FORM (Part A): Inclusion Enrollment Report: Total of All Domestic Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats (Cumulative)

		Total of All Subjects by Race								Total of All Subjects by Ethnicity			
FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White	More Than One Race	Unknown or Not Reported	*Total of All Subjects by Racial Categories (NEW FORM)	Not Hispanic	**Hispanic or Latino	Unknown/ Not Reported	*Total of All Subjects by Ethnic Category
2002	2001	159	798	3,199	52	34,541	560	1,520	40,829	34,662	1,629	4,538	40,829
	%	0.4%	2.0%	7.8%	0.1%	84.6%	1.4%	3.7%	100.0%	84.9%	4.0%	11.1%	100.0%
2003	2002	477	2,586	14,031	220	46,774	989	6,878	71,955	55,575	7,828	8,552	71,955
	%	0.7%	3.6%	19.5%	0.3%	65.0%	1.4%	9.6%	100.0%	77.2%	10.9%	11.9%	100.0%
2004	2003	1,396	4,373	22,307	611	106,260	1,849	4,884	141,680	123,770	10,863	7,047	141,680
	%	1.0%	3.1%	15.7%	0.4%	75.0%	1.3%	3.4%	100.0%	87.4%	7.7%	5.0%	100.0%
2005	2004	1,775	4,920	24,390	462	93,662	3,063	9,048	137,320	118,528	9,773	9,019	137,320
	%	1.3%	3.6%	17.8%	0.3%	68.2%	2.2%	6.6%	100.0%	86.3%	7.1%	6.6%	100.0%
2006	2005	2,724	5,312	23,267	530	118,577	4,077	33,608	188,095	141,688	13,550	32,857	188,095
	%	1.4%	2.8%	12.4%	0.3%	63.0%	2.2%	17.9%	100.0%	75.3%	7.2%	17.5%	100.0%
2007	2006	2,314	4,294	21,141	553	130,085	3,974	58,094	220,455	146,482	21,600	52,373	220,455
	%	1.0%	1.9%	9.6%	0.3%	59.0%	1.8%	26.4%	100.0%	66.4%	9.8%	23.8%	100.0%
2008	2007	2,256	6,314	25,753	713	276,406	11,836	38,279	361,557	289,525	42,003	30,229	361,757
	%	0.6%	1.7%	7.1%	0.2%	76.4%	3.3%	10.6%	100.0%	80.0%	11.6%	8.4%	100.0%

Table 27D. NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	Domestic Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Domestic Protocols with Enrollment data (NEW FORM)
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%	
2007	2006	300	44	454	24	7,360	319	13,099	21,600	44,165	405
	%	1.4%	0.2%	2.1%	0.1%	34.1%	1.5%	60.6%	100.0%	23.9%	
2008	2007	518	228	714	122	22,244	5,369	12,808	42,003	44,115	423
	%	1.2%	0.5%	1.7%	0.3%	53.0%	12.8%	30.5%	100.0%	22.7%	

* These totals must agree.
** These totals must agree.

TABLE 28

Foreign Protocols: Summary of NIH Extramural and Intramural Clinical Research Reported in FY 2002–2008: Enrollment Using U.S. Race/Ethnicity Categories

Table 28A. Seven-Year Summary Totals: Foreign Subjects in Foreign Protocols (OLD + NEW FORMS)

FY Reported	FY Funded	Females	Males	Unknown	Total Foreign Subjects (OLD + NEW FORMS)	Subtotal: Foreign Subjects Enrolled by US Minority Categories	Number of Foreign Protocols with Enrollment data (OLD + NEW FORMS)
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%	
2007	2006	754,633	497,976	15,261	1,267,870	932,686	451
	%	59.5%	39.3%	1.2%	100.0%	73.6%	
2008	2007	729,198	540,115	8,415	1,277,728	864,945	497
	%	57.1%	42.3%	0.7%	100.0%	67.7%	

1. The percent females varied from 39.2% to 59.5% in foreign protocols from 2002 to 2008; the percent males varied from 39.3% to 60.4%.
2. The percent foreign subjects enrolled using OMB racial/ethnic categories in foreign protocols varied from 73.6% to 90.9% from 2002 to 2008.
3. Total foreign enrollment ranged from 946,083 to 4,564,127 during the past 7 years.
4. The number of foreign protocols ranged from 365 to 638 during the past 7 years.

NOTE on FY 2002 Reported Data:

One study in Vietnam had an enrollment of 302,381 subjects (OLD FORM).

NOTE on 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).

NOTE on 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).

NOTE on FY 2005 Reported Data:

One study in India had an enrollment of 2,200,000 subjects (NEW FORM).

NOTE on FY 2006 Reported Data:

One study in India had an enrollment of 2,200,000 subjects (NEW FORM).

One study in India had an enrollment of 2,200,000 subjects (NEW FORM).

NOTE of FY 2007 Reported Data:

No foreign studies reported an enrollment greater than 100,000 subjects.

NOTE 1: The shaded portions of the Tables B, C, and D show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the new 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.

NOTE 2: Data from Tables 26B, 26C, and 26D are combined to provide the summary data in Table 26A.

Table 28B. OLD FORM: Total of All Foreign Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total Foreign Enrollment (OLD FORM)	Foreign Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Foreign Protocols with Enrollment data (OLD FORM)
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%	
2007	2006	0	2	1	1,515	1,685	5	3,208	1,518	6
	%	0.0%	0.1%	0.0%	47.2%	52.5%	0.2%	100.0%	47.3%	
2008	2007	15	26	14	852	3,057	91	4,055	917	6
	%	0.4%	0.6%	0.3%	21.0%	75.4%	2.2%	100.0%	22.6%	

Table 28C. NEW FORM (Part A): Inclusion Enrollment Report: Total of All Foreign Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats (Cumulative)

		Total of All Subjects by Race								Total of All Subjects by Ethnicity			
FY Reported	FY Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	*Total of All Subjects by Racial Categories (NEW FORM)	Not Hispanic	**Hispanic or Latino	Unknown/ Not Reported	*Total of All Subjects by Ethnic Category
2002	2001	3,271	180,022	68,071	14,013	19,970	741	3,153	289,241	278,618	6,064	4,559	289,241
	%	1.1%	62.2%	23.5%	4.8%	6.9%	0.3%	1.1%	100.0%	96.3%	2.1%	1.6%	100.0%
2003	2002	2,018	1,842,941	62,572	14,501	253,745	5,324	7,018	2,188,119	2,158,933	9,623	19,563	2,188,119
	%	0.1%	84.2%	2.9%	0.7%	11.6%	0.2%	0.3%	100.0%	98.7%	0.4%	0.9%	100.0%
2004	2003	193	3,860,259	99,728	11,507	292,142	14,056	46,157	4,324,042	4,275,684	35,788	12,570	4,324,042
	%	0.0%	89.3%	2.3%	0.3%	6.8%	0.3%	1.1%	100.0%	98.9%	0.8%	0.3%	100.0%
2005	2004	1,171	2,390,404	125,305	10,293	187,697	18,857	94,999	2,828,726	2,683,871	52,801	92,054	2,828,726
	%	0.0%	84.5%	4.4%	0.4%	6.6%	0.7%	3.4%	100.0%	94.9%	1.9%	3.3%	100.0%
2006	2005	30,519	2,516,589	219,140	3,318	244,057	143,279	145,105	3,302,007	2,923,885	257,756	120,366	3,302,007
	%	0.9%	76.2%	6.6%	0.1%	7.4%	4.3%	4.4%	100.0%	88.5%	7.8%	3.6%	100.0%
2007	2006	15,587	464,490	293,064	10,580	312,491	8,063	160,387	1,264,662	1,025,736	166,790	72,136	1,264,662
	%	1.2%	36.7%	23.2%	0.8%	24.7%	0.6%	12.7%	100.0%	81.1%	13.2%	5.7%	100.0%
2008	2007	21,218	449,034	258,425	6,795	403,766	13,405	121,020	1,273,663	1,021,912	171,728	80,023	1,273,663
	%	1.7%	35.3%	20.3%	0.5%	31.7%	1.1%	9.5%	100.0%	80.2%	13.5%	6.3%	100.0%

Table 28D. NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	Foreign Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Foreign Protocols with Enrollment data (NEW FORM)
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%	
2007	2006	16,681	550	3,234	1,115	46,034	5,816	93,360	166,790	931,178	445
	%	10.0%	0.3%	1.9%	0.7%	27.6%	3.5%	56.0%	100.0%	73.6%	
2008	2007	19,786	24,515	1,042	1	49,995	11,253	65,156	171,748	864,028	492
	%	11.5%	14.3%	0.6%	0.0%	29.1%	6.6%	37.9%	100.0%	67.8%	

* These totals must agree.

** These totals must agree.

TABLE 29

Foreign Protocols: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY 2002–2008: Enrollment Using U.S. Race/Ethnicity Categories

Table 29A. Part A. Phase III Seven-Year Summary Totals: Foreign Subjects in Foreign Protocols (OLD + NEW FORMS)

FY Reported	FY Funded	Females	Males	Unknown	Total Foreign Subjects (OLD + NEW FORMS)	Subtotal: Foreign Subjects Enrolled by US Minority Categories	Number of Foreign Protocols with Enrollment data (OLD + NEW FORMS)
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%	
2007	2006	96,405	65,755	559	162,719	156,593	44
		59.2%	40.4%	0.3%	100.0%	96.2%	
2008	2007	107,608	93,488	377	201,473	188,851	54
		53.4%	46.4%	0.2%	100.0%	93.7%	

1. The percent females varied from 47.4% to 59.2% in Phase III foreign protocols from 2002 to 2008; the percent males varied from 40.4% to 52.5%.
2. The percent foreign subjects enrolled by U.S. Minority Categories in Phase III foreign protocols increased from 60.4% to 93.7% from 2002 to 2008.
3. Total Phase III foreign enrollment increased from 30,311 to 201,473 during these 7 years.
4. The number of Phase III foreign protocols ranged from 24 to 209 between the years 2002 and 2008.

NOTE 1: The shaded portions of the Tables B, C, and D show the race/ethnicity categories that are identified as minority categories. The data reported in FY 2002 and later are from the new 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.

NOTE 2: Data from Tables 29B, 29C, and 29D are combined to provide the summary data in Table 29A.

Table 29B. OLD FORM: Total of All Foreign Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total Foreign Enrollment (OLD FORM)	Foreign Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Foreign Protocols with Enrollment data (OLD FORM)
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%	
2007	2006	0	2	1	2	1,662	5	1,672	5	1
	%	0.0%	0.1%	0.1%	0.1%	99.4%	0.3%	100.0%	0.3%	
2008	2007	15	36	14	6	3,034	91	3,196	71	2
	%	0.5%	1.1%	0.4%	0.2%	94.9%	2.8%	100.0%	2.2%	

Table 29C. NEW FORM (Part A): Inclusion Enrollment Report: Total of All Foreign Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats (Cumulative)

		Total of All Subjects by Race								Total of All Subjects by Ethnicity			
FY Reported	FY Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	*Total of All Subjects by Racial Categories (NEW FORM)	Not Hispanic	**Hispanic or Latino	Unknown/ Not Reported	*Total of All Subjects by Ethnic Category
2002	2001	0	1	1,448	0	113	0	753	2,315	1,562	0	753	2,315
	%	0.0%	0.0%	62.5%	0.0%	4.9%	0.0%	32.5%	100.0%		0.0%	32.5%	32.5%
2003	2002	7	23	7,610	0	1,095	0	1,260	9,995	8,720	3	1,272	9,995
	%	0.1%	0.2%	76.1%	0.0%	11.0%	0.0%	12.6%	100.0%	87.2%	0.0%	12.7%	100.0%
2004	2003	0	12	21,414	0	553	2,570	753	25,302	21,972	2,572	758	25,302
	%	0.0%	0.0%	84.6%	0.0%	2.2%	10.2%	3.0%	100.0%	86.8%	10.2%	3.0%	100.0%
2005	2004	389	4,272	25,948	0	7,576	0	1,206	39,391	38,122	624	645	39,391
	%	1.0%	10.8%	65.9%	0.0%	19.2%	0.0%	3.1%	100.0%	96.8%	1.6%	1.6%	100.0%
2006	2005	1,906	27,048	27,513	5	8,093	169	26,838	91,572	60,670	17,484	3,418	81,572
	%	2.1%	29.5%	30.0%	0.0%	8.8%	0.2%	29.3%	100.0%	74.4%	21.4%	4.2%	100.0%
2007	2006	7,037	43,070	63,327	2	2,917	171	44,523	161,047	108,210	50,022	2,815	161,047
	%	4.4%	26.7%	39.3%	0.0%	1.8%	0.1%	27.6%	100.0%	67.2%	31.1%	1.7%	100.0%
2008	2007	12,550	88,982	77,421	3	4,949	301	14,071	198,277	171,357	22,354	4,566	198,277
	%	6.3%	44.9%	39.0%	0.0%	2.5%	0.2%	7.1%	100.0%	86.4%	11.3%	2.3%	100.0%

Table 29D. NEW FORM (Part B): Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	Foreign Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Foreign Protocols with Enrollment data (NEW FORM)
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%	
2007	2006	7,033	1	4	0	70	3	42,911	50,022	156,588	43
	%	14.1%	0.0%	0.0%	0.0%	0.1%	0.0%	85.8%	100.0%	97.2%	
2008	2007	12,538	0	1	0	130	292	9,393	22,354	188,777	50
	%	56.1%	0.0%	0.0%	0.0%	0.6%	1.3%	42.0%	100.0%	95.2%	

* These totals must agree.
** These totals must agree.

VI. Budget

Summary of NIH Budgetary Expenditures on Women's Health, Men's Health, and Research Applicable to Both, FY 2007 and FY 2008

The amount of funding that the National Institutes of Health (NIH) invested in research during FY 2007 and FY 2008 is presented in this budget summary. Budget categories include funding specific to women, to men, or applicable to both. The figures presented in this report were provided and submitted by the budget officials at the individual NIH Institutes and Centers (ICs), compiled by the NIH Office of Budget, and submitted to the Office of Research on Women's Health (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:

(1) that are unique to, more serious, or more prevalent in women;

(2) 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

(3) 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.

ORWH has collaborated with the U.S. Department of Health and Human Services (HHS) Coordinating Committee on Women's Health (CCWH), which is convened by the Office on Women's Health in the Office of the Secretary, and includes the HHS Office of Budget, Technology, and Finance, and other women's health offices and programs across HHS agencies to coordinate and standardize the procedures for reporting budgetary expenditures on women's health throughout HHS.

The approach to data collection for this report is similar to that employed for reports since the 1993–1994 report, *NIH Support for Research on Women's Health Issues*. However, the methodology for calculating and coding disease spending has changed, so that amounts in some women's health spending categories appear to have decreased. Changes in methodology include eliminating the multiplication of 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 prior to FY 2003 and FY 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, or for which a specific gender-related consideration exists.

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

(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 should 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 the reporting of 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 not be possible to determine what proportion of the total expenditure should be reported for women or for men. Each IC applied the criteria according to its discretion and judgment of the applicability of a single criterion or combination of criteria. ORWH, along with its advisory and coordinating committees, is aware of possible inconsistencies in the evolving methodology for collecting budget data, and will continue to carefully monitor the outcomes and to coordinate with HHS CCWH's efforts to develop best methods for budget data collection.

Table 30 lists the overall NIH expenditures in FY 2007 and FY 2008 for specific diseases, disorders, and conditions. The health categories and subcategories in Table 30 were developed to accommodate all agencies in HHS. Certain subcategories are not applicable to the NIH mission; for those subcategories, the table will show a "0" across all columns. In some cases, however, a "0" may be shown even when the subcategory is appropriate. This occurs because the table is additive. Funding included in 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." Furthermore, amounts listed for each specific topic area are likely to underestimate the actual expenditures because no overlap in reporting is allowed by the prescribed method for data collection for this report.

As shown in Table 31 for FY 2007 and FY 2008, respectively, approximately 81.3 percent and 82.2 percent of the NIH research budget supported research that benefits both women and men. The total dollars in the research budget expended on both women's and men's health, as defined by the specific parameters for this data collection, increased from FY 2005 to FY 2006, although the percentage of total dollars for such research remained approximately the same for both years. Table 32 provides summary data from the previous biennial report.

The data compiled indicate that the majority of NIH research expenditures are for research that benefits both men and women. In FY 2007 and FY 2008, NIH spent an average of 81.8 percent on research that was not gender-specific, but that addressed health or scientific issues affecting both women and men.

For sex/gender-specific research, 12.4 percent of the NIH research budget was spent on women's health research that was sex/gender specific in both FY 2007 and FY 2008, while 6.3 percent in FY 2007 and 5.4 percent in FY 2008 was spent on men's health research that was sex/gender specific. The higher proportion expended for women's health sex/gender-specific research than for men's health sex/gender-specific research most likely stems

from the fact that there are more sex/gender-specific diseases, disorders, and conditions that affect females—menarche, menopause, reproduction, and gynecologic neoplasms—than there are male-specific diseases, disorders, and conditions.

Another consideration to be noted as the research budget for women's and men's health is reviewed (Table 30) is that actual numbers may differ from that in previous reports because in 2008, NIH implemented the Research, Condition, and Disease Categorization (RCDC) process, which changes entirely the method the NIH uses to report its funding to Congress and the public. This new methodology changes the projects included in each category, which could increase or decrease a category amount, and therefore, probably has an effect on the dollars reported in the categories featured. The RCDC process uses the same category definitions universally and applies them uniformly to all disease research categories at all of the ICs. This new data collection process should yield more precise and consistent figures now and in the future.

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 the "both men and women" category. For example, in FY 2008, sex-specific research on women totaled $3,513,618,000, whereas research funding for both men and women totaled $23,251,857,000. Thus, for NIH in FY 2008, a total of those figures, or $26,765,475,000, would be a truer representation of expenditures.

TABLE 30

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

	FY 2007 Actual				FY 2008 Actual			
	Women	**Men**	**Both**	**Total**	**Women**	**Men**	**Both**	**Total**
Cancer								
Breast cancer (including mammography and other services)	$684,288	$0	$778	$685,066	$656,077	$231	$21,903	$677,980
Reproductive cancers:								
cervical	88,942	279	6,376	95,597	86,640	234	5,262	92,136
ovarian	100,954	0	476	101,430	104,405	0	602	105,007
vaginal, uterine, and other	30,745	0	0	30,745	17,291	0	0	17,291
Lung cancer	160	0	244,834	244,994	1,098	17	257,697	260,519
Colorectal cancer	0	0	277,008	277,008	155	73	307,338	306,322
Other neoplasms	97,084	85,745	3,501,754	3,684,583	106,258	65,417	3,474,705	3,672,376
Subtotal	**1,002,173**	**86,024**	**4,031,226**	**5,119,423**	**971,924**	**65,972**	**4,067,507**	**5,131,631**
Cardiovascular/Pulmonary								
Blood diseases	37,364	49,241	490,349	576,954	29,321	36,972	334,151	400,444
Heart disease	101,967	93,011	741,311	936,289	132,689	127,173	705,216	965,078
Stroke	67,299	66,985	146,055	280,339	44,550	45,226	182,188	271,964
Other cardiovascular diseases/disorders	130,070	104,802	655,225	890,097	85,215	82,642	894,941	1,062,798
Pulmonary diseases	47,901	50,985	437,104	535,990	76,389	70,671	354,465	501,525
Asthma	50,345	41,042	190,998	282,385	42,378	34,968	174,707	252,053
Other	4,835	4,860	214,734	224,429	0	0	426,551	426,551
Subtotal	439,781	410,926	2,875,776	3,726,483	410,542	397,652	3,072,218	3,880,412
Reproductive and Maternal/Child/Adolescent Health								
Contraception	22,241	7,888	4,942	35,071	27,378	8,322	17,664	53,364
Infertility	9,510	3,526	9,453	22,489	4,712	1,252	39,293	45,257
Female reproductive physiology	133,598	0	324	133,922	81,630	1,806	7,012	90,448
Hysterectomy	301	0	0	301	26,808	0	0	26,808
Endometriosis and leiomyomas	7,169	0	0	7,169	652	0	0	652
Pregnancy, pregnancy prevention, maternal health	183,517	79	6,448	190,044	176,479	865	4,623	181,967
Diseases related to DES exposure	3,919	0	0	3,919	32,352	0	0	32,352
Female genital cutting	0	0	0	0	992	0	0	992
Other	6,879	40,697	567,775	615,351	3,645	18,390	528,536	550,571
Subtotal	367,134	52,190	588,942	1,008,266	354,648	30,635	597,129	982,412

	FY 2007 Actual				FY 2008 Actual			
	Women	**Men**	**Both**	**Total**	**Women**	**Men**	**Both**	**Total**
Aging								
Menopause	36,065	130	986	37,181	32,295	0	0	32,295
Menopausal hormone and nonhormone therapy	16,105	3,636	0	19,741	18,842	0	0	18,842
Alzheimer's disease	34,138	15,672	536,583	586,393	32,797	21,834	306,077	360,708
Malnutrition in the elderly	656	279	750	1,685	588	196	7,548	8,332
Osteoarthritis	24,284	318	27,636	52,238	27,196	519	24,641	52,356
Osteoporosis	127,471	3,598	1,820	132,889	117,661	2,659	5,628	125,948
Women's Health Initiative	661	0	768	1,429	1,309	0	153	1,462
Other	55,205	25,043	462,535	542,783	61,732	31,682	631,996	725,410
Subtotal	294,585	48,676	1,031,078	1,374,339	292,420	56,890	976,043	1,325,353
Metabolism/Endocrinology								
Diabetes	66,631	92,633	140,409	299,672	64,573	90,814	119,216	274,603
Obesity	184,077	120,298	129,247	433,622	163,679	87,467	93,286	344,432
Hepatobiliary disease	1,731	99	186,146	187,976	132	2,044	205,464	207,640
Thyroid diseases and conditions	13,920	3,480	5,331	22,731	13,920	3,480	5,872	23,272
Other	4,248	4,281	71,073	79,602	1,074	290	64,392	65,756
Subtotal	270,607	220,791	532,206	1,023,603	243,378	184,095	488,230	915,703
Substance Abuse								
Etiology (unspecified)	1,446	556	91,344	93,346	3,050	944	93,960	97,954
Epidemiology (unspecified)	844	845	22,468	24,157	998	913	15,737	17,648
Prevention (unspecified)	1,165	580	29,490	31,235	1,245	711	30,127	32,083
Treatment (unspecified)	2,326	809	23,031	26,166	1,924	1,027	26,947	29,898
Alcohol	9,691	11,536	103,447	124,674	8,946	10,095	120,806	139,847
Illegal drugs	176,638	588,006	241,995	1,006,639	257,835	352,813	399,225	1,009,873
Prescription drugs	0	0	0	0	0	0	0	0
Tobacco products	111	61	23,894	24,066	80	75	29,025	29,180
Other substances	182	75	6,980	7,237	497	75	13,055	13,627
Co-occurring substance abuse and mental disorders	420	249	8,142	8,811	348	289	6,457	7,094
Subtotal	192,823	602,717	550,791	1,346,331	274,923	366,942	735,339	1,377,204
Behavioral Studies/Programs								
Violence (includes domestic abuse, abused women, and spousal abuse)	7,631	1,476	27,178	36,285	7,168	1,059	25,388	33,615
Tobacco use cessation	0	0	794	794	607	0	2,334	2,941
Physical activity and nutrition (promoting healthy behavior)	1,705	0	78,826	80,531	1,555	181	80,450	82,186
Other behavior change and risk modification	8,665	3,583	211,617	223,865	875	676	10,007	11,558
Caregiving	608	0	7,076	7,684	949	0	16,796	17,745
Other	5,350	524	293,789	299,663	13,498	2,331	484,872	500,701
Subtotal	23,959	5,583	619,280	648,822	24,652	4,247	619,847	648,746

	FY 2007 Actual				FY 2008 Actual			
	Women	**Men**	**Both**	**Total**	**Women**	**Men**	**Both**	**Total**
Mental Health								
Etiology (unspecified)	582	0	7,312	7,894	758	0	17,377	18,135
Epidemiology (unspecified)	0	0	105	105	242	0	3	245
Prevention (unspecified)	0	0	243	243	15	0	905	920
Treatment (unspecified)	388	194	745	1,327	381	191	2,038	2,610
Depression and mood disorders	26,865	3,174	171,213	201,252	20,396	1,892	151,576	173,790
Suicide	707	185	15,073	15,965	701	186	14,696	15,583
Schizophrenia	463	5	144,066	144,534	557	0	147,694	149,637
Anxiety disorders	2,023	2,211	46,436	50,670	105	0	46,561	46,666
Eating disorders	6,399	46	4,358	10,803	6,116	8	4,043	10,167
Psychosocial stress	10,365	201	28,179	38,745	9,848	188	28,763	38,799
Posttraumatic stress disorder	6,546	649	17,087	24,282	5,411	250	15,350	21,011
Other mental disorders (excluding Alzheimer's)	17,643	5,708	632,657	656,008	56,109	45,211	569,745	671,872
Autism	6,753	23,120	53,033	82,906	0	0	7,624	7,624
Subtotal	78,734	35,493	1,120,507	1,234,734	100,639	47,926	1,006,375	1,157,059
Infectious Diseases								
AIDS/HIV	226,691	68,859	2,134,601	2,430,151	146,052	53,124	2,194,901	2,394,077
Tuberculosis	5,449	4,172	140,669	150,290	3,944	6,665	108,120	118,729
Sexually transmitted diseases (STD)	35,245	5,769	160,919	201,933	47,361	2,978	148,887	199,226
Topical microbicides	85,473	0	9,157	94,630	88,671	0	6,573	95,244
Toxic shock syndrome	807	0	0	807	802	0	0	802
Tropical diseases	11,423	5,105	470,429	486,957	20,246	1,094	411,740	433,080
Other	3,197	2,469	84,741	90,407	147	108	502,016	502,271
Subtotal	368,285	86,374	2,993,681	3,455,175	307,223	63,969	3,381,925	3,743,429
Immune Disorders								
Arthritis	39,626	6,699	226,226	272,551	42,849	6,006	236,636	293,284
Lupus erythematosus	55,377	1,825	23,986	81,188	52,015	2,027	22,195	76,237
Multiple sclerosis	21,791	9,292	58,888	89,971	21,132	16,183	77,529	115,177
Myasthenia gravis	1,494	1,309	2,015	4,818	257	139	1,021	1,417
Scleroderma	7,363	0	2,879	10,242	10,436	0	2,765	14,273
Sjögren's syndrome	874	55	0	929	8,788	0	0	12,906
Takayasu disease	0	0	0	0	125	12	0	44,451
Other	433	70	53,104	53,607	128	108	160,299	160,535
Subtotal	126,958	19,250	367,098	513,306	135,730	24,475	500,445	718,280

	FY 2007 Actual				FY 2008 Actual			
	Women	**Men**	**Both**	**Total**	**Women**	**Men**	**Both**	**Total**
Neurologic, Muscular, and Bone								
Trauma research	9,449	13,900	166,983	190,332	6,363	6,588	81,173	94,124
Muscular dystrophy	4,287	25,861	12,104	42,252	3,649	25,021	17,537	46,207
Chronic pain conditions	9,521	7,679	77,951	95,151	11,296	11,360	86,777	109,433
Temporomandibular disorders	237	0	1,157	14,087	12,842	0	830	13,672
Fibromyalgia and eosinophilic myalgia	7,187	153	184	7,524	8,732	0	37	8,769
Migraine	159	0	0	159	119	0	0	119
Sleep disorders	4,237	3,082	32,520	39,839	6,864	5,369	37,361	49,594
Paget's disease	0	0	2,682	2,682	0	0	1,282	1,282
Parkinson's disease	19,406	20,947	98,412	138,765	16,653	17,218	84,905	118,776
Seizure disorders	23,485	20,566	56,343	100,394	18,500	19,050	77,983	115,533
Other	42,614	47,858	801,128	892,857	134,134	140,985	844,659	1,119,778
Subtotal	120,582	140,046	1,249,464	1,524,042	219,152	225,591	1,232,542	1,677,285
Kidney and Urologic								
Urinary tract infection	9,489	222	4,653	14,364	12,529	212	4,748	17,489
ESRD and transplantation	4,134	6,163	111,502	121,799	3,741	6,565	73,282	83,588
Urinary incontinence (cystitis, pyelonephritis)	13,589	0	221	13,810	10,405	0	1,508	11,913
Other	23,727	4,837	227,941	256,505	8,969	6,796	301,534	317,299
Subtotal	50,939	11,222	344,317	406,478	35,644	13,573	381,072	430,289
Ophthalmic, Otolaryngologic, and Oral Health								
Eye diseases and disorders	11,406	17,388	660,998	689,792	12,338	17,484	696,533	726,355
Ear diseases and disorders	14,358	0	360,536	374,894	13,072	0	259,503	272,575
Dental and oral health	0	0	7,889	7,889	2,509	1,071	25,494	29,074
Other	22,749	2,409	286,951	312,109	0	0	314,403	314,403
Subtotal	48,513	19,797	1,316,374	1,384,684	27,919	18,555	1,295,933	1,342,407
Health Effects of the Environment								
Environmental estrogens	9,138	1,561	20,423	31,122	2,502	1,561	19,315	23,514
Health effects of toxic exposure (excluding cancer)	0	0	44,253	44,253	0	0	44,056	43,920
Toxicological research and testing program	0	0	72,142	72,142	0	0	71,539	71,539
Chemical and biological warfare agents	0	0	12,085	12,085	0	0	1,646	2,140
Other	91	0	1,625	1,716	88	0	1,737	1,961
Subtotal	9,229	1,561	150,528	161,318	2,590	1,561	138,293	143,074

	FY 2007 Actual				FY 2008 Actual			
	Women	**Men**	**Both**	**Total**	**Women**	**Men**	**Both**	**Total**
Crosscutting Categories and Special Initiatives								
Treatment, prevention, and services	4,497	4,517	308,979	317,993	1,482	496	306,526	284,730
Access to health care and financing	0	32	2,073	2,105	0	33	4,292	4,325
Education and training for healthcare providers	0	0	5,276	5,276	204	181	14,466	14,851
Health literacy and bilingual information	0	0	14,721	14,721	332	337	18,863	19,532
Cultural influences	132	0	2,134	2,266	164	37	3,120	3,321
Disability research and services	2,035	3,276	77,259	82,570	1,513	4,609	84,317	90,439
Homelessness	0	0	810	810	0	0	138	138
Chronic fatigue syndrome	2,189	1,058	734	3,981	1,154	75	880	2,109
Breastfeeding	409	0	0	409	445	0	809	1,254
Organ donation	0	0	818	818	0	0	1,436	1,436
Genetic services and counseling	0	0	3,011	3,011	0	0	2,699	2,699
Unintentional injury	57	773	18,657	19,487	0	754	18,182	18,936
Alternative and complementary therapies	35,608	26,942	89,224	151,774	33,972	26,352	109,600	47,999
Health statistics and data collection	486	132	4,159	4,777	488	131	5,300	5,919
Office of Women's Health	20,857	0	0	20,857	9,283	0	5	9,288
Other crosscutting	1,422	494	2,398,543	2,400,459	55,216	0	1,672,110	1,727,326
Global health	7,508	414	2,086,261	2,094,183	7,981	1,335	2,516,215	3,890,395
Subtotal	75,200	37,638	5,012,659	5,125,497	112,234	34,340	4,758,958	6,124,697
TOTAL: Women's and Men's Health	3,469,502	1,778,288	22,783,926	28,031,716	3,513,618	1,536,423	23,251,857	28,301,898

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

TABLE 31

NIH Research Budget Summary by Sex/Gender, FY 2007 and FY 2008 (Dollars in thousands)

FY	Women		Men		Both		Total	
	Dollars	Percent	Dollars	Percent	Dollars	Percent	Dollars	Percent
2007	3,469,502	12.4	1,778,288	6.3	22,767,376	81.3	28,015,166	100.0
2008	3,513,618	12.4	1,536,423	5.4	23,251,857	82.2	28,301,898	100.0

TABLE 32

NIH Research Budget Summary by Sex/Gender, FY 2005 and FY 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	81.5	27,775,926	100.0
2006	3,497,870	12.6	1,560,007	5.6	22,617,802	81.7	27,675,679	100.0

VII. Listing of FY 2007–2008 Advisory Committee on Research on Women's Health and Coordinating Committee on Research on Women's Health Members and Office of Research on Women's Health Staff

Advisory Committee on Research on Women's Health, FY 2007

Representative	*Title and Affiliation*
Vivian W. Pinn, M.D. *Chairperson*	Associate Director for Research on Women's Health Director, Office of Research on Women's Health National Institutes of Health Bethesda, Maryland
Joyce Rudick *Executive Secretary*	Director, Programs and Management Office of Research on Women's Health National Institutes of Health Bethesda, Maryland
Alan M. Krensky, M.D. *Ex-Officio*	Director, Office of Portfolio Analysis and Strategic Initiatives (OPASI) Office of the Director National Institutes of Health Bethesda, Maryland

Committee Members

Joanna Cain, M.D. (2008)	Chair and Professor, Department of Obstetrics and Gynecology Director, Center for Women's Health Oregon Health Sciences University Portland, Oregon
Luther Clark, M.D. (2009)	Chief, Division of Cardiovascular Medicine Professor of Clinical Medicine, Division of Cardiology SUNY Downstate Medical Center Brooklyn, New York
PonJola Coney, M.D., FACOG (2009)	Professor of Obstetrics and Gynecology Meharry Medical College Nashville, Tennessee

Advisory Committee on Research on Women's Health, FY 2007 (continued)

Representative	*Title and Affiliation*
Andrea Dunaif, M.D. (2009)	Charles F. Kettering Professor of Medicine Chief, Division of Endocrinology, Metabolism, and Molecular Medicine The Feinberg School of Medicine Northwestern University Chicago, Illinois
Ronald S. Gibbs, M.D. (2011)	Professor and Chairman Department of Obstetrics and Gynecology University of Colorado at Denver and Health Sciences Center Aurora, Colorado
Margaret Heitkemper, Ph.D., RN, FAAN (2008)	Chair and Professor Department of Biobehavioral Nursing and Health Systems Director, Center for Women's Health Research Corbally Professor in Public Service University of Washington School of Nursing Seattle, Washington
Constance Howes, J.D. (2010)	President and CEO Women and Infants Hospital Providence, Rhode Island
Scott J. Hultgren, Ph.D. (2011)	Helen L. Stoever Professor of Molecular Microbiology Washington University School of Medicine St. Louis, Missouri
Linda Kaste, D.D.S., Ph.D., M.S. (2009)	Associate Professor and Director Predoctoral Dental Public Health Department of Pediatric Dentistry University of Illinois at Chicago College of Dentistry Adjunct Associate Professor University of Illinois at Chicago School of Public Health Chicago, Illinois
Nancy Norton (2010)	Founder and President International Foundation for Functional Gastrointestinal Disorders Chairperson, Digestive Disease National Coalition Milwaukee, Wisconsin
Mary Beth O'Connell, Pharm.D., BCPS, FASHP, FCCP (2011)	Associate Professor Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences Detroit, Michigan

Advisory Committee on Research on Women's Health, FY 2007 (continued)

Representative	*Title and Affiliation*
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Eugene Orringer, M.D. (2010)	Executive Associate Dean for Faculty Affairs and Faculty Development School of Medicine University of North Carolina at Chapel Hill Chapel Hill, North Carolina
Sally Rosen, M.D., M.F.S. (2011)	Special Assistant Office of the Provost, Director, Center for Women's Health Research, Leadership, and Advocacy Office of the Vice President for Research Temple University Philadelphia, Pennsylvania
Susan Sloan, M.D. (2010)	Assistant Professor, Department of Medicine Associate Residency Program Director Department of Internal Medicine James H. Quillen College of Medicine East Tennessee State University Johnson City, Tennessee
Phyllis Wise, Ph.D. (2008)	Provost and Vice President for Academic Affairs University of Washington Seattle, Washington
Barbara Yee, Ph.D. (2010)	Professor and Chair Department of Family and Consumer Sciences University of Hawaii at Manoa Honolulu, Hawaii
Carmen Zorrilla, M.D. (2009)	Professor of Obstetrics and Gynecology University of Puerto Rico School of Medicine San Juan, Puerto Rico

Advisory Committee on Research on Women's Health, FY 2008

Representative	*Title and Affiliation*
Vivian W. Pinn, M.D. *Chairperson*	Associate Director for Research on Women's Health Director, Office of Research on Women's Health National Institutes of Health Bethesda, Maryland

Representative	*Title and Affiliation*
Joyce Rudick *Executive Secretary*	Director, Programs and Management Office of Research on Women's Health National Institutes of Health Bethesda, Maryland
Alan M. Krensky, M.D. *Ex-Officio*	Director, Office of Portfolio Analysis and Strategic Initiatives (OPASI) Office of the Director National Institutes of Health Bethesda, Maryland

Committee Members

Luther Clark, M.D. (2009)	Chief, Division of Cardiovascular Medicine Professor of Clinical Medicine, Division of Cardiology SUNY Downstate Medical Center Brooklyn, New York
PonJola Coney, M.D., FACOG (2009)	Professor of Obstetrics and Gynecology Meharry Medical College Nashville, Tennessee
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Linda C. Giudice, M.D., Ph.D. (2012)	The Robert B. Jaffe, M.D., Endowed Professor Chair, Department of Obstetrics, Gynecology, and Reproductive Sciences University of California, San Francisco San Francisco, California
Constance Howes, J.D. (2010)	President and CEO Women and Infants Hospital Providence, Rhode Island

Advisory Committee on Research on Women's Health, FY 2008 (continued)

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Scott J. Hultgren, Ph.D. (2011)	Helen L. Stoever Professor of Molecular Microbiology Washington University School of Medicine St. Louis, Missouri
Linda Kaste, D.D.S., Ph.D., M.S., (2009)	Associate Professor and Director Predoctoral Dental Public Health Department of Pediatric Dentistry University of Illinois at Chicago College of Dentistry Adjunct Associate Professor University of Illinois at Chicago School of Public Health Chicago, Illinois
Nancy H. Nielsen, M.D., Ph.D. (2012)	President, American Medical Association Senior Associate Dean, The State University of New York at Buffalo School of Medicine and Biomedical Sciences Office of Medical Education Buffalo, New York
Nancy Norton (2010)	Founder and President International Foundation for Functional Gastrointestinal Disorders Chairperson, Digestive Disease National Coalition Milwaukee, Wisconsin
Mary Beth O'Connell, Pharm.D., BCPS, FASHP, FCCP (2011)	Associate Professor Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences Detroit, Michigan
Mary I. O'Connor, M.D. (2011)	Chair, Department of Orthopedic Surgery Department of Orthopedics Mayo Clinic Jacksonville, Florida
Eugene Orringer, M.D. (2010)	Executive Associate Dean for Faculty Affairs and Faculty Development School of Medicine University of North Carolina at Chapel Hill Chapel Hill, North Carolina
Sally Rosen, M.D., M.F.S. (2011)	Special Assistant Office of the Provost, Director, Center for Women's Health Research, Leadership, and Advocacy Office of the Vice President for Research Temple University Philadelphia, Pennsylvania

Advisory Committee on Research on Women's Health, FY 2008 (continued)

Representative	*Title and Affiliation*
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Barbara Yee, Ph.D. (2010)	Professor and Chair Department of Family and Consumer Sciences University of Hawaii at Manoa Honolulu, Hawaii
Carmen Zorrilla, M.D. (2009)	Professor of Obstetrics and Gynecology University of Puerto Rico School of Medicine San Juan, Puerto Rico

NIH Coordinating Committee on Research on Women's Health Representatives, FY 2007

Institute, Center, or Office	*Representative*	*Title*
ORWH	Vivian W. Pinn, M.D.	Director, ORWH, Chair
		Director of ORWH Programs and Management
ORWH	Joyce Rudick	Executive Secretary
NINR	Yvonne Bryan, Ph.D.	Program Director
OC	John Burklow	Director, Office of Communications
NIDCR	Maria Canto, D.D. S.	Director, Epidemiology and Health Promotion Research Program
OAR	Vicki Cargill, M.D.	Director of Minority Research, Director of Clinical Studies
OITE	Debbie Cohen	Director, Summer and Postbaccalaureate IRTA Programs
CC	Deborah Dozier-Hall, M.S.W.	Assistant Chief, Social Work Department
NLM	Gale Dutcher, M.S.	Head, Office of Outreach and Special Populations
OLPA	Lenka Fedorkova, Ph.D.	Legislative Analyst
NIBIB	Valery Gordon, Ph.D.	Senior Extramural Policy Officer
OEODM	Marcella Haynes	Director, Division of Policy Evaluation, and Training
NIDDK	Eleanor Hoff, Ph.D.	Science Policy Analyst
FIC	Karen Hofman, M.D.	Director, Advanced Studies and Policy Analysis
NHGRI	M.K. Holohan, J.D.	Health Policy Analyst
NCMHD	Joyce Hunter, Ph.D.	Deputy Director

NIH Coordinating Committee on Research on Women's Health Representatives, FY 2007 (continued)

Institute, Center, or Office	*Representative*	*Title*
OSE	Bonnie Kalberer, M.S.	Contractor
NIDA	Cora Lee Wetherington, Ph.D.	Women and Gender Research Coordinator
NCI	Anna Levy, M.S.	Director, Office of Women's Health
NIAID	Tamara Lewis Johnson, M.P.H., M.B.A.	Women's Health Program Manager
NEI	Ellen S. Liberman, Ph.D.	Director, Lens, Cataract, and Glaucoma Programs
NHLBI	Barbara Liu, M.S.	Deputy Director, Office of Science and Technology
OBSSR	Patty Mabry, Ph.D.	Health Scientist Administrator/Behavioral Scientist
NIGMS	Pamela Marino, Ph.D.	Program Director
NCRR	Sheila McClure, Ph.D.	Health Scientist Administrator
NIA	Kate Nagy, M.A.	Program Analyst
NIEHS	Sheila Newton, Ph.D.	Director, Office of Program Planning and Evaluation
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
NIAAA	Svetlana Radaeva, M.D.	Health Scientist Administrator/Program Director
NIMH	Catherine Roca, M.D.	Chief, Women's Programs
NICHD	Mona Rowe, M.C.P.	Associate Director for Science Policy Analysis and Communication
NIDCD	Lana Shekim, Ph.D.	Director, Voice and Speech Program
OIR	Esther Sternberg, M.D.	Chief, Section on Neuroendocrine Immunology and Behavior
NCCAM	Kate Stoney, M.D.	Program Officer
NIAMS	Maddy Turkeltaub, Ph.D.	Deputy Director, Extramural Programs
CSR	Denise Wiesch, Ph.D.	Scientific Review Officer

NIH Coordinating Committee on Research on Women's Health Alternates, 2007

Institute, Center, or Office	*Alternate*	*Title*
NIAID	Diane Adger-Johnson	Minority Health and Research Training Analyst
NINDS	Cara Allen	Office of Science Policy and Planning
OCPL	Marin Allen, Ph.D.	Deputy Director
NCI	Margaret Ames, Ph.D.	Acting Director, Office of Science Planning and Assessment
NINR	Paul Cotton, Ph.D.	Program Director, Division of Extramural Activities

NIH Coordinating Committee on Research on Women's Health Alternates, 2007 (continued)

Institute, Center, or Office	*Alternate*	*Title*
NIBIB	Anthony Demsey, Ph.D.	Director, Extramural Policy
FIC	Jeanne Flagg Newton, Ph.D.	Special Assistant
NIGMS	Paula Flicker, Ph.D.	Program Director
NIAMS	Julia Freeman, Ph.D.	Contractor
NHGRI	Phyllis Frosst, Ph.D.	Science Policy Analyst
NIEHS	Mary Gant, M.S.	Legislative Officer
NIDDK	Mary Hanlon, Ph.D.	Health Science Policy Analyst
CC	Walter Jones, M.S.	Deputy Director for Diversity Operations
NIA	Karin Kolsky	Writer-Editor
NEI	Natalie Kurinij, Ph.D.	Health Scientist Administrator
NIAMS	Anita Linde, M.P.P.	Director, Office of Program Planning and Evaluation
NIDCD	Lonnie L. Lisle	Office of Health Communication and Public Liaison
OITE	Sharon Milgram, Ph.D.	Director, Office of Intramural Training and Education
OCL	Walter Mitton	Community Relations Specialist
NIDA	Samia Noursi, Ph.D.	Deputy Coordinator, Women and Gender Research
NIDCR	Ruth Nowjack-Raymer, Ph.D., M.P.H.	Program Director, Health Disparities Research
NIMH	Kathleen O'Leary, M.S.W.	Deputy Chief of Women's Programs
NICHD	Estella Parrott, M.D.	Program Director, Reproductive Sciences Branch
OEODM	Rose Pruitt, M.B.A.	Federal Women's Program Manager
NIAMS	Louise Rosenbaum, Ph.D.	Science Policy Analyst
NIAAA	Diedra Roach, M.D.	Health Scientist Administrator
OER	Denise Russo, Ph.D.	Extramural Policy Coordinator
NHLBI	Susan Scolnik	Program Analyst
CSR	Elaine Sierra-Rivera, Ph.D.	Deputy Chief, Oncological Sciences IRG
OSP	Lana Skirboll, Ph.D.	Director
OIR	Barbara Vonderhaar, Ph.D.	Chief, Molecular and Cellular Endocrinology Section
NCMHD	Kester Williams, M.A.	Special Assistant to the Director

NIH Coordinating Committee on Research on Women's Health Representatives, FY 2008

Institute, Center, or Office	*Representative*	*Title*
ORWH	Vivian W. Pinn, M.D.	Director, ORWH, Chair
		Director of ORWH Programs and Management
ORWH	Joyce Rudick	Executive Secretary
NCI	Margaret Ames, Ph.D.	Acting Director, Office of Science Policy and Analysis
NIDCR	Jane Atkinson, D.D.S.	Health Scientist Administrator
NINR	Yvonne Bryan, Ph.D.	Program Director

NIH Coordinating Committee on Research on Women's Health Representatives, FY 2008

Institute, Center, or Office	*Representative*	*Title*
OC	John Burklow	Director, Office of Communications
OAR	Vicki Cargill, M.D.	Director of Minority Research, Director of Clinical Studies
OITE	Debbie Cohen	Director, Summer and Postbaccalaureate IRTA Programs
CC	Deborah Dozier-Hall, M.S.W.	Assistant Chief, Social Work Department
NLM	Gale Dutcher, M.S.	Head, Office of Outreach and Special Populations
OLPA	Lenka Fedorkova, Ph.D.	Legislative Analyst
NIBIB	Valery Gordon, Ph.D.	Senior Extramural Policy Officer
OEODM	Marcella Haynes	Director, Division of Policy, Evaluation, and Training
NIDDK	Eleanor Hoff, Ph.D.	Science Policy Analyst
FIC	Karen Hofman, M.D.	Director, Division of International Science Policy, Planning, and Evaluation
NHGRI	M.K. Holohan, J.D.	Health Policy Analyst
OSE	Bonnie Kalberer, M.S.	Contractor
NIDA	Cora Lee Wetherington, Ph.D.	Women and Gender Research Coordinator
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OBSSR	Patty Mabry, Ph.D.	Health Scientist Administrator/Behavioral Scientist
NIGMS	Pamela Marino, Ph.D.	Program Director
NCRR	Padma Maruvada, Ph.D.	Health Scientist Administrator
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NEI	Lisa Neuhold, Ph.D.	Retinal Diseases Program Director
NIEHS	Sheila Newton, Ph.D.	Director, Office of Program Planning and Evaluation
NIMH	Kathleen O'Leary, M.S.W.	Deputy Chief of Women's Programs
ODS	Mary Frances Picciano, Ph.D.	Senior Nutrition Research Scientist
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NIDCD	Lana Shekim, Ph.D.	Director, Voice and Speech Program
OIR	Esther Sternberg, M.D.	Chief, Section on Neuroendocrine Immunology and Behavior
NCMHD	Derrick Tabor, Ph.D.	Centers of Excellence Program
CSR	Denise Wiesch, Ph.D.	Scientific Review Officer
OPASI	Elizabeth Wilder, Ph.D.	Director, Division of Strategic Coordination

NIH Coordinating Committee on Research on Women's Health Alternates, FY 2008 (continued)

Institute, Center, or Office	*Alternate*	*Title*
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OCPL	Marin Allen, Ph.D.	Deputy Director
NHGRI	Sanja Basaric	Program Analyst
NINR	Paul Cotton, Ph.D.	Program Director, Division of Extramural Activities
NIBIB	Anthony Demsey, Ph.D.	Director, Extramural Policy
NIGMS	Paula Flicker, Ph.D.	Program Director
NIAMS	Julia Freeman, Ph.D.	Contractor
NHGRI	Phyllis Frosst, Ph.D.	Science Policy Analyst
NIEHS	Mary Gant, M.S.	Legislative Officer
NINDS	Giovanna Guerrero, Ph.D.	Emerging Leaders Intern
NIDDK	Mary Hanlon, Ph.D.	Health Science Policy Analyst
CC	Walter Jones, M.S.	Deputy Director for Diversity Operations
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NIMH	Cathy Roca, M.D.	Contractor
NIAMS	Louise Rosenbaum, Ph.D.	Science Policy Analyst
FIC	Milagros Ruiz	Program Analyst/Contractor
OER	Denise Russo, Ph.D.	Extramural Policy Coordinator
NHLBI	Susan Scolnik	Program Analyst
CSR	Elaine Sierra-Rivera, Ph.D.	Deputy Chief, Oncological Sciences IRG
OSP	Lana Skirboll, Ph.D.	Director
NCMHD	Nathanial Stinson, M.D.	Director, Office of Scientific Programs
NCI	Susanne Strickland, M.S.	Chief, Strategic Coordination Branch and Women's Health Center

NIH Coordinating Committee on Research on Women's Health Alternates, FY 2008 (continued)

Institute, Center, or Office	*Alternate*	*Title*
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Office of Research on Women's Health Staff Roster, FY 2007

Vivian W. Pinn, M.D.	Associate Director for Research on Women's Health, OD, NIH Director, Office of Research on Women's Health
Lisa Begg, Dr.P.H., RN	Director, Research Programs
Joyce E. Rudick	Director, Programs and Management
Lynn Armentrout	Program Assistant
Angela C. Bates	Program Analyst
Erika Elvander	Public Health Analyst
Sharon Gist	Program Specialist (Office Manager)
Eleanor Z. Hanna, Ph.D.	Associate Director for Special Projects and Centers
Teresa R. Kendrix	Administrative Officer
Kimberly S. Kurilla-Gray	Secretary to the Director
Mary G. Lawrence	Program Analyst
Marsha Love	Communications Director
Jennifer Polhaus, Ph.D.	AAAS Fellow
Janine Smith, M.D.	Special Assistant to the Director
Charles A. Wells, Ph.D.	Senior Advisor

Office of Research on Women's Health Staff Roster, FY 2008

Vivian W. Pinn, M.D.	Associate Director for Research on Women's Health, OD, NIH Director, Office of Research on Women's Health
Janine Austin Clayton, M.D. (formerly Smith)	Deputy Director
Lisa Begg, Dr.P.H., RN	Director, Research Programs
Joyce E. Rudick	Director, Programs and Management
Lynn Armentrout	Program Assistant
Angela C. Bates	Program Analyst
Erika Elvander	Public Health Analyst
Sharon Gist	Program Specialist
Eleanor Z. Hanna, Ph.D.	Associate Director for Special Projects and Centers

Office of Research on Women's Health Staff Roster, FY 2008 (continued)

Teresa R. Kendrix	Administrative Officer
Kimberly S. Kurilla-Gray	Secretary to the Director
Mary G. Lawrence	Program Analyst
Marsha Love	Communications Director
Jennifer Polhaus, Ph.D.	AAAS Fellow
Charles A. Wells, Ph.D.	Program Analysis Officer

Reports of the Institutes and Centers

National Cancer Institute

Executive Summary

Cancer continues to take a devastating toll on American women. The American Cancer Society estimated that 692,000 women would be diagnosed with cancer and 271,530 women would die from cancer in 2008. Despite these grim statistics, significant progress has been made. Overall cancer incidence rates among women decreased between 1998 and 2005, and overall cancer death rates among women have continued to decrease since the early 1990s. These data indicate real progress; however, improvement has not been equal among all cancers or all populations.

The National Cancer Institute (NCI) coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their loved ones. NCI supports numerous research programs and projects that address cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. These efforts are conducted within or supported by many of NCI's Divisions and Centers. The programs and projects—several of which are collaboratively administered by multiple Divisions and Centers—include basic, translational, clinical, population-based, and dissemination research.

Many basic and translational research projects related to women's health are being carried out in model systems. Cultured cells are being used to characterize cervical cancer progression and elucidate the contributions of stress hormones to the tumor microenvironment. Mouse models have also contributed to a number of studies. They have been used to study cancer metastasis, providing insight into how neighboring cells can influence this process as well as revealing that metastasis may occur much earlier in tumor progression than traditionally thought. Mouse models have also provided a venue for testing novel therapeutic strategies for breast cancer, including a therapeutic vaccine and an approach to restore sensitivity to tamoxifen-resistant cells.

Numerous NCI-supported clinical studies are looking for better ways to prevent and treat cancers that commonly afflict women. Several novel chemopreventive approaches for breast cancer are being pursued, including new hormone modulators, anti-inflammatory agents, statins, and green tea extract. Other clinical trials are investigating techniques such as hyperthermia and intensity-modulated radiation therapy that may improve treatment of breast, cervical, and/or ovarian cancers. To help optimize its clinical trial process, NCI has established the NCI Coordinating Center for Clinical Trials, which currently has mechanisms in place to address the design and prioritization of Phase III and select Phase II clinical trials for breast and gynecologic cancers.

NCI also supports and conducts a number of population-based projects, the results of which inform future basic, translational, and clinical research. Numerous large-scale studies have been undertaken to identify expression profiles or genetic variants that can predict cancer risk, prognosis, or response to therapy. Some of these studies may help identify genes or proteins that contribute to cancer progression; others will help clinicians decide whether a precancerous breast or cervical lesion should be treated conservatively or aggressively. These studies will undoubtedly help expand personalized treatment of women with cancer. Other population-based studies examine various risk factors and outcomes. A correlative study has provided insight into how hormone therapy and mammography use have influenced breast

cancer incidence, and another study illustrated that equal access to care can eliminate disparities in ovarian cancer survival often observed between African-American and White women.

NCI is dedicated to speeding the delivery of knowledge and beneficial interventions to the community in order to truly reduce the burden of cancer. The Office of Communications and Education develops and disseminates numerous resources about cancer, including many related to women's health. NCI helped develop and publish guidelines for clinical management of women with cervical abnormalities. Another ongoing initiative supports several Centers of Excellence in Cancer Communication, which emphasize research on patient-centered communications needed to improve clinical outcomes across the entire cancer care continuum.

These and other examples of NCI accomplishments and efforts related to women's health across the discovery-development-delivery continuum are highlighted in this report. Additional information about women's health issues related to cancer can be found on the award-winning NCI Web site (http://www.cancer.gov/), which includes a page devoted to Women's Cancers (http://www.cancer.gov/cancertopics/types/womenscancers).

Introduction

Cancer continues to take a devastating toll on American women. The American Cancer Society estimated that 692,000 women would be diagnosed with cancer and 271,530 women would die from cancer in 2008. Despite these grim statistics, significant progress has been made in the fight against cancer. Overall cancer incidence rates among women decreased between 1998 and 2005, reflecting declines in the incidence of 6 of the 15 most common cancers among women—breast, colorectal, uterine, ovarian, cervical, and oral cavity and pharynx. Overall death rates from cancer have continued to decrease in both men and women since the early 1990s. Between 2002 and 2005, death rates decreased for 10 of the 15 most deadly cancers among women, including colorectal, stomach, kidney, brain, breast, uterine cervix, and bladder cancers as well as non-Hodgkin lymphoma, myeloma, and leukemia. These data indicate real progress in cancer control due to a combination of primary prevention, early detection, and treatment; however, improvement has not been equal among all cancers or all populations. Incidence rates among women increased for lung, thyroid, pancreas, bladder, kidney, and brain cancers as well as non-Hodgkin lymphoma, melanoma, and leukemia. Cancers with increasing mortality trends among women over this timeframe include pancreatic and liver cancers. Furthermore, many minority and underserved women continue to be burdened by increased incidence and mortality rates of many cancers despite improvements in overall trends.

The National Cancer Institute coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and loved ones. NCI supports numerous research programs and projects that address cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. This research focuses on all stages of disease, from disease prevention through cancer survivorship. NCI-funded researchers engage in research across the discovery-development-delivery continuum. These projects range from molecular and subcellular basic science experiments to population-based studies and community-based interventions. NCI strives to integrate its vast research portfolio to eliminate the burden of cancer experienced by all women, including the unequal burden imposed upon women from many minority and medically underserved populations.

NCI is also committed to disseminating research advances to the scientific community as well as the general public. The NCI Office of Communications and Education oversees the development and dissemination of numerous resources related to women's health. The award-winning NCI Web site, Cancer.gov (http://www.cancer.gov/), is the Institute's central vehicle for the dissemination of information to a diverse range of audiences. In April 2007, NCI launched the Spanish-

language version of this site, Cancer.gov en español (http://www.cancer.gov/espanol). NCI also produces the NCI Cancer Bulletin (http://www.cancer.gov/ncicancerbulletin/cancerbulletin), a biweekly online newsletter that provides useful, timely information about cancer research. NCI's Cancer Information Service (CIS) provides the latest, most accurate information about cancer treatment, clinical trials, early detection, and prevention for cancer patients, their families, and the public. U.S. residents can reach English- or Spanish-speaking NCI information specialists by calling toll-free at 1–800–4–CANCER (1–800–422–6237). An instant-messaging service called LiveHelp is also available on the NCI Web site.

Although far from comprehensive, the following pages provide a representative sampling of the activities and accomplishments of the National Cancer Institute relative to women's health in fiscal years 2007 and 2008. Disease areas included in this report are breast, cervical, ovarian, endometrial, lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome) and AIDS-associated malignancies. Research activities that directly address cancer health disparities are marked with an asterisk. NCI's investment in women's health is Institute-wide, as evidenced by the breadth of the accomplishments of the Divisions, Offices, and Centers that contributed to this report; in addition, there are several cross-cutting initiatives related to women's health involving transdisciplinary and multidisciplinary collaboration within NCI.

NCI Women's Health Officer

The Women's Health Officer at NCI is organizationally located within the Office of Science Planning and Assessment in the Office of the Director. The incumbent facilitates communication across the Divisions, Offices, and Centers of the Institute and promotes collaboration between NCI and other National Institutes of Health (NIH) Institutes and Centers, Federal agencies, and nongovernmental organizations. The Women's Health Officer develops and disseminates reports and information on NCI's research and research progress on cancers in women and coordinates NCI responses to agency requests for information.

Accomplishments

Center for Cancer Research (CCR)

Targeted Radiotherapy for Treatment of Ovarian Cancer

A radiolabeled drug targeting the HER2 oncogene may be useful for treating residual disease following surgical excision of ovarian cancer. Preclinical studies combining this targeted radioimmunotherapy with chemotherapy yielded promising results and revealed that dosage and administration sequence significantly influence the efficacy of the treatment paradigm. A Phase I clinical trial to investigate this immunoconjugate is currently being pursued as treatment for advanced ovarian cancer.

Unusual Association Between Cell Survival Proteins and Ovarian Cancer Aggressiveness

An international team led by NCI researchers has found that elevated levels of certain proteins typically associated with keeping cancer cells alive may actually correspond with improved patient survival in ovarian cancer. These proteins, all members of cellular networks that regulate apoptosis (programmed cell death) and responses to stress, together form a prognostic protein signature that provides key information about the tumor. If additional research verifies these findings, clinicians may be able to use this protein signature to gauge the aggressiveness of a woman's ovarian tumor at the time of diagnosis, as well as to identify patients who could benefit from various therapies.

Imaging of Ovarian Cancer Metastases to Improve Patient Outcomes

NCI scientists have developed optical fluorescent imaging probes that may help clinicians detect ovarian cancer implants (cancer cells that have implanted in nearby tissue). This could facilitate removal of the implants during surgery and potentially improve patient survival. A variety of potential agents developed by the research team are currently being tested in human ovarian cancer specimens. In addition, toxicity studies are being conducted

to prepare for translation of this innovation into clinical practice.

Prediction of Drug Sensitivity of Ovarian Cancers

Molecular profiling can help identify the molecular characteristics of tumor cells that correlate with success or failure of various treatments. This, in turn, should contribute to the personalization of cancer therapy. Toward this end, NCI researchers are using ovarian cell lines to evaluate expression of proteins in pathways that strongly influence the anticancer activities of numerous chemotherapeutic drugs, including cisplatin and trabectedin. This may help identify biomarkers in addition to pharmacologically pertinent pathways.

MicroRNAs in Cervical Cancer

MicroRNAs (miRNAs) are single-stranded RNA molecules of 21–23 nucleotides in length that regulate gene expression and can also play important roles in cancer development. NCI investigators are studying miRNA expression in normal cervix and cervical cancer tissues and have determined partial contributions of aberrantly expressed tumor-suppressor and oncogenic miRNAs to cell growth and proliferation. Understanding the roles of miRNA in cervical carcinogenesis may lead to novel therapeutics for prevention or treatment.

Potential Prognostic Biomarker for Breast Cancer Identified in Mice

Researchers have identified a pattern of gene activity in mice that may help predict survival and risk of metastases in breast cancer patients. A single gene called bromodomain 4 (Brd4) regulates the expression of this gene signature, which should improve understanding of the mechanisms underlying cancer progression in humans.

Newly Identified Genetic Variant May Affect Breast Cancer Risk

Researchers have identified a genetic variant on chromosome 6 that appears to be associated with risk for breast cancer. Women with the variant have a 1.4-fold greater risk of developing breast cancer than those without the variant. Identifying the gene(s) responsible for this increased risk may provide a new target for therapy.

Researchers Develop Method To Evaluate Mutations of Breast Cancer Susceptibility Gene

Researchers have developed a new method to predict whether certain mutations in BRCA2 prevent it from functioning normally within the cell. Mutations that disrupt BRCA2 function are known to increase risk of breast and ovarian cancers. If validated through epidemiological studies, the assay could become a useful and viable tool for genetic counselors. Furthermore, it may be useful for analyzing mutations found in other disease-related genes.

Therapeutic Vaccine Shows Promise in Mouse Model of Breast Cancer

Researchers have shown that administering a vaccine against HER2/neu (an oncogene in a significant fraction of breast cancers) elicits an immune response in mice capable of killing large, established breast cancer tumors and tumor cells that have spread to the lungs. A therapeutic vaccine may offer advantages over current HER2/neu-targeted treatments (e.g., Herceptin®) because it (1) results in continuous antibody production, eliminating the need for repeated drug infusions, (2) may induce production of antibodies targeting multiple regions of the receptor, and (3) may induce antibodies that work by different mechanisms than currently available therapies. Production of a human version of the vaccine is beginning in preparation for a clinical trial in breast cancer patients.

Targeted Drug Reduces Spread of Breast Cancer Cells to the Brain in Mice

The small molecule lapatinib (Tykerb®), which disrupts the HER2/neu signaling pathway, was shown to prevent outgrowth of large brain metastases in a mouse model of breast cancer. When administered shortly after injection of breast cancer cells, lapatinib reduced the number of large brain lesions that occurred. Lapatinib is the first HER2-directed drug to be validated in a preclinical prevention model for activity against brain metastasis of breast cancer.

Restoration of Tamoxifen Sensitivity to Resistant Breast Cancer Cells in Mice

The widely used breast cancer drug tamoxifen (Nolvadex®) becomes less effective over time; developing a way to overcome this resistance would be an important clinical advance. A recent study showed that the effectiveness of tamoxifen in cultured cells and mice could be restored by a compound called disulfide benzamide, or DIBA. Mice injected with tamoxifen-resistant breast tumor cells were used for the study; as expected, tamoxifen alone did not have a significant effect on tumor growth, but treatment with DIBA and tamoxifen reduced tumors to undetectable levels. These results suggest that an agent with activity similar to DIBA may be useful for restoring tamoxifen sensitivity to resistant human breast tumors.

Identification of Molecular Culprits of Cervical Cancer Progression

Most women who become infected with human papillomavirus (HPV) do not develop invasive cervical lesions, indicating that additional exogenous or genetic factors may determine whether HPV-associated lesions progress to cancer. Identification of these factors would be facilitated by a deeper understanding of the molecular changes that accompany progression to malignancy. Gene expression patterns that occur along the continuum of cervical cancer progression were collected and used to create the first genomically based model of cervical carcinogenesis. The model identifies gene expression changes that accompany transitions from early viral infection through invasive tumor development. Expansion and modification of this genomically based model through additional research should help illuminate factors that facilitate progression from HPV infection to cancer. The genes and pathways identified may also contribute to the discovery of biomarkers useful for cervical cancer screening.

Division of Cancer Epidemiology and Genetics (DCEG)

Genome-Wide Association Studies Identify Gene Variants Associated With Breast Cancer

Genome-wide association studies have been used to identify gene regions associated with the risk of many cancers, including breast cancer. Prior studies led to the discovery of gene regions associated with risk of early-onset breast cancer; however, much less is known about gene regions associated with late-onset breast cancer. A recent study genotyped over a half million single-nucleotide polymorphisms (SNPs) from postmenopausal women with invasive breast cancer and controls, all of self-identified European ancestry. Results identified four SNPs in the FGFR2 gene highly associated with late-onset breast cancer. This association was confirmed by three additional studies.

Accumulating data suggest that different types of breast cancers may have different risk factor profiles and thus might result from different etiologic pathways. A recent analysis used data from 20 studies to examine whether previously identified SNPs at five loci vary in their association with clinically important tumor characteristics. Results revealed that an SNP in FGFR2 is more strongly related to estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, low-grade, node-positive tumors. An SNP in 8q24 was also more strongly represented among ER-positive, PR-positive, low-grade tumors. Three SNPs showed weak but significant associations with ER-negative disease, the strongest association being for an SNP in TNRC9. These findings show that common genetic variants influence the pathological subtype of breast cancer and provide further support for the hypothesis that ER-positive and ER-negative disease are biologically distinct. Understanding the etiologic heterogeneity of breast cancer may ultimately result in improvements in prevention, early detection, and treatment.

Efforts to confirm putative genetic associations with breast cancer are being undertaken by the Breast Cancer Association Consortium, which conducts combined case-control analyses to augment statistical power. A

recent analysis used data from up to 15 studies to genotype 9 SNPs for which there was some prior evidence of an association with breast cancer. Two of the nine SNPs evaluated showed significant associations with invasive breast cancer: CASP8 D302H, an important initiator of apoptosis, and TGFB1 L10P, which regulates normal mammary gland development. These results demonstrate that common breast cancer susceptibility alleles with small effects on risk can be identified with sufficiently powerful studies.

A More Accurate Tool for Estimating Breast Cancer Risk in African-American Women*

The Breast Cancer Risk Assessment Tool (BCRAT) has been the standard computational tool to estimate breast cancer risk in women; however, the tool was developed using data exclusively from White women. To adjust the BCRAT to more accurately predict risk of invasive breast cancer in African-American women, data from African-American women enrolled in the Women's Contraceptive and Reproductive Experiences (CARE) Study were used to calculate relative and attributable risks based on a number of known breast cancer risk factors. Data on actual breast cancer cases from the Women's Health Initiative validated the CARE model's predictions. The CARE model (available at http://www.cancer.gov/bcrisktool/) is recommended for counseling African-American women regarding their risk of breast cancer and determining their eligibility for breast cancer prevention trials.

Contributions of Menopausal Hormone Therapy and Mammography to Breast Cancer Incidence

The incidence of breast cancer in the United States has risen steadily in recent decades until 2003, when it began to decline. Rates of menopausal hormone therapy use and screening mammography have also changed over time, but the relative contributions of these factors to breast cancer incidence are unclear. In order to elucidate the relationships among these factors, trends in breast cancer incidence, dispensed menopausal hormone therapy prescriptions, and screening mammography use among women enrolled in a large health plan from 1980 through 2006 were analyzed. The analysis revealed that the rise in breast cancer incidence rates through the late 1990s is consistent with the effects of mammography screening and increasing use of hormone therapy. The recent decline in incidence is consistent with the drop in menopausal hormone use.

Risk of Benign and Malignant Pathology Among Offspring of Women Exposed In Utero to DES

Animal studies suggest that prenatal exposure to the synthetic estrogen diethylstilbestrol (DES) causes epigenetic changes that may be transmitted to the next generation, particularly in the incidence of reproductive tumors among female offspring. To investigate these findings in human populations, cancer and benign pathology diagnoses occurring in offspring of women prenatally exposed to DES were assessed. Data were ascertained from mothers' reports of cancers occurring in 8,216 sons and daughters, and pathology-confirmed cancers and benign diagnoses self-reported by 793 daughters. No overall increase of cancer was observed, and there was no association between DES exposure and risk of benign breast disease or reproductive tract conditions in daughters. Based on three cases, the incidence of ovarian cancer was higher than expected; while preliminary, this finding supports continued monitoring of daughters of women exposed prenatally to DES.

Distinguishing High-Risk and Low-Risk Endometrial Hyperplasia

Endometrial hyperplasia (EH) is a pathologically heterogeneous diagnosis that ranges from histologically subtle (and potentially spontaneously reversible) to incipient carcinoma. The ability to distinguish low-risk EH lesions that can be conservatively managed from high-risk lesions necessitating surgery would have important clinical implications. EH progression was evaluated in women later diagnosed with endometrial carcinoma and controls who did not progress to carcinoma within a similar timeframe. The study revealed that simple hyperplasia, complex hyperplasia, and disordered proliferative endometrium

*Relative to health disparities.

were low-risk lesions that may be amenable to conservative management with close surveillance. In contrast, atypical hyperplasia and complex atypical hyperplasia were associated with significantly elevated risk of carcinoma within 1 to 5 years. On the basis of these findings, a dichotomous classification of nonatypical versus atypical EH, along with refined detection and classification of endometrial hyperplasia, could improve clinical management of endometrial lesions.

PTEN as a Marker of Progression to Endometrial Carcinoma

Multiple lines of evidence support a role for the PTEN tumor suppressor gene as a marker for endometrial carcinoma. A recent study examined PTEN expression in endometrial hyperplasia. PTEN status (normal versus null) was compared between women who were later diagnosed with endometrial carcinoma and those who did not progress to carcinoma during equivalent followup. Loss of PTEN expression in endometrial biopsies was not associated with increased risk of subsequent progression to endometrial carcinoma.

Cigarette Smoking and Lung Cancer Risk in Men and Women

There has been much debate about whether there are sex differences in susceptibility to tobacco carcinogens, and it is generally held that women are more susceptible than men. To address this question, incidence rates of lung cancer by smoking status in 279,214 men and 184,623 women from the NIH-AARP cohort were compared. Smoking was strongly associated with lung cancer risk in both men and women. Incidence rates of adenocarcinoma, small-cell carcinoma, and undifferentiated tumors were similar in men and women; incidence rates of squamous tumors were approximately twice as high in men as in women. These findings suggest that women are not more susceptible than men to the carcinogenic effects of cigarette smoking in the lung; in fact, among smokers, incidence rates tended to be higher in men than women with comparable smoking histories, although differences were modest. Future studies should confirm whether incidence rates are higher in women who have never smoked than in men who have never smoked.

Differences in Risk Factors for Breast Cancer Subtypes

An NCI-sponsored breast cancer study in Poland investigated whether pathologic features and etiologic associations differ among molecular subtypes. Cases were classified into five molecular subtypes: luminal A, luminal B, HER2-expressing, basal-like, and unclassified. Results showed that compared with the predominant luminal A tumors, other subtypes—especially HER2-expressing and basal-like tumors—were associated with unfavorable clinical features at diagnosis. Increasing body mass index significantly reduced the risk of luminal A tumors among premenopausal women, but not for basal-like tumors. On the other hand, reduced risk associated with increasing age at menarche was stronger for basal-like than luminal A tumors. Although family history increased risk for all subtypes (except for unclassified tumors), the magnitude of the relative risk was highest for basal-like tumors. Analysis of data from this study supports the hypothesis that risk or protective factors differ by tumor subtype, suggesting that a better understanding of breast cancer etiology may provide opportunities for improved prevention.

Environment and Genetics in Lung Cancer Etiology (EAGLE) Study

In collaboration with Italian colleagues, NCI researchers launched a population-based case-control study in the Lombardy region of Italy to identify the genetic and environmental determinants of lung cancer and smoking. Using tumor and nontumor tissue samples from current, former, and never smokers, the investigators found a unique gene expression pattern in smokers that includes cell cycle genes. This pattern strongly differentiated current and former smokers' lung tumors from those of nonsmokers. Furthermore, it was present in lung tumors and early-stage tumor tissue, but not in normal lung tissue. The expression of two of these cell cycle genes in noninvolved lung tissue of current or former smoker lung cancer patients was associated with a threefold increased risk of mortality.

Additional biomarkers and common genetic variants are being evaluated in this study.

Office of HIV and AIDS Malignancy (OHAM)

Women's Interagency HIV Study (WIHS)

The WIHS study—started in 1993 and jointly sponsored by NCI, the National Institute of Allergy and Infectious Diseases, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)—was established to investigate the impact of HIV infection on women. Participants include over 3,500 HIV-positive and -negative women. More than 80 percent of participants represent minority populations. This cohort provides researchers an excellent opportunity to monitor the occurrence, distribution, and determinants of HIV-associated malignancies. It also allows investigation of the interplay of viruses, coinfections, and immune dysregulation in cancer pathogenesis. WIHS utilizes Pap tests, colposcopies, and biopsies to prevent and study cervical cancer in the susceptible HIV-positive population. Results have revealed that Pap test abnormalities are more common among HIV-positive than HIV-negative women; furthermore, HIV-positive women treated for cervical intraepithelial neoplasia (CIN) are more likely to experience a recurrence of their cancer than their HIV-negative counterparts.

HPV Vaccine Study in India

India has one of the highest cervical cancer incidence rates in the world; however, little is known about the prevalence and incidence of cervical HPV infection in Indian women and less is known about HPV infection and CIN in HIV-positive Indian women. A study has been initiated to investigate the safety of the Merck HPV vaccine among HIV-positive women in Mumbai, India. The study will also investigate the effect of the vaccine on HIV viral load and CD4+/CD8+ levels, determine the serologic response of HIV-positive women to the vaccine, and evaluate CIN and the spectrum of HPV types in HIV-positive women at baseline and after 1 year. This study will directly address the important problem of HPV-associated cancers in HIV-positive women.

Training in the Epidemiology of HPV/ Cervical Neoplasia Among HIV-Positive Women

A project has been initiated to build resource capacity by providing training in clinical/epidemiological studies of HPV-associated disease in HIV-positive women. This effort builds on previously established training programs between the New York State AIDS International Training and Research Program (NYS-ITRP) and three countries in Central Europe (Czech Republic, Hungary, and Poland). This project focuses primarily on Poland, where HIV rates are higher than in other Central European countries and where HPV and cervical cancer have become a significant public health problem. The primary goals of this project are to build human resource capacity by providing training in clinical/epidemiologic studies of HPV-associated disease in HIV-positive women, build in-country (Polish) research capacity, and use existing in-country (Polish) training assets to enhance regional training efforts. The proposed training should result in development of clinical and public health investigators in Poland with appropriate backgrounds and experience to follow trends in cervical disease and HPV among HIV-positive women in Poland.

Division of Cancer Biology (DCB)

Three-Gene Combination Can Predict Aggressive Ductal Carcinoma In Situ

Not all ductal carcinomas in situ (DCIS) become aggressive breast tumors; it is therefore difficult for clinicians to decide whether aggressive therapy should be administered. Researchers examined the molecular characteristics of DCIS tumors obtained from breast cancer patients and correlated these molecular profiles with clinical outcomes. Expression of three genes—p16, Cox-2, and Ki6—predicted whether the DCIS lesion was likely to develop into an aggressive tumor. Tumors expressing these genes may be the best candidates for aggressive therapy.

Novel Predictors of Tamoxifen Responsiveness

Some breast tumors that express estrogen receptors exhibit tamoxifen resistance, either initially or after chronic exposure to the drug. The ability to identify patients with tamoxifen-resistant tumors a priori would be a significant clinical advance. Comparison of tamoxifen-sensitive and -resistant breast tumors led to the discovery that the Wwox protein is expressed at significantly lower levels in tamoxifen-resistant than tamoxifen-sensitive tumors. Furthermore, Ap2gamma, a protein that binds to Wwox and is normally retained in the cytoplasm, was found to be present in the nucleus of tamoxifen-resistant tumor cells. Thus, Wwox and Ap2gamma may be useful for predicting tamoxifen response.

Aromatase Inhibitor and Antiestrogen Combination Therapy Less Effective Than Either Alone

Estrogen and progesterone play important roles in breast cancer. Hormonal treatment for breast cancer involves either blocking the action of estrogen receptors (using antiestrogens or selective estrogen receptor modulators) or inhibiting synthesis of estrogen (using aromatase inhibitors). To determine whether using both types of inhibitors simultaneously would be advantageous, investigators tested the paradigm in mice harboring mammary tumors. Surprisingly, combination treatment caused tumors to grow larger. These results suggest that patients should not be given both estrogen receptor inhibitors and aromatase inhibitors simultaneously.

FOXC2 Associated With Aggressive Estrogen Receptor-Negative Breast Cancer

Breast cancers may be either estrogen receptor-positive or -negative. There are several treatment options for ER-positive breast cancers and the prognosis for these patients is generally good; however, ER-negative breast cancers are more aggressive and have limited treatment options. Research on the biology of ER-negative tumors is a high-priority area as it may lead to identification of new treatment targets. Analysis of ER-negative tumors has revealed high expression of FOXC2. This protein, which is normally expressed only during embryogenesis, appears to play an important role in the aggressive nature of ER-negative breast cancers.

Epithelial to Mesenchymal Transition Confers Stem-Like Cell Properties to Breast Cancer Cells

The epithelial-mesenchymal transition, a normal part of human development, often occurs during cancer invasion and metastasis. A recent study revealed that breast epithelial cells that have acquired mesenchymal traits express markers of self-renewing stem cells and exhibit behaviors similar to stem cells. These findings illustrate a direct link between epithelial-mesenchymal transition and the gain of stem cell properties. This discovery may help elucidate how tumor cells travel to and colonize distant tissues.

Nearby Cells Increase Metastatic Ability of Human Breast Cancer Cells

Researchers have determined how mesenchymal stem cells, which are derived from bone marrow cells, can cause weakly metastatic breast cancer cells to become highly metastatic. Breast cancer cells stimulate secretion of special factors from the mesenchymal stem cells, which then enhance the ability of the breast cancer cells to migrate and metastasize. This enhanced metastatic ability is reversible and demonstrates how cells in the immediate neighborhood are able to influence tumor cell behavior. These studies were conducted using human breast cancer and mesenchymal stem cells injected into mice.

Novel Paradigm of Breast Cancer Dissemination in Early-Stage Disease

Traditionally, metastasis has been thought of as a trademark of late-stage cancer, but a recent study suggests a new paradigm. Researchers found that normal mammary cells injected into the bloodstream of a mouse could colonize in the lung. These cells remained viable for a long period of time but did not develop into tumors until an oncogene was activated. These results demonstrate that tumor cells may metastasize during the early stages of tumorigenesis and accumulate the genetic changes necessary for metastatic

growth long after they have colonized a distant site. Thus, metastatic tumors could develop characteristics distinct from primary tumors to optimize growth in a different environment; these differences may result in varied responses to therapy.

HOXB13: A Novel Biomarker for Hormone-Resistant Ovarian Cancer

HOXB13, a gene correlated with aggressive clinical course and poor outcomes for breast cancer, has also been shown to promote ovarian cancer progression. In addition to having proliferative and pro-survival functions, HOXB13 may play an important role in the development of tamoxifen resistance in patients with estrogen receptor-positive ovarian cancer.

Equal Care Eliminates Racial Disparities in Ovarian Cancer Survival*

The 5-year survival rate of White women with ovarian cancer increased between 1975 and 2002, but rates for African-American women fell during the same time period. To examine potential contributors to this disparity, NCI-funded investigators used a cohort of women with equal access to medical care within a single institution to further examine racial differences in ovarian cancer survival. No differences in disease-free and overall survival were observed, indicating that White and African-American women with ovarian cancer will have equal outcomes if provided equal care.

New Mouse Model of Endometrial Cancer

The etiology of endometrial cancer (cancer of the uterine epithelium) is not fully understood, and progress in this area has been hindered by a lack of animal models. NCI-funded investigators recently created mice that develop endometrial cancer by deleting the PTEN gene in the endometrium. This mouse model mimics several features of human endometrial cancer and will allow scientists to examine factors that contribute to endometrial cancer initiation and progression.

* Related to health disparities.

Inflammation, Estrogen, and Endometrial Cancer

The key role of estrogen in endometrial pathophysiology is well known, and a recent study also highlights the contributions of inflammation to estrogen activity in the uterus. Treatment with an inflammatory protein resulted in increased estrogen synthesis by endometrial cells and created conditions favoring conversion of estrogen to more hormonally active and carcinogenic metabolites.

Advances from the Mouse Models of Human Cancers Consortium

Many mouse models developed through the NCI Mouse Models of Human Cancers Consortium (MMHCC) are being used to study cancers that disproportionately affect women. Some of these preclinical models are used to identify potential biomarkers for early detection of cancer. One set of researchers developed a staged pipeline of comparative proteomics to facilitate biomarker discovery. This approach resulted in the discovery that a protein called osteopontin has potential as a plasma biomarker of early HER2/neu-positive breast cancer. Another group is using a mouse model of human endometroid ovarian cancer to identify sugar molecules on the surface of ovarian cells that may be useful as serum biomarkers.

Researchers are also finding ways to use mouse models to study cancer stem cells. One group found that a subset of tumors that form in a model of p53-deficient breast cancer arises from cancer stem cells. In addition to providing in vivo data to support the existence of cancer stem cells, this model should be useful for identifying additional breast cancer stem cell markers and testing their functional importance.

Division of Cancer Control and Population Sciences (DCCPS)

Healthy Lifestyles and Breast Cancer

There is accumulating evidence that engaging in healthy lifestyles can help women reduce their risk of morbidity and mortality due to breast cancer. Analysis of data from the Breast Cancer Surveillance Consortium

showed that overweight or obese postmenopausal women face an increased risk of breast cancer. This increased risk is unrelated to differences in mammography accuracy or rates of use, suggesting that biology may play a role. Evaluation of participants in the NCI-funded California Teachers Study—a prospective study of current and retired female California public school teachers and administrators—revealed that strenuous, long-term physical activity confers protection against breast cancer, particularly estrogen receptor-negative breast cancer.

Changing Trends in Hormone and Mammography Use

A recent analysis revealed that breast cancer incidence in the United States remained low in 2004 after sharply declining in 2003. This trend, which follows more than two decades of rising breast cancer incidence, parallels the decline in hormone replacement therapy use that was spurred by the 2002 report linking certain hormones to health risks, including breast cancer. The result provides further support for the notion that discontinuation of hormone replacement therapy leads to decreased breast cancer incidence. It is still unclear whether the decrease in incidence will lead to a decrease in mortality from breast cancer.

Although the study described above did not find breast cancer screening habits to be a major contributor to the observed decline in breast cancer incidence, the declining use of mammography identified by analysis of Centers for Disease Control and Prevention (CDC) National Health Interview Survey data is causing concern. Screening rates were found to be lower in nearly all groups of women examined, including groups defined by age, insurance status, and socioeconomic status. Decreased screening could result in later diagnosis as well as an increase in mortality from breast cancer. In response to this study, Senator Barbara Mikulski (D-MD) invited all female Senators to a special public meeting on mammography, which included discussion by a panel of experts from NCI, CDC, the American Cancer Society, and Susan G. Komen for the Cure.

Improving Outcomes for Older Women With Breast Cancer

Older women are often underrepresented in the clinical trials that lead to treatment and followup guidelines for breast cancer; however, several recent studies conducted through the NCI-sponsored HMO Cancer Research Network reinforce the importance of understanding this vulnerable population and ensuring these women receive optimal care. Two studies revealed that older breast cancer survivors—who are more likely than younger survivors to experience recurrence—are less likely to adhere to followup care guidelines, including tamoxifen and mammography use. These data are particularly troubling in light of other research focused on breast cancer patients over the age of 65. One study demonstrated that annual mammography dramatically lowers risk of death from breast cancer among breast cancer survivors in this age group—a cumulative reduction in risk of 88 percent over 4 years. A second study showed that older women with breast cancer who receive radiation therapy and 5 years of tamoxifen following breast-conserving surgery have reduced risk of cancer recurrence compared with women who have surgery only.

Connecting Social Context and Health Disparities*

Two sites funded through the NCI Centers for Population Health and Health Disparities program focus on understanding breast tumor growth, progression, and treatment among inner-city women. One of these centers is investigating why Black women in the United States and West Africa develop breast cancers at younger ages and with more aggressive courses than women of Northern European ancestry. The multidisciplinary center draws upon the expertise of social workers, psychologists, physicians, and molecular geneticists to examine medical, biological, and social contributors to these observed disparities. Neighborhood and community factors such as rates of violent crime, living situations, and social connectedness are an important focus of the effort. Insights gained from animal models of social isolation and cell culture models of chronic

* Related to health disparities.

exposure to stress hormones will be applied to studies of human populations to illuminate contributions of these environmental factors to disparities in breast cancer. The second center is exploring neighborhood effects on the stage of breast cancer at time of diagnosis; interestingly, a recent study showed that both initial neighborhood disadvantage and upward neighborhood socioeconomic change were associated with greater odds of metastasis at the time of breast cancer diagnosis.

Stress and Depression Linked to Changes in Ovarian Tumors

Researchers have found that patients with ovarian cancer who have experienced symptoms of depression and stress have elevated levels of an enzyme called MMP9 in their macrophages, influential cells in the tumor microenvironment. MMP9 has been previously shown to induce cancer cells to invade and metastasize. The ability of stress hormones to directly increase levels of MMP9 in macrophages was confirmed in laboratory studies. These findings provide a new understanding of biobehavioral influences on the tumor microenvironment and may have implications for targeted pharmacologic or behavioral interventions for ovarian cancer patients.

Math Model Projects Health and Economic Effects of HPV Vaccine

Effects of HPV vaccination on cervical cancer outcomes in the United States will not become evident for many years, but researchers have used a mathematical model to project the cost-effectiveness of the vaccination in order to aid decisions regarding vaccination and screening. The calculations—built on a model of sexual behavior and the carcinogenic effects of the virus on cervical tissue—showed that routine vaccination of 12-year-old girls along with routine cervical screening would likely be economically attractive. Cost-effectiveness decreased if older girls were also vaccinated. On the other hand, cost-effectiveness could be increased if high vaccination coverage were combined with less frequent screening. Overall, the cost-effectiveness of HPV vaccination will depend on the duration of vaccine immunity and will be optimized if high vaccination rates are achieved. Cost-effectiveness could also likely be improved by modification of screening guidelines.

Tobacco Use and Women

A survey of nearly 8,000 pregnant women from 9 developing nations in Latin America, Asia, and Africa indicates that cigarette smoking during pregnancy is a current or emerging problem in several countries. Furthermore, many pregnant women as well as their young children are frequently or always exposed to secondhand smoke. The findings of the study—which was conducted by NCI and NICHD with support from the Office of Women's Health and the Bill and Melinda Gates Foundation—highlight the need to implement evidence-based interventions to prevent and control tobacco use among pregnant women in these countries.

Tobacco Control Policies: Effects Among Women and Girls of Low Socioeconomic Status*

The Low Socioeconomic Status Women and Girls Project, which is part of the Tobacco Research Network on Disparities (TReND), published a report titled Tobacco Control Policies: Do They Make a Difference for Low Socioeconomic Status Women and Girls? (http://cancercontrol.cancer.gov/tcrb/ses_women-girls_project/September08.pdf) in September 2008. The report is the result of a collaborative effort that began in 2005 with a meeting sponsored by TReND. The report contains a summary of the meeting discussions and key recommendations for strengthening the evidence base to better inform tobacco-related health and social policies. The report also highlights key findings from eight peer-reviewed studies that resulted from the meeting discussions.

Lung Cancer Incidence Rates Among Women Who Have Never Smoked

Although tobacco use remains the predominant cause of lung cancer, a new study of six large cohort populations has revealed that lung cancer rates among people who have never smoked are higher among women than men.

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* Related to health disparities.

Researchers have not identified the underlying cause(s) of this disparity, but potential risk factors include secondhand smoke exposure; occupational exposures to asbestos, chromium, or arsenic; environmental exposures such as domestic radon; indoor pollutants; previous lung disease; dietary factors; family history; and genetic factors. A better understanding of the factors responsible for lung cancer in never smokers is necessary to improve treatments and outcomes for this population.

Division of Cancer Prevention (DCP)

Raloxifene Approved for Breast Cancer Risk Reduction

In September 2007, the U.S. Food and Drug Administration (FDA) approved raloxifene hydrochloride tablets (Evista®) for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer. This decision was largely based on 2006 results of the NCI-supported Study of Tamoxifen and Raloxifene (STAR), which showed that raloxifene is as effective as tamoxifen in reducing a postmenopausal woman's risk of developing invasive breast cancer (a reduction of about 50 percent).

Novel Approaches to Breast Cancer Chemoprevention

Previous studies of tamoxifen and aromatase inhibitors have illustrated the potential of drug therapy to reduce the risk of developing breast cancer among high-risk women. Research on additional chemopreventive approaches is under way. For example, because approximately 10 percent of women are unable to produce the active form of tamoxifen (4-hydroxytamoxifen) after the drug is administered, one study is testing whether directly delivering 4-hydroxytamoxifen through the skin might help protect these women from breast cancer. Also, a third-generation estrogen receptor modulator, acolbifene, will soon be tested in women at increased risk of breast cancer.

Several other types of agents are also being investigated for breast cancer prevention, including sulindac (a nonsteroidal anti-inflammatory drug), polyphenon E, atorvastatin, and flaxseed lignan. Analysis is currently under way for a trial examining the ability of isoflavones to reduce breast cancer risk.

Biorepository Available for Breast Cancer Research

A biorepository has been created that includes White blood cells and serum from more than 33,000 women at increased risk of developing breast cancer, as well as tissue from 230 breast tumors. The biospecimens were collected from the participants of STAR and its predecessor trial, the Breast Cancer Prevention Trial (BCPT). These materials are available to the scientific community as an open resource. The National Surgical Adjuvant Breast and Bowel Project (the cooperative group that coordinated the trials) has used the specimens to examine molecular factors that may contribute to breast cancer risk.

Removal of Ovaries to Reduce Cancer Risk

The lifetime risk of ovarian cancer in the general population is about 1.4 percent by age 70, but women with mutations in the BRC or BRCA2 genes face a cumulative risk of 16–40 percent. Preventive removal of the ovaries and fallopian tubes lowers the risk of ovarian and breast cancer, but the magnitude of these risk reductions is still uncertain. A trial jointly supported by the NCI intramural Clinical Genetics Branch, the Gynecologic Oncology Group, and the Cancer Genetics Network will more precisely quantify the extent of cancer risk reduction after preventive surgery. The study will also assess quality of life, measure incidence of noncancer diseases related to premature menopause, and evaluate a novel approach to ovarian cancer screening.

Cervical Cancer Prevention in the HPV Vaccine Era

The HPV vaccine is a milestone for cancer prevention efforts and has the potential to dramatically affect cervical cancer rates. Elimination of HPV16- and HPV18-associated abnormalities will lower cervical cancer risk in vaccinated populations; however, protection against HPV subtypes not included in

current HPV prophylactic vaccines is needed. New agents—such as Polyphenon E (a green tea extract), DIM (3′3′-Diindolymethane), and carrageenan—may have potential as adjunct interventions for cervical cancer prevention.

Maintaining cervical cancer screening at the current intensity in vaccinated populations will result in redundancy of prevention efforts at enormously increased cost, without necessarily reducing cervical cancer mortality; effective integration of vaccination and modified screening approaches will be a critical and evolving challenge.

It is often difficult for clinicians to integrate scientific findings in order to communicate overall risk to patients. DCP is collaborating with NCI's DCEG to develop a cervical cancer prediction tool that would provide individual risk assessment based on a patient's age, cytology results, and other risk factors.

DCP collaborates with DCEG to support a 7,000-woman vaccine study in Costa Rica. Early findings from this trial have shown that the vaccine does not accelerate clearance of prevalent HPV infection. The trial will continue to provide crucial data on aspects of vaccination efficacy and immunology, as well as the long-term effects of vaccination on screening. DCP also supports an officer in the U.S. Public Health Service who is working to implement a "Screen and Treat" protocol into its humanitarian missions in order to decrease the burden of cervical cancer in countries in South and Central America and the Caribbean.

Guidelines for Managing Women With Cervical Abnormalities

Millions of women receive abnormal cervical cancer screening results each year, but recommendations for medical care did not reflect the most recent scientific information. In 2007, updated evidence-based national consensus guidelines for management of women with cervical abnormalities were published in two peer-reviewed journals. These guidelines were developed by 146 experts representing 29 organizations at a 2006 workshop cosponsored by DCP and the American Society for Colposcopy and Cervical Pathology. The results of the NCI-sponsored atypical squamous cells of undetermined significance (ASCUS)/low-grade squamous intraepithelial lesion (LSIL) Triage Study (ALTS) contributed substantially to the guidelines. Completed in 2000, the ALTS trial was designed to find the best way to manage the mild abnormalities often revealed by Pap tests.

Division of Cancer Treatment and Diagnosis (DCTD)

Hyperthermia To Improve Treatment of Breast, Cervical, and Ovarian Cancers

Hyperthermia (i.e., temperatures a few degrees above 37°C) is being evaluated for enhancing response to standard treatment of breast cancer recurring in the chest wall, as well as for locally advanced and recurrent cervical and ovarian cancer. Preclinical and pilot clinical studies have yielded very encouraging results. An international Phase III trial was initiated in 2003 to determine if the addition of concurrent hyperthermia to standard chemoradiotherapy would improve local control, failure-free survival, and overall survival of patients with locally advanced cervical cancer. The trial is being carried out at Duke University Medical Center as well as sites in Germany, Italy, Norway, and the Netherlands. Phase I/II clinical trials in patients with relapsed or refractory ovarian cancer have been conducted to test hyperthermia in combination with intraperitoneal chemotherapy administration and liposome-encapsulated chemotherapy, with promising results. An ongoing Phase I study is testing low-temperature-sensitive liposomal doxorubicin with hyperthermia in breast cancers with chest wall recurrences.

Intensity-Modulated Radiation Therapy for Treatment of Breast Cancer

Intensity-modulated radiation therapy (IMRT) employs sophisticated computerized treatment planning to sculpt the radiotherapy treatment field to the tumor in order to avoid sensitive normal tissues adjacent to the tumor. For treatment of breast cancer, this requires shaping the radiation field to the curved surface of the chest to minimize the dose to the heart. This effort is complicated by movement of the chest wall and heart during breathing. NCI-funded researchers have studied heart

motion during respiration in patients using an active breathing control device. These data will be used to design treatment regimens that minimize cardiac exposure to radiation during radiotherapy.

Imaging to Aid in Cancer Detection, Diagnosis, and Staging

Women with breast cancer have an elevated risk of cancer occurrence in the opposite (contralateral) breast. A study is being conducted to determine whether magnetic resonance imaging (MRI) can detect these cancers at an earlier stage than clinical breast exams or mammography.

Positron emission tomography/x-ray computed tomography (PET/CT) is being tested as a technique to identify cervical cancer that has metastasized to abdominal lymph nodes. Development of reliable imaging markers for this purpose could potentially spare the considerable morbidity associated with invasive lymph node sampling.

Imaging and Imaging Agents to Predict Therapeutic Response

Development of noninvasive techniques to predict tumor response to potential therapies would facilitate a more personalized approach to cancer treatment and have significant clinical implications. A clinical trial is under way to determine whether MRI might provide insight into how women with Stage III breast cancer will respond to therapy. PET and PET/CT are also being used in conjunction with various imaging agents to determine whether these approaches can predict response of breast and cervical cancers to treatment. One agent, 18fluoroestradiol, is being tested in breast cancer patients as a marker for response to hormone therapy. 64Cu-ATSM (copper(II)-diacetyl-bis(N4-methylthiosemicarbazone)) is being tested as a predictor of treatment outcome in women with invasive squamous cell cervical carcinoma.

Emerging Devices for Breast Cancer Management

The NCI Cancer Imaging Program is supporting the development of several novel devices with potential to significantly alter clinical management of breast cancer. A photoacoustic tomography device that can be employed in conjunction with conventional ultrasound imaging has the potential to improve spatial resolution and may provide a real-time imaging tool for sentinel lymph node mapping and auxiliary staging. A cost-effective handheld optical imaging device meant to measure response to neoadjuvant therapy is also being developed. Another optical assay device is undergoing clinical validation studies—this device has the capacity to analyze the margins of breast tissue removed during surgery in real time and may help ensure that tumors are completely removed, reducing the likelihood that a second surgery will be needed.

Specialized Programs of Research Excellence (SPOREs)

SPOREs, which are funded through specialized center grants, promote interdisciplinary research with potential to reduce cancer incidence and mortality as well as improve the quality of life of cancer patients and survivors. Laboratory and clinical scientists work collaboratively to plan, design, and implement research programs that may impact cancer prevention, detection, diagnosis, and treatment. Several SPOREs focus on cancers that disproportionately or exclusively affect women; these include 11 Breast SPOREs, 2 Gynecologic SPOREs, and 5 Ovarian SPOREs. Other organ-site-specific SPOREs also often address issues related to women's health.

Ovarian Cancer SPOREs

Using samples from the Nurses' Health Study and the New England-based Case-Control study, investigators from the Dana Farber/Harvard Cancer Center SPORE noted a 36 percent increase in risk of ovarian cancer and a 60 percent risk of serious invasive cancer among women who used talc on a regular basis (i.e., more than once per week). The investigators are in touch with the FDA regarding potentially adding a warning on talcum powder.

University of Texas M.D. Anderson Cancer Center Ovarian SPORE investigators are developing and evaluating new statistical techniques that may be able to combine information

about multiple biomarkers over time for early detection of ovarian cancer.

Breast Cancer SPOREs

The 11 Breast Cancer SPOREs conduct collaborative 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, Bay Area Breast Cancer SPORE researchers have identified a promising new prognostic biomarker combination, which, after appropriate validation, may be able to predict the development of invasive breast cancer in women diagnosed with ductal carcinoma in situ, a common precancerous condition. Baylor Breast Cancer SPORE investigators recently provided clinical evidence of a subpopulation of chemotherapy-resistant breast-cancer-initiating cells and their sensitivity to a tyrosine kinase inhibitor, lapatinib.

Gynecologic Cancer SPOREs

The SPORE in Endometrial Cancer at the University of Texas M.D. Anderson Cancer Center conducts innovative translational research for the prevention and treatment of uterine tumors. SPORE investigators recently identified serum adiponectin as a strong predictor of endometrial cancer risk.

The Cervical Cancer SPORE at the Johns Hopkins University School of Medicine is focused on the development of new vaccines intended for treatment and prevention of cervical cancer. The SPORE has multiple interactions with the NCI Rapid Access to Intervention Development (RAID) and Intramural Programs, as well as companies, foundations, and universities.

Lung Cancer SPOREs

Estrogen receptor beta has been detected in non-small cell lung cancer (NSCLC) cell lines and tumor specimens. Fulvestrant (a drug that downregulates estrogen receptors) blocked estradiol-stimulated tumor growth and gene transcription in NSCLC preclinical models. Additive effects were observed when fulvestrant was used in combination with the epidermal growth factor receptor (EGFR) inhibitor gefitinib. The safety and tolerability of combination therapy with gefitinib and fulvestrant were explored in an early-phase clinical trial with 22 postmenopausal women. The regimen was well tolerated and demonstrated disease activity. Based on these results, a Phase II study combining erlotinib with fulvestrant is under way, and the research group is also developing a dose escalation study of fulvestrant with vandetanib, a multitargeted inhibitor, in lung cancer. While the Phase I study focused solely on women, both Phase II trials are enrolling pre- and postmenopausal women and men in order to more fully understand the role of estrogen blockade in NSCLC.

Coordinating Center for Clinical Trials (CCCT)

The Coordinating Center for Clinical Trials is charged with coordinating implementation of the recommendations of the Clinical Trials Working Group (http://restructuringtrials.cancer.gov/files/ctwg-report.pdf) and the Translational Working Group (http://www.cancer.gov/aboutnci/trwg/Order-final-report) in conjunction with NCI's operating Divisions, Offices, and Centers.

Disease-Specific Scientific Steering Committees (SSCs) are being developed to leverage existing Intergroup, Cooperative Group, SPORE, and Cancer Center structures for each major disease area as well as for symptom management/supportive care to address, design, and prioritize Phase III trials. This system is designed to promote an open, collaborative process for setting clinical trial priorities and reducing redundancy.

The Scientific Steering Committees are designed to provide robust analysis of proposed concepts and facilitate exchange of ideas among a broad range of stakeholders. Major goals of the SSCs and their associated Task Forces are to increase the efficiency of clinical trial collaborations, curb the potential for duplicative Phase II and III clinical trials, and increase information exchange at early stages of trial development. Each SSC evaluates and prioritizes clinical trial concepts, drawing on the expertise of its constituent members, including NCI Cooperative Group Disease Committee Chairs, SPORE investigators, R01/

P01 translational scientists, biostatisticians, community oncologists, patient advocates, NCI staff, as well as liaisons from the NCI Investigational Drug Steering Committee and Symptom Management & Health-Related Quality of Life Steering Committee.

Thus far, SSCs directly related to women's health include the Gynecologic Cancer Steering Committee (GCSC) and the Breast Cancer Steering Committee (BCSC). The GCSC currently includes three disease-specific task forces focused on ovarian, cervical, and uterine cancers. The GCSC will review all Phase III and select randomized Phase II concepts involving Intergroup and international collaborations. The GCSC has approved 15 trials since May 2006 and supported State of the Science meetings on Endometrial Cancer (November 2006) and Cervical Cancer (September 2007). The BCSC held its first meetings in late 2008. The three BCSC task forces will begin working on prioritized concepts starting in early 2009.

Initiatives

Although not comprehensive, the following section lists several emerging and ongoing NCI initiatives that address various aspects of women's health.

Selected Requests for Applications

- **Centers of Excellence in Cancer Communication Research (CECCR) II**
  The CECCR II program funds transdisciplinary research in cancer communication with the purpose of contributing directly to positive health outcomes and quality of life for individuals. A distinguishing characteristic of this second round of CECCRs is a special emphasis on the patient-centered communications needed to improve clinical outcomes across the entire cancer care continuum. Many of the newly funded Centers focus on communication issues relevant to women, including women from minority or underserved populations. (RFA-CA-08-004)

- **Cancer Intervention and Surveillance Modeling Network (CISNET)**
  CISNET is a consortium of NCI-sponsored investigators that use statistical modeling to improve understanding of the effects of cancer control interventions on population trends in incidence and mortality. A breast cancer modeling group is examining the impact of screening, treatment advances, and risk factors on breast cancer incidence and mortality, with a special focus on high-risk and underserved populations. These models have been used to investigate optimal screening strategies. (RFA-CA-05-018)

- **Long-Term Cancer Survivors Research Initiative**
  This initiative, issued in 1997 and reissued in 2003, resulted in funding for numerous research projects related to long-term cancer survivorship. Many studies addressed issues relevant to women, including the impact of breast cancer on older survivors and quality of life in female colorectal cancer survivors. (RFA-CA-04-003)

- **Breast Cancer and Environment Research Centers**
  This joint effort with the National Institute of Environmental Health Sciences is examining the role of environmental factors in female pubertal development. The research is based on the hypothesis that chemical, physical, and social factors in the environment interact with genetic factors to affect mammary gland development during puberty and across the lifespan in ways that can alter breast cancer risk in later life. (RFA-ES-03-001)

- **A1Breast Cancer Surveillance Consortium (BCSC)**
  The BCSC is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. It is a collaborative network of five mammography registries and two affiliated sites with linkages to pathology and/or tumor registries. As of May 2008, the BCSC database contains information on 7.5 million screening mammographies, 86,700 breast cancer cases, and over 2 million women. BCSC data are available to outside investigators for research purposes. (RFA-CA-98-025)

Selected Program Announcements

- **Research on Malignancies in AIDS and Acquired Immune Suppression**
  This goal of this program, which is jointly supported by NCI and the National Institute of Dental and Craniofacial Research, is to advance understanding of the risks, development, progression, diagnosis, and treatment of malignancies observed in individuals with underlying HIV infection or AIDS. A wide range of research projects is sought, including basic science, molecular epidemiology, and preclinical studies. Applicants are encouraged to propose analyses of data acquired from existing cohorts, including the Women's Interagency HIV Study. (PA-07-454, PA-07-455)

Selected Intramural Initiatives

- **Cohort Consortium**
  The Cohort Consortium, which includes both intramural and extramural efforts, addresses the need for large-scale collaborations in order to have sufficient data and biospecimens to study gene–gene and gene–environment interactions in the etiology of cancer. The mission is to foster communications, promote collaborative projects, and identify common challenges and solutions. Two initiatives of the Cohort Consortium relevant to women's health are the Breast and Prostate Cancer Cohort Consortium and the Vitamin D Pooling Project Rarer Cancer Consortium, the latter of which is conducting analyses of associations between serum vitamin D and certain rarer cancers, including ovarian and endometrial cancers.

- **Cancer Genetic Markers of Susceptibility (CGEMS)**
  CGEMS, which includes both intramural and extramural components, conducts whole-genome association studies to identify genes contributing to breast and prostate cancer risk using data from ongoing population-based cohort studies. The project capitalizes on new knowledge of human genetic variation and technical advances in ultra-high-throughput genotyping.

- **HPV Natural History Studies**
  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 United States, to better define risk factors for progression of precancerous lesions among HPV-infected women. The Costa Rican study will assess the various roles of mucosal immune response, HLA alleles, chromosomal alterations, contraceptive and reproductive practices, diet, cigarette smoking, and infection with sexually transmitted agents other than HPV. The U.S. study is investigating specific immune responses to viral infection and risk of persistence and/or progression of lesions.

- **Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial**
  PLCO is a large-scale clinical trial designed to determine whether certain cancer screening tests reduce deaths from prostate, lung, colorectal, and ovarian cancer. The 155,000 PLCO participants were divided into two groups—one received routine health exams and the other received screening tests for the cancers of interest. Screening has been completed and followup will continue for up to 10 more years. Numerous epidemiologic and ancillary studies are being conducted as part of PLCO. The PLCO Etiology and Early Marker Studies are utilizing biospecimens and risk factor information collected prior to disease diagnosis to identify biomarkers of early disease. PLCO data and biospecimens are available to all qualified researchers through a peer-review process.

- **Molecular Epidemiology and Biology of Mammographic Density**
  This study seeks to advance the understanding of biologic correlates and tissue biomarkers of dense breast tissue, which is a major risk factor for breast cancer. The study, which is being conducted at the University of Vermont, involves recruitment of women undergoing breast biopsies, some of whom are subsequently referred for breast resections. Biologic samples are used for biomarker discovery and for validation studies. Special funding for this project has been obtained from the sale of breast cancer stamps.

- **Breast Imaging Study in Women at High Genetic Risk of Breast Cancer**
  This study will evaluate the effectiveness of the newest breast screening procedures to detect cancers early and determine if breast tissue characteristics in mutation carriers differ from those in women with a normal gene. Participants in the study are between the ages of 25 and 56 and have been identified as having an altered BRC or BRCA2 gene through genetic testing. The study will develop and evaluate new tools that will assist in finding malignant or premalignant changes in breast cells, before cancer can be detected clinically.

- **Mississippi Delta Cervical Cancer Screening Project***
  NCI researchers are collaborating with the Deep South Network for Cancer Control to investigate a new approach to cervical cancer screening in the Mississippi Delta. Self-collected cervical specimens will be tested using sensitive HPV DNA assays to assess HPV status. The study will determine whether self-testing for HPV can be used to screen women reluctant or unable to obtain Pap tests.

- **Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED)**
  This study 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.

Selected Conferences and Workshops

- **Cancer Survivorship Biennial Conference**
  The June 2008 conference was sponsored by NCI, the American Cancer Society, and the Lance Armstrong Foundation. It highlighted key issues facing those with a history of cancer and their caregivers and healthcare providers. It also included research focused on the unique physical, psychosocial, behavioral, and economic outcomes associated with cancer survivorship. Many issues relevant to female cancer survivors were addressed.

- **Understanding the Biology of Estrogen Receptor-Negative Breast Cancer: An NCI Workshop***
  NCI organized a Think Tank in November 2007 on Health Disparities in Estrogen Receptor-Negative Breast Cancer. The Think Tank featured widespread participation by NCI Centers and Divisions, both intramural and extramural. The goal of the meeting was to discuss priorities and opportunities related to health disparities in ER-negative breast cancer for the purpose of guiding development of a proposal for NCI investment in this area.

- **Cervical Cancer State-of-the-Science Meeting on Pretreatment Evaluation and Prognostic Factors**
  The NCI Coordinating Center for Clinical Trials organized a state-of-the-science meeting in September 2007 to identify and prioritize the most important future clinical trials in cervical cancer and build international collaborations. The meeting was attended by experts from national and international organizations conducting clinical trials in cervical cancer, NCI experts, and patient advocates. The meeting focused on pretreatment evaluation and prognostic markers in cervical cancer. Based on discussions at the meeting, studies to address the gaps identified are in the planning process and will include several international collaborations.

- **Endometrial Cancer State-of-the-Science Meeting**
  The NCI Coordinating Center for Clinical Trials cosponsored a state-of-the-science meeting on endometrial cancer in November 2006 in Manchester, England. A multidisciplinary group of clinical scientists from 18 countries and representing 14 clinical trial groups attended the meeting. The main objectives of the meeting were to review the current state of understanding of endometrial cancer and develop a consensus of the key issues for clinical trials and the most important trials needed. As a direct result of

* Related to health disparities.

the discussions at this meeting, several key national and international trials have been or are currently being developed.

NATIONAL EYE INSTITUTE

Executive Summary

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 that affect both men and women include glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataracts; however, several eye conditions affect women more frequently than men. These conditions are optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; dry eye, a common condition that is associated with decreased tear secretion that in most cases causes mild discomfort, but in more severe cases may result in corneal scarring and blindness; corneal endothelial dystrophy, a slowly progressive disease that occurs when endothelial cells deteriorate as a result of cell loss 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; age-related macular degeneration, a deterioration of the region of the retina that is responsible for high-resolution vision; idiopathic intracranial hypertension (IIH), a central nervous disorder characterized by optic nerve compression; and thyroid eye disease, an autoimmune disease that leads to loss of vision.

Accomplishments

Optic Neuritis

Optic neuritis is an acute debilitating inflammation of the optic nerve that affects more that 25,000 Americans each year, primarily women between the ages of 18 and 45. People with this disease usually have rapid vision loss and ocular pain. The NEI-supported Optic Neuritis Treatment Trial (ONTT) compared oral corticosteroid, intravenous steroid followed by oral corticosteroid, and placebo for the treatment of new cases of optic neuritis. 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 treatment, though accelerating visual recovery, provided no long-term benefit to vision and not treating is a viable option. Based on data collected from 2 years of followup of patients enrolled in the ONTT, researchers found that treating first-time optic neuritis patients with a combination of intravenous and oral corticosteroids lowers their risk of developing multiple sclerosis 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 3 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 5 years, and confirmation of these results was provided by LONS. LONS investigators have completed 15-year followup examinations of enrolled patients and are in the process of analyzing study data.

Dry Eye

Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition. Dry eye can result from insufficient secretion of fluid by the lacrimal glands; or from defects in the surface of the eye, mucin or mucous production, or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, such as, in Sjögren's syndrome, but also occurs in association with aging, nerve dysfunction, radiation therapy, and with antidepressant and antipsychotic drug therapy. It is characterized by complaints of eye irritation, eye pain, foreign-body sensation, chronic red eyes, photophobia, fluctuation in vision, and/or loss of vision.

Lacrimal insufficiencies affect roughly 2 million Americans, and dry eye is the most common complaint to present in the ophthalmologist's office, with 10–20 percent of adults in the United States suffering from it. It appears to be more common in women than in men, particularly postmenopausal women.

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 they reach their 50s or 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 factors therapeutically 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. Keratoconus has become better understood through 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 multi-center, 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 factors 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 lens wearers to corneal scarring was found, thus suggesting that modifying lens fit can reduce this risk factor. Investigators are continuing to analyze data and publish study results.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is not only the leading cause of blindness in patients over the age of 65, but is now the most common cause of blindness in the United States. The incidence of AMD continues to rise in the population as the result of the increasing percentage of elderly persons, with women at 50 percent greater risk 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. One of these factors may be estrogen. According to a recent report in the Archives of Ophthalmology looking at AMD in women participating in the Nurses' Health Study, there is a preliminary association between women who received hormone replacement therapy after menopause and 34 percent higher risk of early AMD, but a 48 percent lower risk of the late-stage neovascular form of the disease was observed. These findings suggest a role for estrogen in the pathogenesis of AMD that requires further research in specific early and late signs of disease.

The Age-Related Eye Disease Study (AREDS) 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.

Idiopathic Intracranial Hypertension

IIH typically occurs in women of childbearing age and the incidence is 1/100,000 in normal-weight women and 20/100,000 in obese women. The disease is characterized by an increase in intracranial pressure (> 250 mm H2O); the cause is unknown, but involves obstruction of cerebral venous outflow. This, in turn, results in transient blurred vision, diplopia, and permanent vision loss. The role that obesity and hormonal changes play in contributing to this disorder is currently being investigated. While some medications and surgical treatments are available, there is no consensus of treatment strategies.

Thyroid Eye Disease

Thyroid eye disease, also known as Graves' disease, is an autoimmune disease that causes hyperthyroidism and tends to affect 2 percent of all women (7:1 compared to men) between the ages of 20 and 40. Excessive thyroxine causes swelling of the muscle and other tissues around the eye, resulting in proptosis, corneal exposure, optic nerve compression, and ultimately loss of vision. Current treatments of Graves' disease are only marginally effective, and therefore treatments involving new drugs are underway.

Initiatives

The NEI and the National Advisory Eye Council (NAEC) have established, in their strategic plan called A National Plan for Eye and Vision Research, goals and objectives, and research priorities for improving visual health and preventing blindness, including diseases that have a higher incidence and prevalence for women than for men. These include studies on:

- **Optic Neuritis**
  Research priorities are to develop an animal model of this disease to better understand the pathogenesis of the disorder, to develop immunomodulating therapies to limit optic

nerve damage from inflammation, and to understand the relationship between optic neuritis and multiple sclerosis.

- **Dry Eye**
  The overall objective is to determine the role of sex hormones on lacrimal gland function. A body of experimental evidence supports the notion that androgen sex hormones and prolactin modulate lacrimal gland function, thus providing an explanation for the observed gender bias of this condition and suggesting hormone modulation as a possible treatment.

- **Corneal Endothelial Dystrophy**
  Research priorities are aimed at understanding the biologic and functional structures of endothelial cells.

- **Keratoconus**
  An overarching objective is to understand the genetic basis of kerataconous. 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. Alongside these tests, retinal nerve fiber layer thickness appears to be influenced by estrogen levels. A longitudinal study is being conducted to determine the effects of female hormones on these measures of glaucomatous damage.

- **Cataracts**
  A role for estrogen in the pathophysiology of cataract formation has been observed. However, the evidence is unclear whether this role is protective or deleterious. Studies are underway to determine how estrogen influences the development of cataracts.

The Women's Health Initiative Observational Study affords the NEI the opportunity to pursue epidemiological studies in women-only cohorts. This has allowed gender-specific analyses of risk factors in major blinding and debilitating diseases. Approximately 2000 women from 3 sites participating in the Women's Health Initiative Observational Study were enrolled in the Carotenoids and Age-Related Eye Disease Study. Women aged 50–79 were selected to participate in the study if their dietary intake of lutein plus zeaxanthin was judged to be either high or low. The presence of age-related macular degeneration was assessed by fundus photography. Findings from CAREDS include the following:

- Diets rich in lutein and zeaxanthin among women aged less than 75 years may be protective against intermediate AMD.
- High-serum Vitamin D (25 [OH] D) among women aged less than 75 years may be protective against intermediate AMD.

The NEI has funded a Clinical Study Planning Grant to design a clinical trial examining the role of essential fatty acids (EFAs) in the treatment of moderate to severe dry-eye disease (DED). Despite being a widespread, growing problem with serious consequences, at present DED is inadequately treated. Because EFAs have been shown in laboratory studies, animal models, and some human studies to ameliorate inflammatory reactions and they are widely available over the counter (OTC), they are gaining in popularity to combat or prevent diseases associated with inflammation, including DED. But as with any treatment, results of a large, randomized double-blind clinical trial are needed to assess efficacy and safety. The current project is attempting to lay the groundwork for a definitive trial.

The NEI is working with the National Institute of Dental and Craniofacial Research (NIDCR) and the Office of Research on Women's Health (ORWH) to enhance research opportunities in the diagnosis, epidemiology, and treatment of Sjögren's syndrome.

- The NEI is cofunding 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 (United States, Argentina, China, Denmark, Japan, and United Kingdom) have been established. There is a plan to add India as a site pending approval of the Indian government. All sites have started accruing patients, which includes the use of the standardized "Baseline Eye Exam Form" and "Baseline Eye Exam Standard Operating Procedures" developed by the consortium.

The NEI is working with the ORWH to evaluate different diagnostic and treatment options for idiopathic intracranial hypertension and Graves' disease.

- The NEI is supporting the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC), which is prepared to conduct clinical studies on two neuro-ophthalmology-related diseases that occur predominantly in women. These are IIH and Graves' disease. The objective is to provide a unique opportunity to recruit and study statistically significant numbers of hard-to-find patients in order to evaluate different diagnostic and treatment options.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and 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, healthcare 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 enhancing the health of women by reducing the burdens of cardiovascular, lung, and blood diseases. As articulated in its Strategic Plan (http://apps.nhlbi.nih.gov/strategicplan/Default.aspx), the Institute's broad goals are to improve understanding of the molecular and physiological basis of health and disease and use that knowledge to develop better approaches to disease diagnosis, treatment, and prevention; to improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis, and treatment; and to generate a clearer understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

For many years, the NHLBI has been diligent in ensuring that its clinical research projects include adequate representation of women and that its overall research portfolio addresses gaps in knowledge of how to diagnose, prevent, and treat disease in women. This effort has included not only careful monitoring of recruitment for clinical trials and other studies, but also support of certain studies conducted entirely in cohorts of women. This report highlights a variety of research results; new programs and solicitations; and educational campaigns in cardiovascular, lung, and blood diseases that illustrate the Institute's recent activities of importance to women's health.

The report also includes a special focus on lifestyle approaches for weight management and physical fitness. Obesity is the most pressing health challenge facing Americans today—since 1980, its prevalence has doubled in adults and tripled in children and teenagers.

It is a well-known risk factor for cardiovascular disease (CVD), including coronary heart disease (CHD), hypertension, congestive heart failure, and peripheral vascular disease, as well as type 2 diabetes, dyslipidemia, and respiratory complications such as asthma and sleep apnea, all of which are responsible for substantial morbidity and mortality in the overweight population. Serious concerns have been raised that the gains in life expectancy of recent decades—gains that were due in large part to reductions in CVD—will be lost because of the increasing prevalence of obesity. The obesity epidemic presents a challenge unlike any the scientific, medical, and research communities have previously encountered: successfully combating obesity will require broad behavioral changes in the face of modern lifestyles and occupations, the effects of which are compounded by a built environment that often discourages physical activity and healthy diets. The NHLBI is committed to reversing the obesity trend in the United States, and in this spirit coleads the NIH Obesity Research Task Force. Highlights of the Institute's extensive portfolio on obesity, including studies primarily or entirely in women, are presented herein.

NHLBI Entities With a Designated Focus on Women's Health

The National Institutes of Health (NIH) Women's Health Initiative is administered by the NHLBI through its Division of Prevention and Population Studies.

The NHLBI Division for the Application of Research Discoveries has responsibility for The Heart Truth.

Accomplishments

The Women's Health Initiative (WHI)

The WHI is a major 15-year research program designed to address the most frequent causes of death, disability, and diminished quality of life in postmenopausal women—CVD, cancer, and osteoporosis. It includes more than 160,000 women enrolled in clinical trials and an observational study, all of which have been completed. Followup studies and data analyses are now underway.

Studies of Genetic and Biological Markers of Disease

In January 2007, the WHI entered a new phase, funding investigations using blood, DNA, and other biological samples and clinical data from WHI participants. The studies will help explain the clinical trial findings and will investigate the impact of genetic and biological markers on common diseases affecting postmenopausal women. Twelve 2-year contracts were awarded that address the following topics:

- Adipolines (physiologically active proteins from body fat cells) and risk of obesity-related diseases.
- Physical activity, obesity, inflammation, and CHD in a multiethnic cohort of women.
- Endogenous estradiol and the effects of estrogen therapy on major outcomes of WHI.
- Identification and validation of circulating biomarkers for the early detection of breast cancer in preclinical specimens.
- Proteomics and the health effects of postmenopausal hormone therapy.
- High-dimensional genotype in relation to breast cancer and WHI clinical trial interventions.
- Genome-wide association study to identify genetic components of hip fracture.
- Predictive value of nutrient biomarkers for coronary heart disease death.
- Ancestry association analyses of WHI traits.
- Biochemical antecedents of fracture in minority women.
- Hormone therapy, estrogen metabolism, and risk of breast cancer or hip fracture in the WHI hormone trial.
- Interaction effects of genes in the inflammatory pathway and dietary, supplement, and medication exposures on general cancer risk.

A second round of contract proposals for studies using WHI biological specimens

was solicited in October 2007 (BAA-NHLBI-WH-09-01). The NHLBI expects to make 12–14 awards in January 2009.

The NHLBI is investing substantial resources in activities to develop genotypic data on the participants in its large cohort studies. Such data can then be married with the wealth of already available data about participant characteristics and health indicators to refine understanding of the genetic influences on disease risk and on disease manifestations and progression. This work includes a large genotyping effort of African-American and Hispanic women from the WHI.

Postmenopausal Hormone Therapy

The WHI included two randomized clinical trials of postmenopausal hormone therapy—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 trials 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 had a lower incidence of colon cancer and fewer hip fractures, the overall balance of risks and benefits was unfavorable. In March 2004, the estrogen-alone trial also was halted ahead of schedule. After an average of nearly 7 years of treatment, estrogen therapy had no effect on CHD risk, but it increased risk of stroke and of 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.

In a secondary analysis published in April 2007, investigators combined data from the two trials to examine the outcomes according to age and years since menopause. They found that women who began taking hormones relatively soon after menopause had less hormone-associated CHD risk than women who began taking hormones farther from menopause. The analysis also suggested that the increased risk of CHD due to hormone therapy in older women occurred primarily among those who had hot flashes and night sweats. Study participants who had those symptoms were more likely to have risk factors for CHD (e.g., hypertension, high blood cholesterol), but it was not clear whether that explained their higher risk on hormone therapy. Other results from the analysis are the following: the increased risk of stroke associated with hormone therapy was not influenced by age or time since menopause, estrogen–progestin therapy increased risk of breast cancer even in women within 10 years of menopause, and a nonsignificant trend toward reduced risk of death was observed in younger hormone users (Rossouw, J.E., et al. *Journal of the American Medical Association* 297:1465-1477, 2007).

Another study involved 1,064 participants in the estrogen-alone trial who were 50–59 years of age at enrollment. About a year after treatment ended, researchers used computed tomography to measure the level of calcium in the women's coronary arteries—a marker for future risk of CHD. Those who had taken estrogen were 30 to 40 percent less likely to have measurable levels of calcium than those on placebo. These findings lend support to the theory that estrogen may slow early stages of plaque buildup in the arteries, and they offer some reassurance to younger women who have had a hysterectomy and wish to use hormone therapy on a short-term basis to ease menopausal symptoms. Nonetheless, current recommendations that hormone therapy should be taken only at the lowest dose for the shortest time possible remain relevant and appropriate (Manson, J.E., et al. *New England Journal of Medicine* 356:2591-2602, 2007).

An analysis of a subgroup of participants in both trials for whom blood cholesterol measurements had been obtained found that healthy postmenopausal women with normal or lower cholesterol levels did not have an increased short-term risk of heart attack when taking hormone therapy. In particular, over the course of 4 years, women taking estrogen or estrogen–progestin pills who had no history of CHD and a favorable ratio of LDL (low-density lipoprotein) to HDL (high-density lipopro-

tein) cholesterol experienced no more fatal or nonfatal heart attacks than their counterparts taking placebo pills. Identifying which women are more or less likely to experience a CHD event as a consequence of hormone therapy can help women and their physicians make better informed decisions about whether the benefits of hormone therapy outweigh the risks (Bray, P.F., et al. *American Journal of Cardiology* 101:1599-1605, 2008).

Finally, a followup study of the full cohort of women in the estrogen–progestin trial revealed that the health risks of long-term use of hormone therapy persist even a few years after stopping the drugs and clearly outweigh the benefits. Researchers found that 3 years after the women stopped taking the combination therapy, many of the health effects such as increased risk of CHD diminished, but risks of stroke, blood clots, and cancer remained high. Moreover, the study reported that some earlier benefits of hormone therapy, such as decreased risk of colorectal cancer and hip fractures, also stopped when the therapy ended (Heiss, G., et al. *Journal of the American Medical Association* 299:1036-1045, 2008).

Other Reports from the WHI

The WHI continues to generate many publications on a wide variety of women's health issues. A complete list can be found at http://www.nhlbi.nih.gov/whi/references.htm. Representative papers include the following:

- Calcium/Vitamin D Supplementation and Cardiovascular Events (Hsia, J., et al. *Circulation* 115:846-854, 2007)
- Calcium Plus Vitamin D Supplementation and the Risk of Postmenopausal Weight Gain (Caan, B., et al. *Archives of Internal Medicine* 167:893-902, 2007)
- Low-Fat Dietary Pattern and Risk of Treated Diabetes Mellitus in Postmenopausal Women (Tinker, L.F., et al. *Archives of Internal Medicine* 168:1500-1511, 2008)
- Prehypertension and Cardiovascular Disease Risk in the Women's Health Initiative (Shia, J., et al. *Circulation* 115:855-860, 2007)
- Prospective Study of Leukocyte Count as a Predictor of Incident Breast, Colorectal, Endometrial, and Lung Cancer and Mortality in Postmenopausal Women (Margolis, K.L., et al. *Archives of Internal Medicine* 167:1837-1844, 2007)
- Factors Associated With 5-Year Risk of Hip Fracture in Postmenopausal Women (Robbins, J., et al. *Journal of the American Medical Association* 288:2389-2398, 2007)
- Major and Minor ECG Abnormalities in Asymptomatic Women and Risk of Cardiovascular Events and Mortality (Denes, P., et al. *Journal of the American Medical Association* 297:978-985, 2007)

Women's Heart Disease Awareness Campaign

The recently published 20th anniversary edition of The Healthy Heart Handbook for Women (http://www.nhlbi.nih.gov/health/public/heart/other/hhw/hdbk_wmn.pdf) contains the latest scientific information about heart disease in women and offers practical suggestions that women can use to reduce their risk of heart-related problems. The 122-page, full-color handbook includes new tips on following a nutritious eating plan, tailoring a physical activity program to specific personal goals, and getting the whole family involved in heart-healthy living. It includes a sample eating plan and a chart on how to read a nutrition label. It also describes the warning signs of heart attack and how to get help quickly. It includes tools to help women assess their susceptibility to heart disease, such as the "What's Your Risk?" quiz, and suggests appropriate questions for women to ask their doctors. Since its first edition, the Handbook has reached hundreds of thousands of women with valuable information about protecting their heart health.

The Handbook is part of The Heart Truth (http://www.nhlbi.nih.gov//educational/hearttruth/), the NHLBI's national awareness campaign for women about heart disease, which continues to spread the word to millions that heart disease is a major women's health concern. Since The Heart Truth began in 2002, awareness among women that heart disease is their leading cause of death has risen dramatically—from 34 percent to 62 percent. The Heart Truth encourages women to talk

with their doctors about their personal risk of heart disease and to take action to reduce it.

The Heart Truth's Red Dress—the symbol of women and heart disease awareness—is quickly becoming one of the most recognizable health symbols in the United States. 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.

More than 28 corporate partners are helping to spread the campaign message by featuring The Heart Truth and Red Dress symbol on grocery store displays, newspaper coupon inserts, corporate Web sites, and billions of product packages. In addition, a wide range of community organizations and media groups actively contribute to the campaign. Nearly 2.1 billion media impressions had been achieved by the beginning of 2008.

The Heart Truth Road Show helps participants learn about heart disease risk factors, provides free health screenings, and disseminates educational materials. From April 2005 to May 2008, the Road Show reached tens of thousands of women in 15 cities across the United States. The "Heart Truth Champions" program, initiated in 2006 to recruit health advocates and educators in local communities to increase awareness about women and heart disease, has trained more than 100 activists who are reaching out to women by organizing heart health activities in their communities. Since the start of The Heart Truth Women of Color Initiative in early 2005, campaign messages have reached thousands of African-American and Hispanic women throughout the United States. During 2007 and 2008, three leading organizations representing women of color—The Links, Inc., the National Coalition of Pastors' Spouses, and the National Latina Health Network—implemented community events, including workshops and health screenings, that increased awareness of heart disease among African-American women and Latinas across the country.

The Heart Truth is conducted in partnership with the American Heart Association, the Office on Women's Health of the U. S. Department of Health and Human Services, WomenHeart–The National Coalition for Women with Heart Disease, and other organizations committed to the health and well-being of women.

Heart Attack Symptoms in Women—Are They Different?

An NHLBI-funded analysis has shed light on the question of whether women and men experience different symptoms during a heart attack. Investigators examined 35 years of research that yielded 69 studies, ranging from large trials to single-center studies and interviews. They found that about one-third of patients in the large studies and one-fourth of patients in the smaller studies presented without chest pain, the characteristic symptom of a heart attack. An absence of chest pain was noted in 30 to 37 percent of women (compared with 17 to 27 percent of men). Study authors also observed that older people were more likely to have heart attack without chest discomfort. However, because women are on average nearly a decade older than men at the time of an initial heart attack, more studies are needed to determine the degree to which gender independently influences heart attack symptoms. The authors also found that women were more likely than men to experience other forms of cardiac chest pain syndromes, such as unstable angina, and to report a wide range of symptoms associated with heart attack (e.g., pain in the middle or upper back, neck, or jaw; shortness of breath; nausea or vomiting; indigestion; loss of appetite; weakness or fatigue; cough; dizziness; palpitations) (Canto, J.G., et al. *Archives of Internal Medicine* 167:2405-2413, 2007).

The investigators concluded that current research does not indicate a need to differentiate heart attack symptoms in women from those in men. However, absence of chest pain is a strong predictor for missed diagnosis and treatment delay, so it is especially important that women be aware of other symptoms that may herald the onset of a heart attack. The NHLBI public education program Act in Time to Heart Attack Signs includes special information for women (http://www.nhlbi.nih.gov/actintime/haws/women.htm) that emphasizes the importance of seeking medical attention promptly if symptoms of a heart attack appear.

Treatment of Acute Coronary Syndromes

Researchers combined data from eight randomized trials in patients with acute coronary syndromes (unstable angina or heart attack) to compare the effects of invasive management strategies (angiography followed by revascularization, if appropriate) versus conservative treatment strategies (drug treatment first, and then angiography for those with continuing uncontrolled symptoms) on subsequent events (death, heart attack, rehospitalization). Findings from 12 months of followup showed that both men and high-risk women (i.e., those with elevated levels of biomarkers of heart damage) benefited from invasive strategies, but women at lower risk (i.e., without elevated biomarkers) derived no benefit from the invasive strategies and may actually have been harmed. The results highlight the importance of understanding differences in treatment effects between men and women, especially when considering inherently risky procedures (O'Donoghue, M., et al. *Journal of the American Medical Association* 300:71-80, 2008).

Acute Myocardial Infarction (AMI) in Young Women

A new observational study, Young Women with Acute Myocardial Infarction (YWAMI), will address an important knowledge gap. Although heart attacks are uncommon in young women, the prognosis is worse than in men of similar age, and little research has been done in this area. YWAMI will include 2,000 adult women under 55 years of age with AMI, as well as a comparison cohort of 1,000 men, enrolled from 88 hospitals across the United States and Canada. The team of investigators includes expertise in CVD sex disparities, outcomes research, epidemiology, statistics, genetics, biomarker research, health status measurement, psychosocial research, cardiology, and emergency medicine. The project will investigate gender differences in four major areas: outcomes following AMI (e.g., mortality, hospitalization, health status); prevalence of demographic, clinical, and psychosocial risk factors; quality of care; and prevalence of selected biological factors (e.g., sex hormones, biomarkers, genetic variations). The goal is to identify key determinants of recovery from AMI and other factors that may ultimately lead to improved care.

Gender Difference in Response to Antiarrhythmic Therapy

Findings from a study of patients newly diagnosed with atrial fibrillation, a common arrhythmia, indicate that treatment with the antiarrhythmic drug amiodarone affects women differently from men. The data showed that although both men and women treated with amiodarone were at increased risk of subsequently needing a permanent pacemaker implanted (to control an abnormally slow heart rate), the risk was substantially greater in women than in men, even after accounting for differences such as weight and use of other cardiac medications. The results send a cautionary note about the use of amiodarone in general, and especially for women (Essebag, V., et al. *Archives of Internal Medicine* 167:1648-1653, 2007).

Use of Implantable Cardioverter-Defibrillators (ICDs)

Research has established the ICD as a lifesaving approach for primary and secondary prevention of sudden cardiac death, yet many patients do not receive the benefit of this technology. Researchers analyzed data (from 1999 though 2005) from over 230,000 Medicare beneficiaries who were at high risk of sudden cardiac death. They found that women were less likely than men to receive an ICD to prevent sudden cardiac death, even when they had a history of prior cardiac arrest. The results highlight the need for continued investigation of sex differences in the utilization of healthcare procedures, a step toward ensuring quality health care for both men and women (Curtis, L.H., et al. *Journal of the American Medical Association* 298:1517-1524, 2007).

Trials of Treatments for Heart Failure With Preserved Systolic Function

Heart failure (HF) is a major cause of death among elderly Americans and the most common hospital discharge diagnosis in patients 65 years of age and older. Therapeutic trials of HF management have focused almost exclusively on patients who have systolic dysfunction (a decrease in the heart's ability

to contract and propel blood into the circulation). However, HF with preserved systolic function is quite common, especially among elderly women, and its prognosis is poor. A clinical trial initiated by the NHLBI, TOPCAT, is evaluating use of the drug spironolactone for treating such patients. Spironolactone is an inhibitor of the hormone aldosterone, which increases in HF, causing fibrosis (scarring) of the heart muscle. Conducted at over 150 clinical centers, TOPCAT is recruiting 4,500 adults who have the classic signs and symptoms of HF, but adequate systolic function. Each will be randomly assigned to receive either spironolactone or placebo pills, and the effectiveness of the treatment will be measured primarily in terms of CVD mortality, cardiac arrest, and hospitalization for HF management. The NHLBI is also supporting a smaller, investigator-initiated clinical trial, RELAX, to assess the effectiveness of sildenafil in improving exercise capacity in patients who have HF with preserved systolic function. Sildenafil, commonly known as Viagra®, increases the supply of blood to the lungs and reduces the workload of the heart, but its usefulness in such HF patients has not been rigorously tested.

Aortic Valve Disease in Turner Syndrome

Intramural researchers from the NHLBI and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development studied the structure of the aortic valve in a large group of girls and women with Turner syndrome, a genetic disorder in which all or part of one X chromosome is absent. Thoracic imaging with echocardiography and magnetic resonance revealed that a large proportion (30 percent) of the 250 girls and women studied had a bicuspid aortic valve (an abnormal aortic valve with two leaflets, rather than the usual three). The images also showed that a bicuspid aortic valve was strongly associated in this group with aortic root dilation, a serious condition that can lead to rupture of the aorta. The findings emphasize the importance of screening the aortic valve and aortic root in asymptomatic girls and women with Turner syndrome to identify potentially serious structural problems as soon as possible (Sachdev, V., et al. *Journal of the American College of Cardiology* 51:1904-1909, 2008).

Coronary Artery Calcification (CAC) and CHD Risk

To investigate the association between CAC and subsequent heart disease in initially healthy women, researchers analyzed data from participants in the NHLBI-supported Multi-Ethnic Study of Atherosclerosis (MESA), an epidemiological study of subclinical atherosclerosis in individuals without known CVD. Almost 90 percent of the women studied were initially categorized as having a low risk for developing CHD within the following 10 years according to the widely used Framingham risk algorithm. The researchers found that any level of detectable CAC (measured by computed tomography [CT] scans) put the women at some increased risk of cardiovascular disease during the 3.75 years of the study, and that this risk was substantially increased in women with very high levels of CAC. The study provides important information for clinicians and others tasked with evaluating the costs and benefits of more widespread screening for CAC (Lakoski, S.G., et al. *Archives of Internal Medicine* 167:2437-2442, 2007).

Antioxidants and B Vitamins in Women at High Risk for CVD

Data from the NHLBI Women's Antioxidant and Cardiovascular Study (WACS) have revealed no cardioprotective benefits from long-term supplementation with antioxidant vitamins or B vitamins in the high-risk women studied. Specifically, the antioxidant component of the WACS found that taking vitamin C, vitamin E, or beta carotene did not affect risk of having a major CVD event (heart attack, stroke, revascularization, or death from CVD) during the 9.4 years of the study. The only benefit observed was a reduced risk of stroke among women taking both vitamin C and vitamin E, compared with those taking neither (Cook, N.R., et al. *Archives of Internal Medicine* 167:1610-1618, 2007). Supplementation with combined folic acid, vitamin B6, and vitamin B12 also failed to affect CVD risk during the 7.3-year course of that part of the study (Albert, C.M., et al. *Journal of the American Medical Association* 299:2027-2036, 2008). In addition, the investigators reported that supplementation with folic acid and the B vitamins had no effect on risk of developing breast

cancer, or any other invasive cancer, during the study period (Zhang, S.M., et al. *Journal of the American Medical Association* 300:2012–2021, 2008).

Dietary Components and Risk of CHD

Data from 82,800 women participating in the long-running Nurses' Health Study showed that a diet relatively low in carbohydrates and high in protein and fat was not associated with an increased risk of CHD during 20 years of followup. In fact, lower-carbohydrate diets in which fat and protein were derived mainly from vegetable, rather than animal, sources were linked with a somewhat lower risk of CHD (Halton, T.L., et al. *New England Journal of Medicine* 355:1991-2002, 2006). Another longitudinal study, which involved 33,000 women, found that higher levels of trans fatty acids in the participants' red blood cells were associated with increased risk of CHD. Indeed, women with the highest amounts of trans fats in their red blood cells were three times more likely to develop CHD during the 6 years of the study than those with the lowest blood levels of trans fats (Sun, Q., et al. *Circulation* 115:1858-1865, 2007).

CVD and Abuse/Trauma in Women

The NHLBI recently funded two projects that address the cardiovascular ramifications of violent or traumatic events affecting women.

The first is using data from the Nurses' Health Study II to examine how the incidence and timing of physical, sexual, and emotional abuse influence the appearance of hypertension, hypercholesterolemia, diabetes, and CVD events. The research will also determine whether certain genetic variations interact with a history of abuse to alter CVD risk in women. Available data on social support, coping style, depressive symptoms, socioeconomic status, and lifestyle risk factors for CVD will enable exploration of factors that modify the observed risk associations.

The second project is addressing the relationship between post-traumatic stress disorder (PTSD) and risk factors for CVD. An association of PTSD with poor cardiovascular health has been observed, but most studies have involved male combat veterans. This study will examine CVD risk factors and cardiovascular reactivity and recovery in response to psychological stressors in women 18 to 39 years of age. Women diagnosed with PTSD will be compared with women who are depressed or who have no psychiatric diagnosis, as one of the objectives is to determine whether PTSD confers any risk beyond that associated with depressive symptoms. The project also seeks to determine whether PTSD induces in its victims a consistent tendency to view the environment as threatening and a consequent heightened vascular response to stress—a phenomenon that would likely be amenable to treatment.

Chronic Obstructive Pulmonary Disease (COPD)

COPD, the fourth most common cause of mortality in the United States, is responsible for about 130,000 deaths annually, more than half of which occur in women. Despite the ease with which the disease can be diagnosed and the availability of approaches to reduce symptoms and exacerbations and improve quality of life, many cases go unrecognized and untreated. COPD: Learn More, Breathe Better is a national education effort to raise awareness that COPD, although serious, is treatable and that susceptible individuals should be screened for it. Launched in January 2007 by the NHLBI in partnership with leading professional societies and patient advocacy organizations, the campaign is using a variety of avenues to inform Americans about the risk factors and symptoms of COPD. Its messages are directed primarily toward men and women over age 45, especially those who smoke or have smoked and those who are at risk of developing COPD by virtue of their genetic background or other environmental exposures. It encourages people at risk to have their breathing tested and speak with their doctors about treatment options.

Two recent studies investigated differences between men and women who participated in the National Emphysema Treatment Trial (NETT), an evaluation of the utility of lung-volume-reduction surgery in patients with severe emphysema, a form of COPD. One project identified gender differences in severity of emphysema symptoms and airways

architecture. It found that women experienced more shortness of breath than men even at similar levels of airflow obstruction and disease severity. Anatomically, the women had smaller airway lumens and disproportionately thick airways (Martinez, F.J., et al. *American Journal of Respiratory and Critical Care Medicine* 176:243-252, 2007). The second study found that the women who were followed as part of the non-surgical control group of the NETT had more frequent hospitalizations for respiratory problems than did the men. Other research has identified gender differences in clinical management, use of medications, and healthcare resources that may account for this phenomenon, but further work is needed to clarify the mechanisms involved (Fan, V.S., et al. *Archives of Internal Medicine* 167:2345-2353, 2007).

These studies suggest the existence of a complex interplay of factors that leads to differences between men and women with COPD. Improved understanding of gender differences in patients with mild to moderate COPD, as well as in those with more severe disease, holds promise for new treatment strategies that better address the symptoms and progression of COPD among women. The NHLBI is actively striving to recruit more women in its clinical studies and trials of COPD, and anticipates that analyses of possible gender differences in genetic susceptibility to COPD and in responses to treatments will soon be feasible. Indeed, a new clinical trial to assess the benefits of long-term, around-the-clock oxygen therapy in patients with less-than-severe COPD has set a goal of recruiting substantial numbers of women. In FY 2009, the NHLBI plans to conduct a workshop to evaluate current needs and opportunities in COPD, which will include the role that gender plays in this disease.

Gender Differences in Development of Asthma

A recent study in children ages 5 to 18 years showed a dramatic difference in airway responsiveness (i.e., airway sensitivity to inhalation of an irritant, considered a harbinger of persistence and severity of asthma later in life) between boys and girls as they mature. The boys became much less responsive to airway provocation (tested with the drug methacholine) after age 11, but the girls experienced little change in airway responsiveness from age 11 to 18 years. The findings are especially intriguing because in childhood, asthma is more prevalent among boys than girls, but in adulthood, more women than men have the disease (Tantisira, K.G., et al. *American Journal of Respiratory and Critical Care Medicine* 178:325-331, 2008).

The NHLBI recently funded an epidemiological study that seeks to describe the natural history of asthma during the transition from childhood through adolescence. The project will determine whether the age-related gender reversal in asthma prevalence reflects a greater frequency of new-onset asthma in adolescent girls or a greater rate of asthma remission in boys. It will also address putative asthma risk factors (e.g., early onset of puberty, obesity, pollutants, and early-life exposures such as parental smoking and breastfeeding) and attempt to identify prognostic factors that may suggest interventions to prevent asthma persistence and recurrence in adulthood. The research will be conducted in a cohort of boys and girls who were enrolled as newborns nearly two decades ago.

Pulmonary Hypertension (PH)

Research on PH—a rare, progressive, fatal disease that affects two to three times as many women as men—continues to be a high priority of the NHLBI. The Specialized Centers of Clinically Oriented Research (SCCOR) in Pulmonary Vascular Disease program, established in FY 2007, funds innovative research to understand the molecular and genetic basis of PH, the complex lung vascular and right-heart interactions and remodeling that occur in PH, and the effect of these interactions on PH morbidity and mortality. The program also supports research on the mechanisms leading to pulmonary vascular injury in the immature lung and the effects of lung injury on lung growth, development, and vascular disease in infants and children, including those with PH.

In December 2006, the NIH convened a scientific conference, Evolution of Pulmonary Hypertension: Emerging Diseases and Novel Therapeutics Meeting, to explore the latest scientific evidence regarding PH. Sponsored by

the NHLBI, the NIH Office of Rare Diseases, and the Clinical Center Critical Care Medicine Department, the meeting included presentations from scientists, academic researchers, physicians, and patient advocates from around the world. Scientific sessions addressed the pathology of PH, emerging diseases found to contribute to its development, current and new therapies, research opportunities, and future strategies for patient management.

Lymphangioleiomyomatosis (LAM)

The NHLBI has a longstanding interest in research on LAM, a progressive and often fatal lung disease of women. Institute-funded scientists found that sirolimus (rapamycin) mimics the function of missing or abnormal proteins needed to control the size and growth of LAM cells. Its potential as a therapy for LAM is being tested in the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial, funded by the Office of Rare Diseases and administered by the National Center for Research Resources. The view that LAM behaves like a "cancer" suggests that multiple-drug therapy may be called for and that additional drugs should be sought and tested. Also, the role of estrogen is being explored to elucidate why LAM affects women almost exclusively whereas tuberous sclerosis complex (TSC)—a genetic disease seen in many LAM patients—does not.

The NHLBI transferred the collection, processing, and distribution of LAM tissue to the National Disease Research Interchange (NDRI), an NIH-supported not-for-profit corporation that specializes in human tissues needed to facilitate research on rare diseases. The new system for managing LAM tissue has a Web-based inventory and provides easier, faster access to tissue.

The NHLBI continues to cofund the annual scientific conference organized by the LAM Foundation and participates in the trans-NIH TSC coordinating committee meetings organized by the National Institute of Neurological Diseases and Stroke. The Institute has revised and updated the LAM Fact Sheet on its Diseases and Conditions Index Web page (http://www.nhlbi.nih.gov/health/dci/Diseases/lam/lam_whatis.html).

Guidelines for the Diagnosis, Evaluation, and Management of Von Willebrand Disease

In February 2008, the NHLBI issued the first clinical guidelines ever published in the United States for the diagnosis and management of von Willebrand Disease (vWD). The most common inherited bleeding disorder, vWD affects equal numbers of men and women, but is more likely to cause serious symptoms in women during the childbearing years. The guidelines address the management of heavy menstrual bleeding in women who have vWD and the challenges that pregnancy and childbirth present for these women. Recommendations for future research on these topics are also included.

The guidelines were developed by a working group convened by the NHLBI in consultation with the American Society of Hematology. They are available on the NHLBI Web site and as printed documents (http://www.nhlbi.nih.gov/guidelines/vwd/). They were also published in the journal, Haemophilia (Nichols, W.L., et al. *Haemophilia* 14:171-232, 2008).

Call to Action to Prevent Deep Vein Thrombosis (DVT) and Pulmonary Embolism

In September 2008, the Acting Surgeon General issued a Call to Action to reduce the number of cases of DVT and pulmonary embolism in the United States, emphasizing the need for increased awareness about DVT and pulmonary embolism, evidence-based practices for DVT diagnosis and management, and more research into the causes, prevention, and treatment of DVT.

Women face special issues related to DVT and pulmonary embolism because both pregnancy and use of oral contraceptives increase risk of blood clots. Moreover, as documented by the WHI postmenopausal hormone trials, use of estrogen-plus-progestin or estrogen-alone pills is associated with higher rates of blood clots in the legs.

The initiative was based on a workshop on DVT held May 2006, which was sponsored in part by the NHLBI. In an introductory message to the Call to Action, Dr. Elizabeth G. Nabel, Director, NHLBI, reiterated the Insti-

tute's commitment to supporting research to advance understanding and improve treatment of venous diseases and their complications.

Special Focus

Research on Lifestyle Approaches for Weight Management and Physical Fitness

NHLBI efforts in this area address the development of healthy habits during childhood and adolescence to prevent weight gain and establish a lifestyle that includes frequent and vigorous physical activity, as well as programs for adults to maintain a healthy weight, facilitate weight loss, and promote overall fitness.

Childhood and Adolescence

- **Risks of Overweight in Girls as Young as 9 Years of Age**
  New results from the NHLBI Growth and Health Study (NGHS)—an observational study that followed cohorts of White and Black girls from childhood to early adulthood—highlight the importance of teaching girls as young as age 9 about behaviors to maintain a healthy weight. Rates of overweight increased through adolescence from 7 percent to 10 percent among White girls in the study and from 17 percent to 24 percent among Black girls, with the greatest jump in weight gain occurring at ages 9 to 12 years. Girls who were overweight during childhood were 11 to 30 times more likely to be obese in young adulthood. Moreover, overweight was significantly associated with elevated systolic and diastolic blood pressure, high-density lipoprotein cholesterol, and triglyceride levels. The NGHS findings underscore the importance of establishing healthy behaviors early in girlhood to reduce subsequent CVD risk in women (Thompson, D.R., et al. *Journal of the American Academy of Pediatrics* 150:18-25, 2007).

- **Trial of Activity for Adolescent Girls (TAAG)**
  The TAAG, initiated in 2000, linked middle schools in six geographically diverse U.S. areas with community partners (e.g., YWCAs, local health clubs, recreation centers) to provide girls with increased opportunities for physical activity during and outside of the school day. Programs such as lunchtime dancing, afterschool step aerobics, and before-school open gym were offered. Results showed that after 3 years, girls in the TAAG schools were engaging in moderate-to-vigorous physical activity for about 2 minutes per day more than the girls in the control schools. Although the magnitude of this improvement was disappointing, researchers estimate that even this modest increase in physical activity could forestall a weight gain of about 2 pounds per year on average, which if sustained over time, could prevent the girls from becoming overweight in high school (Webber, L.S., et al. *American Journal of Preventive Medicine* 34:173-184, 2008).
  Other findings from TAAG were recently reported on the following topics:

- Weekend schoolyard accessibility, physical activity, and obesity in middle school girls (Scott, M.M., et al. *Preventive Medicine* 44:398-403, 2007).
- School design and physical activity among middle school girls (Cohen, D., et al. *Journal of Physical Activity and Health* 5:719-731, 2008).
- Commercial facilities as supports for physical activity in adolescent girls (Dowda, M., et al. *Preventive Medicine* 45:163-168, 2007).
- Differences among Black, Hispanic, and White adolescent girls in their perceptions about physical activity (Grieser, M., et al. *The Journal of School Health* 78:314-320, 2008).
- Associations between physical activity and body composition in middle school girls (Stevens, J., et al. *American Journal of Epidemiology* 166:1298-1305, 2007).

Girls Health Enrichment Multisite Studies (GEMS)

GEMS sought 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 were then evaluated in randomized, controlled trials. Results from one of the trials—conducted at community centers in Memphis, TN—were recently reported. The program tested an intervention that encouraged 8- to 10-year-old children to eat healthfully (increasing consumption of fruits and vegetables and decreasing consumption of sweetened beverages) and increase their physical activity. The girls were taught helpful skills for reaching their goals (e.g., dance steps and preparation of healthful snacks). A comparison group engaged in a program that promoted self-esteem, but did not focus on diet or physical activity. At the start of the study, the girls in both groups were already at high risk for obesity—about 41 percent were overweight, their consumption of fruits and vegetables was low, their intake of fats was high, and their daily physical activity was below recommended levels. After 2 years, the girls in the intervention group experienced a gain in body mass index (BMI) of only half that of the girls in the comparison group. They improved their eating habits, decreasing daily intake by 162 calories and consuming more vegetables and water and fewer sweetened beverages. However, no difference in physical activity was observed between the two groups.

We Can! (Ways to Enhance Children's Activity and Nutrition)

We Can! is a national education program designed for communities to help children 8 to 13 years of age maintain a healthy weight. It offers parents and caregivers suggestions and enjoyable activities to encourage healthy eating, increase physical activity, and reduce sedentary time (particularly "screen time") in their children. We Can! provides a variety of educational materials and flexible, easy-to-use resources for implementing community-wide programs.

Community involvement is an essential component of We Can! Since its launch in June 2005, more than 965 community sites have put its programs into operation at YMCAs, schools, hospitals, parks and recreation departments, universities, and private companies. In addition, We Can! has created partnerships with over 40 national organizations that help spread its messages widely. For example, a collaboration with the U.S. Fish and Wildlife Service and the National Park Service helped support events all over the country during Father's Day weekend 2008 to encourage families to get outdoors and participate in healthful physical activities.

We Can! was developed by the NHLBI in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Cancer Institute. Additional information and We Can! materials can be obtained at http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/.

Other Studies of Interest

During FY 2007–FY2008, the NHLBI funded several new studies of obesity prevention in children, including the following:

- Evaluating Parental Influences on Obesity among Mexican-American Children, an observational study examining family eating habits and the effects of socioeconomic status and cultural factors on parental behaviors.
- Bright Start: Obesity Prevention in American Indian Children, a school- and home-based program for kindergarteners and first graders on two Lakota reservations in South Dakota.
- Preschool-based Obesity Prevention Effectiveness Trial, a study of predominantly minority children in the Chicago school district that uses a teacher-delivered weight control program featuring friendly, colorful puppets that represent the seven food groups (e.g., Miss Grain, Miss Sugar, and Mr. Vegetable).

Adulthood

The Challenge of Maintaining Weight Loss

A new report from a study in overweight and obese women emphasizes the importance—and challenge—of sustaining high levels of physical activity in order to maintain weight loss. More than 200 women were assigned to

one of four unsupervised exercise regimens (moderate versus vigorous intensity, lower versus higher energy expenditure), provided treadmills for use at home, instructed in weight-loss eating strategies, and supported by group meetings and phone calls. Average weight losses after 6 months (about 8 to 10 percent of initial weight) were about the same regardless of exercise-group assignment, a phenomenon that researchers attributed, at least in part, to nonadherence by many of the women to their assigned activity regimens. For most participants, physical activity increased initially, but then dropped off over time. Keeping the weight off was perhaps a greater challenge—after 2 years, the women had regained about half of the weight, again irrespective of exercise assignment. Overall, only about 25 percent of the women in the study were able to maintain a weight loss of at least 10 percent over 2 years. Not surprisingly, the successful women were exceptionally physically active, participating in an additional 5 hours of activity per week above their baseline activity level, as well as remaining very careful about their caloric intake (Jakicic, J.M., et al. *Archives of Internal Medicine* 168:1550-1559, 2008).

The Weight Loss Maintenance Trial

This NHLBI-supported trial reported that two practical, easy-to-sustain approaches—a personal counseling strategy and an interactive Web-based strategy—showed some promise for helping people maintain a recent weight loss. Over 1,000 overweight or obese adults with hypertension or elevated blood lipid levels (63 percent of whom were women) who had lost an average of 18.7 pounds during a previous 6-month intervention enrolled in the trial. Participants were assigned to one of three approaches—personal counseling, an interactive Web-based strategy, or a self-directed strategy comprising only printed materials—and all succeeded in keeping off at least some of the weight they had lost. After 2½ years, those who received personal counseling were the most successful. The Web-based strategy also was more effective than the self-directed strategy, but its benefit waned over time. Results were similar for men and women and across racial/ethnic groups. The study provides insight into practical programs that could be developed and implemented to reach large numbers of women and men as they try to keep off weight they worked hard to lose (Svetkey, L.P., et al. *Journal of the American Medical Association* 299:1139-1148, 2008).

Lifestyle Interventions

The NHLBI has recently funded a number of research projects—some as a result of grant solicitations, some investigator initiated—that are developing or evaluating programs to improve diet and physical activity in a variety of settings. Examples of projects of relevance to women are the following:

- ACTION! Wellness Program for Elementary School Personnel, a program to reduce overweight and obesity among grade-school staff, most of whom are women, in New Orleans schools.
- A Home Exercise Program (on DVD) for Women with Infants and Young Children, an evaluation of an exercise DVD for new mothers that includes a range of aerobic and strengthening exercises to create personalized exercise sessions that may or may not include the baby.
- Evaluating the Link between Neighborhood Environments and Obesity in African-American Women, which is using data from the Black Women's Health Study to examine how neighborhood environments (e.g., street layout, the presence of sidewalks, proximity to parks) influence the occurrence of obesity among urban African-American women.
- Work, Weight, and Wellness Program—The 3W Program, a project to increase physical activity, improve diet, and reduce obesity in hotel workers in Hawaii, an ethnically diverse, predominantly low-socioeconomic status population.
- Promoting Activity and Changes in Eating (PACE) to Reduce Obesity, a weight-control intervention at worksites in the Pacific Northwest that have a high proportion of blue-collar and pink-collar employees who tend to be sedentary.
- Effects of Worksite Wellness Interventions in Overweight or Obese Female Employees at the NIH, a study to determine whether

weight loss through supervised nutritional counseling and daily exercise confers health benefits (on vascular function, insulin sensitivity, and high-density lipoprotein) beyond those achieved with improved fitness alone.

- Comparison of Workplace Obesity Management Programs, a project at several manufacturing sites operated by the Dow Chemical Company in Louisiana and Texas that includes, among other approaches, a high-intensity program in which senior managers help develop a worksite culture that is highly supportive of employee efforts to improve weight and manage health.
- Church-based Program To Promote Physical Activity and Healthy Dietary Habits in African-Americans, a program in predominantly Black South Carolina churches that involves participation of trained local health committee members, church pastors, and cooks.
- Interventions to Control Obesity in Colleges, a comparison of a Web-based weight loss program versus a cash-incentive weight loss program in employees at North Carolina universities and colleges.
- Evaluating Weight Loss Programs for Obese People at Risk for Heart Disease (The POWER Study), a comparison of a program that uses in-person visits with health counselors from Johns Hopkins University versus one that uses only telephone, Web sites, and e-mail to contact and counsel participants.
- Latina Lifestyle Program, an intervention that addresses diet, physical activity, stress management, social support, and smoking cessation to reduce CHD risk in postmenopausal Hispanic women with type 2 diabetes.
- Be Fit, Be Well, a project that offers educational and motivational information via a Web site and automated telephone calls to reduce blood pressure levels and encourage weight loss among low-income, ethnically diverse patients at community health centers in Boston.

Gender Analysis

As noted under Accomplishments, researchers recently identified a number of gender differences with regard to heart attack symptoms in women, response to invasive treatment of acute coronary syndromes, response to antiarrhythmic drug therapy, utilization of ICDs, COPD symptoms and progression, and asthma development in childhood and adulthood. The long-running Framingham Heart Study (FHS) continues to yield comparisons of CVD risk in women and men, and the Jackson Heart Study and the new Hispanic Community Health Study are expected to provide sources of data on gender differences.

The NHLBI has devoted substantial resources to developing its genomics and personalized medicine portfolio—an investment that will enable careful investigation of genetic and environmental disease risk factors according to gender and provide unprecedented opportunities for gender-specific personalized medicine. One example is its single-nucleotide polymorphism (SNP)-Health Association Resource (SHARe) activities to develop genotypic data on the participants in its epidemiological studies and clinical investigations. Such data are then merged with the wealth of phenotypic data already available from those participants to refine understanding of the genetic influences on disease risk and on disease manifestations, progression, and response to therapy. The initial program in SHARe has been the FHS whereby genotyping was performed on approximately 10,000 participants (with informed consent). The genomic and clinical information was made available to biomedical researchers, in a de-identified form, through the NIH Database of Genotypes and Phenotypes (dbGaP) in October 2007. Genotyping has also been conducted on participants in the NHLBI's large asthma network and, as noted above, will be done on African-American and Hispanic women in the WHI. In addition, the Institute played a lead role in the formulation of the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS) and in the development of dbGaP. As a result of the GWAS policy, all of the results of NIH-funded GWAS and their underlying data will be

widely available to investigators for their use in formulating and testing new approaches to personalized therapies.

Initiatives

Request for Proposals (RFPs)

Women's Health Initiative Memory Study (WHIMS)—Renewal

This initiative supports a 4-year renewal of the WHIMS, a WHI ancillary study to assess the relationship between postmenopausal hormone therapy and development of cognitive impairment and dementia (RFP-NHLBI-WH-08-17).

Broad Agency Announcement (BAA)

- **Toward Maximizing the Scientific Value of the Biological Specimens from the Women's Health Initiative II**
  This initiative solicited proposals for investigations using blood, DNA, and other biological samples and clinical data from WHI participants (BAA-NHLBI-WH-09-01).

Requests for Applications (RFAs)

- **Targeted Approaches to Weight Control for Young Adults**
  This solicitation supports clinical research studies to develop, refine, and test innovative behavioral and/or environmental approaches for weight control in young adults at high risk for weight gain. Interventions can address weight loss, maintenance of a healthy weight, or prevention of excessive weight gain during pregnancy (RFA-HL-08-007).

- **Mentored Career Development Award To Promote Faculty Diversity/Re-Entry in Biomedical Research**
  The goal of this solicitation is to increase the number of highly trained investigators coming from diverse backgrounds or having experienced an interruption in their research careers who are skilled in the advanced methods and experimental approaches needed to solve problems related to cardiovascular, pulmonary, hematologic, and sleep disorders (RFA-HL-08-015).

Program Announcements (PAs)

- **Right Heart Function in Health and Chronic Lung Diseases**
  The NHLBI issued this solicitation to support research on the relationship between the right ventricle and the lungs in health and disease and to stimulate research to develop a more complete understanding of the mechanisms of right-heart failure associated with chronic lung diseases, such as pulmonary hypertension and COPD (PA-07-043).

- **Nutrition and Diet in the Causation, Prevention, and Management of Heart Failure**
  The NHLBI, the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the Office on Dietary Supplements issued this solicitation to stimulate research on the role of nutrition and diet in the causation, prevention, and treatment of cardiomyopathies and heart failure. Its overall goal is to develop a satisfactory science base for preventive approaches in high-risk individuals and for rational nutritional management of patients in various stages of heart failure (PA-07-139).

- **Sarcoidosis: Research into the Cause of Multiorgan Disease and Clinical Strategies for Therapy**
  This initiative supported by the NHLBI and eight other NIH components, including the Office of Research on Women's Health (ORWH), was issued to encourage innovative, multidisciplinary basic and clinical research on the etiology and management of sarcoidosis (PA-07-136).

- **Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases**
  This solicitation by the NHLBI and six other NIH components was intended to stimulate research on the lymphatic system, to characterize its function at multiple levels, to explore pathophysiologic mechanisms that cause disease, to develop new methods for imaging and/or quantitating lymph flow, and to discover new therapeutic interventions (PA-07-165).

- **Improving Heart Failure Disease Management**
  This initiative of the NHLBI, NINR, and NIA seeks to stimulate innovative research to address questions about disease management in clinical practice for chronic heart failure. Its goal is to identify, improve, implement, and disseminate clinically effective disease management tools to reduce heart failure morbidity and mortality and improve patient outcomes (PA-07-355).

- **Lymphatic Biology in Health and Disease**
  The NHLBI and several other NIH components issued this solicitation to stimulate research on the biology of the lymphatic system at the molecular, cellular, tissue, organ, and whole-body levels and to develop innovative approaches for identifying and intervening in lymphatic diseases across all age groups and disease states (PA-07-420).

Conferences and Workshops

- **Evolution of Pulmonary Hypertension: Emerging Diseases and Novel Therapeutics Meeting**
  This December 2006 conference, sponsored by the NHLBI, the NIH Office of Rare Diseases, and the Clinical Center Critical Care Medicine Department, addressed clinical and research issues of importance to PH.

- **Trans-NIH Working Group Meeting on Lymphatic Research**
  This Working Group met September 6–7, 2007, to make recommendations for future research on lymphatic disorders.

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 ongoing project has enrolled 5,500 African-American women and men living in the Jackson, MS, area. It 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 fiscal year 2006, the NHLBI awarded contracts for the Hispanic Community Health Study, a long-term population study, analogous to the JHS, in Latinos. As many as 16,000 individuals—4,000 at each of four sites—will undergo a series of physical examinations and interviews to identify the prevalence of a wide variety of conditions, including heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing disorders, diabetes, kidney and liver disease, and cognitive impairment. The study will assess risk factors such as diet, physical activity, obesity, smoking, blood pressure, blood lipids, acculturation, social and economic disparity, psychosocial factors, occupation, healthcare access, the environment, and medication and supplement use. It will also determine the role of cultural adaptation and disparities in the prevalence and development of disease. Participants will range in age from 18 to 74 years and be Mexican-Americans, Puerto Ricans, Cuban-Americans, and Central/South-Americans.

National Human Genome Research Institute

Executive Summary

The National Human Genome Research Institute (NHGRI) led the National Institutes of Health's (NIH's) contribution to the International Human Genome Project (HGP). With the achievement of its goal, the finished sequence of the human genome in April 2003, this project was successfully completed ahead of schedule and under budget, and has already begun to change the way we address medicine and disease. Numerous projects have since stemmed from the original HGP and have

greatly facilitated and accelerated the pace of biomedical research.

In 1994, NHGRI investigators were among the first to report that women carrying BRC or BRCA2 mutations have a higher risk of developing both breast and ovarian cancer than women without such mutations. 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, NHGRI also supports research that explores the effect of educating women of different ages and ethnic groups about benefits of genetic screening in evaluating their risk of inherited diseases.

Accomplishments

Breast Cancer

NHGRI is involved in several ongoing breast cancer studies. These studies explore various aspects of breast cancer research.

An intramural NHGRI laboratory investigates mutations in two known breast cancer-linked genes, breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2), and their roles in inherited breast and ovarian cancer susceptibility. In 1994, this laboratory was among the first to report that women carrying BRC or BRCA2 mutations have a higher risk of developing both breast and ovarian cancer than women without such mutations. The group also discovered an unusually high frequency of specific BRC mutations in the Jewish population. They recently helped identify eight distinct protein-shortening mutations and another six rare variations of BRCA2 in a group of African-American breast and ovarian cancer patients.

The team is continuing to study these two populations to better understand the risk of cancer associated with specific mutations and is collecting information on all identified mutations in these two genes worldwide. Currently, more than 2,000 distinct BRC and BRCA2 mutations have been identified. Because women with BRC mutations account for only 5 percent of all breast cancer cases diagnosed every year, there is a growing scientific consensus that not all BRCA mutations carry the same risk of cancer.

The group also is investigating how normal BRCA genes help maintain healthy cells. They previously demonstrated that the normal BRC protein regulates key effectors that control the G2/M DNA damage checkpoint, a cell-cycle checkpoint that prevents cells with genomic damage from entering mitosis and reproducing. The carboxyl terminus of BRC contains two motifs found in several DNA-repair and cell-cycle checkpoint proteins. The laboratory also demonstrated that these motifs also bind to a number of other nuclear proteins critical to DNA replication. This segment of BRC also interacts with several histone deacetylases, proteins that modulate the transcriptional activity of genes leading to cell growth arrest, cellular differentiation, and apoptosis (programmed cell death).

Research has found that the amino terminus of BRC is a RING finger protein, a class of proteins that have ligase activity. This ligase catalyzes a key enzymatic step in the ubiquitination pathway, a cellular pathway that recognizes misfolded proteins and targets them for degradation, thus keeping the cell functioning normally. Defects in the normal ubiquitination pathway are implicated in a range of illnesses, including cancer. This particular team is working to identify all the molecules in the ubiquitination pathway that interact with BRCA1.

In addition, NHGRI funds numerous extramural projects related to breast cancer. These include developing an interactive CD−ROM on cancer genetics for Hispanic populations, analyzing parent communication of BRCA1/2 testing results to children, economic evaluations of emerging genomics tests for early-stage breast cancer, and many high throughput cancer genome sequencing and mapping centers.

Ovarian Cancer

About one-fifth of ovarian cancers are found at an early stage. Early detection improves the chances that it can be treated successfully. Nine out of 10 women treated for early ovarian cancer will live longer than 5 years after the cancer is found. Unfortunately,

there is no reliable test for finding this cancer early, but several large studies are in progress to learn how best to find ovarian cancer in its earliest stage.

Currently, NHGRI researchers are in the pilot phase of a collaborative project to identify locations in the genome that are important for the regulation of gene expression in ovarian cancers. By using sequencing to identify sites of abnormal methylation (a DNA modification) in promoter regions, this project hopes to determine which regulatory regions and which genes are factors in the occurrence of ovarian cancer. Investigators at NHGRI were among the first to report that women carrying BRC or BRCA2 mutations have a higher risk for Hereditary Breast Ovarian Cancer (HBOC) Syndrome. NHGRI noticed a lack of studies regarding knowledge, attitudes, and behaviors related to cancer genetics among Hispanic women at increased risk for HBOC among various Hispanic ethnic groups.

NHGRI has awarded a grant to better understand cultural differences that may affect utilization of BRCA1/2 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 a public health department setting to educate Hispanic women at increased risk for HBOC about genetic counseling and testing for HBOC and possibly other hereditary cancers.

Uterine/Endometrial Cancer

Endometrial cancer, which affects the endometrium (the lining of the uterus), is the most common gynecological malignancy in the United States. There are 41,200 new cases of endometrial cancer diagnosed each year, along with 7,350 deaths attributable to this disease. Most patients present with "type I" tumors and have a good prognosis, but around 15 percent are diagnosed with "type II" tumors that are clinically aggressive. Patients with type II tumors have a 5-year survival rate of less than 40 percent.

Over the past few years, it has become evident that certain types of chromosomal and genetic alterations may be exploited as therapeutic targets in the treatment of certain cancers. For example, the drug imatinib is highly effective in the treatment of chronic myelogenous leukemia caused by a chromosome translocation. Similarly, a subset of non-small cell lung cancers with specific mutations that affect the catalytic domain of the epidermal growth factor receptor (EGFR) responds to the drugs gefitinib and erlotinib. An NHGRI team of investigators aims to identify the genetic alterations that cause serous and clear-cell tumors of the endometrium en route to developing new therapies for type II endometrial cancers.

Toward that end, the research group is using high-density, single-nucleotide polymorphism (SNP) genotyping to identify genome-wide copy-number changes and other genetic events in type II endometrial tumors. Parallel studies include extensive collaborations with the NIH Intramural Sequencing Center for performing mutational screens of all exons that encode the catalytic domains of 90 known tyrosine kinases. In addition, these efforts include searching for structural chromosomal alterations in endometrial tumors. Once specific genetic alterations are found to be associated with tumor development, more extensive examination of the clinicopathologic features of mutation-harboring tumors will be performed in an attempt to implicate individual genes or functional pathways that could be targeted for therapeutic intervention.

An inherited susceptibility to endometrial cancer is usually associated with increased risk for hereditary nonpolyposis colorectal cancer (HNPCC). In fact, endometrial cancer is the second most common form of malignancy diagnosed in women with HNPCC. Susceptibility to endometrial cancer is also associated with an increased risk for Cowden syndrome, which first produces symptoms in people in their late twenties and causes multiple noncancerous growths called hamartomas on the skin and mucous membranes. Cowden syndrome is also linked to the development of breast, thyroid, and endometrial malignancies. There are a few families that lack either the clinical manifestations or molecular characteristics of HNPCC or Cowden syndrome, yet still have a clustering of endometrial cancer cases, which suggests a tissue-specific etiology. It is possible that predisposition to endometrial cancer in

these families is linked to one or more mutations that have varying risk, rather than a single mutation that always results in disease.

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 HNPCC, another NHGRI research project explores how patients perceive their risk of developing cancer, and monitors the influence of education and counseling on mood, behavior, and family relationships.

Premature Birth, Maternal Health, and Birthweight

Preterm labor resulting in the delivery of a premature infant is a complex problem with an enormous impact on individuals, families and society. About 500,000 children will be born prematurely in the United States this year, and worldwide 5 million will die of prematurity and its complications. It is the single largest contributor to disability adjusted life years (DALYs), a measure of the lifetime impact of a disease. Despite the importance of the problem and its disproportionate occurrence in poor and minority populations, insufficient resources have been targeted to discover its underlying etiology. The largest single cause of prematurity is spontaneous preterm labor, and suspected triggers for this include infection, stress, poor nutrition, and genetic factors. Numerous family and twin studies provide strong evidence that genetic factors underlie about 40 percent of the risk for prematurity. The single best predictor for preterm delivery is a previous preterm birth. A major challenge in studying genetic factors in prematurity is that the risk could reside either in the mother and her uterus or in the infant/placenta. Thus, any approach to studying preterm birth should account for both infant and maternal risk and environmental covariates and interactions.

The Danish National Birth Cohort Study is a well-established, prospective cohort study that has the advantage of enrolling women early in pregnancy when the outcome is still unknown, so that bias in data collection and sampling is minimized. The Danish study has followed over 96,000 women beginning in the first trimester of pregnancy and has extensive biological and epidemiologic data on the outcomes of both mother and child. In this research study, the team is performing a genome-wide case/control analysis using 1,000 very well characterized cases of spontaneous preterm birth, with biological samples on the mother and infant, drawn from the Danish National Birth Cohort Study. These are then matched to 1,000 mother/infant controls, born at 39 or 40 weeks gestation. Extensive epidemiologic variables are used as covariates in the analysis. To replicate positive findings, researchers can access the deep resource of additional controls from the same Danish National Birth Cohort Study as well as more than 1,000 mother/father/preterm infant triads available from a large sample collection in the United States, and a further 1,000 U.S. case/controls enriched for African-Americans, a population known to have high rates of preterm labor. Positive results involving environmental factors can be further investigated, as the Danish cohort has maternal serum samples from early and mid-pregnancy, as well as additional epidemiologic and outcome data.

The study should enable a better understanding of the biology of parturition, identify common genetic factors that play a role in prematurity, and suggest environmental modifications that can prolong gestations, with the goal of improving both neonatal and adult outcomes.

In a surprising new twist, a study published in October 2007, led by NHGRI intramural researchers, showed that pregnant women who have very low cholesterol levels might face a greater risk of delivering their babies prematurely. The study found that low maternal cholesterol levels, which may be related to a woman's genetic makeup, diet, or other health factors, might also lead to low birthweight. Researchers noted a differing impact of low cholesterol levels on the rates of premature delivery in White and African-American mothers, which is of particular interest because premature delivery is a leading cause of health disparities.

While most health advice warns against too much cholesterol, this study suggests dangerous implications from having too little cholesterol and emphasizes the importance of a moderate cholesterol intake during preg-

nancy. These findings give researchers renewed impetus to refine our understanding of cholesterol levels in pregnant women, and to explore the genetic, nutritional, and other factors that influence maternal cholesterol. They also help us better understand the biology of birth defects, thus suggesting more effective strategies for preventing them.

Low and high birthweights are a major cause of neonatal morbidity and mortality, and epidemiological data have established an association between birth weight and later risk of adult metabolic disease. Fetal growth is determined by complex interactions between fetal genes and the maternal uterine environment. Subtle or overt variation in maternal glucose tolerance, which is, in part, genetically determined, is related to fetal size at birth. New emerging data suggest that genetic variation in the fetus can impact maternal metabolism.

Given the above, an NHGRI-funded research team hypothesizes that during pregnancy, gene–environment interactions in the context of the maternal–fetal unit impact fetal size at birth and maternal metabolism. To address this hypothesis, the team is proposing to perform genome-wide association (GWA) mapping on a subset of ~37,000 DNA samples that were collected from mothers and their offspring as part of the NIH-funded Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. HAPO is a multicenter, international study in which high-quality phenotypic data related to fetal growth and maternal glucose metabolism has been collected from 25,000 pregnant women of varied racial and sociodemographic backgrounds using standardized protocols that were uniform across centers. The team plans to genotype 1,500 infants and their mothers of European descent to examine the interaction between maternal genes, the intrauterine environment, and fetal genes to identify interactions that modulate genetic regulation of size at birth and fetal genetic variation that impacts maternal glucose tolerance. A replication study will be performed in additional infants and mothers of European descent with followup studies also planned in Afro-Caribbeans, Hispanics of Mexican descent, and Thais.

The Human Microbiome Project

Within the body of a healthy adult, microbial cells are estimated to outnumber human cells by a factor of 10 to 1. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence upon human development, physiology, immunity, and nutrition.

The human microbiome consists of all the DNA, or genomes, of all the microorganisms present in or on the human body. Launched in 2007 as part of the NIH's Roadmap for Medical Research, the Human Microbiome Project is a 5-year effort that will produce a resource for researchers who are seeking to use information about the microbiome to improve human health.

Initially, researchers plan to sequence 600 microbial genomes, completing a collection that will total some 1,000 microbial genomes. The remaining microbial genomes are being contributed to the collection by individual NIH institutes and internationally funded projects. Those data will then be used to characterize the microbial communities present in samples taken from healthy human volunteers. The samples will be collected from five areas of the body: the digestive tract, the mouth, the skin, the nose, and the vagina.

Following the precedents set by other large-scale genomics efforts, such as the Human Genome Project and the International HapMap Project (HMP), data from the Human Microbiome Project will be swiftly deposited in public databases. The HMP has the potential to transform the ways we understand human health and prevent, diagnose, and treat a wide range of conditions, particularly for women.

National Institute on Aging

Executive Summary

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease and other dementias, menopause and menopausal

hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During FY 2007–2008, NIA-supported researchers made important progress in a number of women's health-related areas, including:

- **Reproductive Health/Menopause**
  Research continued on the etiology and predictors of hot flashes in women around menopause, as well as other symptoms that may accompany the menopausal transition.
- **Cognitive Health and Alzheimer's Disease**
  The effects of the decline in estrogen levels following menopause and menopausal hormone therapy on cognition, as well as the mechanisms through which estrogen and related hormones work on the brain, continue to be elucidated.
- **Osteoporosis**
  A recent study demonstrated that the use of selective serotonin reuptake inhibitors (SSRIs) is associated with reduced bone mass in both women and men, and a separate study suggested a possible mechanism behind this loss of bone.
- **Sex and Gender Differences**
  Investigators continued to explore the reasons behind the sex differentials in disability and mortality across the life span.

NIA has several ongoing research initiatives dealing specifically with women's health. These include:

- **Study of Women's Health Across the Nation (SWAN) and the SWAN Sleep Study**
  The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in women of various racial/ethnic backgrounds. The SWAN Sleep Study has been developed to examine sleep patterns and factors that may affect sleep during the menopausal transition.
- **The Women's Health Initiative Study of Cognitive Aging (WHISCA)**
  The WHISCA project is an ancillary project of the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative (WHI), a long-term study that focuses on strategies to prevent heart disease, breast and colorectal cancer, and fractures in postmenopausal women. 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. Another study of WHISCA participants is underway to identify genetic and hormonal contributions to age-related cognitive decline and dementia.
- **MsFLASH**
  In 2008, NIA, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Complementary and Alternative Medicine (NCCAM), and the Office of Research on Women's Health (ORWH), established the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) initiative, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition. MsFLASH was created in response to recommendations from the 2005 State-of-the-Science Conference on the Management of Menopause-Related Symptoms.

In addition, NIA supports 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.

Introduction

Older women outnumber older men in the United States, and the proportion of the population that is female increases with age. In 2006, women accounted for 58 percent of the population age 65 and over and for 68 percent of the population age 85 and over. Despite living longer, however, older women are more likely to live alone (a potential indicator or risk factor for isolation, lack of caregivers, or lack of support), are institutionalized earlier than men, and live in poverty at a disproportionately high rate.

NIA supports a diverse portfolio of research on older women's health, including studies on:

- Cognitive aging, including Alzheimer's disease and other types of dementia
- Menopause and menopausal hormone therapy
- Osteoporosis and hip fracture
- Physical disability
- Caregiver burden
- Decline in function of older women
- Age-related muscle loss
- Cancer in older women

A Women's Health Coordinator in the Office of Planning, Analysis, and Evaluation coordinates NIA activities related to women's health and serves as 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 below.

Accomplishments

Menopause and Beyond: The Study of Women's Health Across the Nation

NIA's major study of the menopausal transition is the Study of Women's Health Across the Nation, which evaluates longitudinal changes in a wide range of parameters—biological, behavioral, and psychosocial—in women as they transition from pre- to postmenopause. SWAN is cofunded by the National Institute of Nursing Research and the National Insitutes of Health (NIH) Office of Research on Women's Health. Selected findings from SWAN in 2007–2008 include the following:

Depression

SWAN investigators found that most women do not experience high levels of depressive symptoms (as measured using standard psychometric instruments) at midlife; however, women are more likely to experience high levels of depressive symptoms when peri- or postmenopausal or using hormone therapy than when premenopausal. Investigators also identified factors that may predict a first episode of depression, including baseline role functioning due to physical health, a lifetime history of an anxiety disorder, hot flashes, and a very stressful life event prior to depression onset.

Mammographic Density

Women who have extensive dense breast tissue, as visualized on a mammogram, have a significantly increased risk of breast cancer relative to women of the same age who do not. SWAN investigators have identified a number of factors that are associated with amount of mammographic density; notably, older age at menarche and being premenopausal are associated with greater density, while history of premenstrual cravings and bloating and younger age at first full-term birth are associated with less. However, these associations were not independent of other factors, including body size, age, race/ethnicity, and smoking. In a separate study, mammographic density varied by race/ethnicity, but the pattern differed by method of classifying density. Density was not highest among racial/ethnic groups with the highest breast cancer rates, but was lower in more acculturated Asian women. Finally, higher mammographic breast density was associated with lower bone mineral density; this observation was especially apparent in early perimenopausal women, and less obvious in premenopausal women.

Sleep

SWAN investigators identified several potential hormonal mediators of sleep duration and perceived sleep quality: Follicle-stimulating hormone, estradiol, and testosterone all appear to be implicated. In addition, they identified racial/ethnic differences in difficulties staying asleep and early morning awakening, but no significant differences in falling asleep.

Cardiovascular Disease

SWAN investigators found that women with hot flashes were more likely to have evidence of subclinical cardiovascular disease (i.e., endothelial dysfunction, aortic calcification) than women without hot flashes. They also found that levels of C-reactive protein (CRP), a marker for inflammation that has been associated with heart disease risk, vary with ethnicity;

the highest levels were found in African-American women, followed in order by Hispanic, Caucasian, Chinese, and Japanese women. Modifiable risk factors, particularly body mass index, appeared to account for much, but not all, of the differences in CRP levels between ethnic groups. Finally, they found that a history of breastfeeding is associated with a lower prevalence of metabolic syndrome in midlife.

Vasomotor Symptoms

Various factors were found to be associated with higher likelihood of reporting vasomotor symptoms (e.g., hot flashes), including childhood abuse and neglect and both increased abdominal adiposity and total percentage of body fat. Factors such as mood, symptom sensitivity, sleep problems, duration of vasomotor symptoms, age, and race are associated with "bothersomeness" of vasomotor symptoms, above and beyond the frequency of vasomotor symptoms.

Urinary Incontinence

Women with urinary incontinence in peri- and post-menopause were more likely to report improvement and less likely to report worsening of their incontinence symptoms as compared to premenopausal women over 6 years of followup. Meanwhile, aging, increases in waist-to-hip ratio, and weight cycling were associated with worsening incontinence symptoms. Incontinence that develops for the first time in mid-life is mild, with a higher proportion of urge incontinence than other types of incontinence; midlife women also have different risk factors for incontinence than younger and older women. African-American and overweight women appear to be at the greatest risk of developing incontinence in midlife.

Cognitive Health and Alzheimer's Disease

Some change in cognitive function is normal with advancing age, although the mechanisms underlying these changes are not fully understood in either men or women. However, for some people, cognitive change can be the harbinger of a more serious underlying condition. Alzheimer's disease (AD) is the most common cause of dementia among people age 65 and older, and is a major public health issue for the United States because of its enormous impact on individuals, families, the healthcare system, and society as a whole. Scientists now estimate that as many as 4.5 million people currently suffer with the disease, and this number is expected to increase to 13.2 million by 2050, an almost three-fold increase. Currently, nearly half of all Americans ages 85 and older have AD. Risk of developing AD at any specific age is similar for women and men; however, because women live longer, there are significantly more women than men with AD, and in a recent epidemiological study, the overall lifetime risk of developing AD for a woman was nearly twice that for a man (32 percent vs. 18 percent).

Most Americans with AD today are cared for outside the institutional setting by an adult child or in-law, a spouse, another relative, or a friend, and the stress of caring for a loved one with AD often has a profoundly negative impact on health and well-being. Research has shown that caregivers are disproportionately likely to be women. NIA-supported investigators have found that a personalized intervention consisting of home visits, structured telephone support sessions, and telephone "check-ins" can significantly improve the quality of life for AD caregivers. The study, Resources for Enhancing Alzheimer's Caregiver Health II (REACH II), was funded by NIA and the National Institute of Nursing Research and is the first randomized, controlled trial to look at the effectiveness of an AD caregiver support intervention for ethnically diverse populations.

Movement throughout the day is associated with better cognitive function in older women.

A number of observational studies have found that older adults who are more active have higher levels of cognitive function and lower risk of impairment and dementia. However, these studies have relied mostly on self-report of activity levels. In a recent study, over 2,700 women, mean age 83, were assessed for movement using watch actigraphy over several days. Their cognitive function was assessed using standard instruments. After adjusting for age, race, and education, women who showed the highest levels of daytime movement (highest quartile) throughout the day had better mean cognitive scores and were

less likely to be cognitively impaired than those in the lowest quartile of daytime movement. The associations were independent of self-reported walking, medical comorbidities, physical function, and other health-related behaviors. This study provides additional objective evidence that more active older women experience higher levels of cognitive function than their less active age-matched peers.

Anti-inflammatory and antioxidant agents in the prevention of cognitive decline in women.

Evidence from epidemiologic studies has suggested that antioxidants, anti-inflammatory drugs, and folic acid may be protective against cognitive decline and dementia, but large-scale prevention trials are needed to test these observations. Trials of Prevention of Cognitive Decline in Women is an NIA-sponsored cognitive add-on study to the Women's Health Study (WHS) and Women's Antioxidant Cardiovascular Study (WACS), two large-scale randomized trials of chronic disease prevention interventions sponsored by the National Heart, Lung, and Blood Institute. WHS tested low-dose aspirin and antioxidant (vitamin E) supplementation in healthy women, and WACS tested antioxidant and folate supplements in women who already had heart disease. Trials of Prevention of Cognitive Decline in Women is examining whether the treatments from these two trials provide any protection against cognitive decline. Both WHS and WACS have been completed and results are being analyzed. Completed analyses from the WHS demonstrated that low-dose aspirin may provide some benefits for maintaining executive function, but there was no impact on other cognitive domains. For vitamin E, no overall benefit was observed.

Protection of the brain is all in the timing.

Recent studies have described seemingly contradictory actions of estrogens in ischemic stroke injury, with the Women's Health Initiative reporting no beneficial effect of estrogen against stroke and others suggesting that 17-estradiol (E2) may exert a protective effect by quelling stroke-associated inflammation in the brain. However, results of a recent study in mice demonstrate that a prolonged period of estrogen deficiency (e.g., occurs post menopause) disrupts both neuroprotective and anti-inflammatory actions of E2. These findings may help to explain the results of the Women's Health Initiative, as the majority of the WHI participants initiated estrogen treatment after an extended period of estrogen deficiency.

Menopausal Hormone Therapy and AD

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 Women's Health Initiative, contradicted these previous findings, with results suggesting that women ages 65 and older receiving either conjugated equine estrogens alone or Prempro™, a particular form of estrogen plus progestin hormone therapy, could be at increased risk of developing dementia, including AD. These studies were stopped earlier than planned when researchers found that the hormone therapy increased health risks and failed to prevent heart disease.

However, research suggests that menopausal hormone therapy may have other beneficial health effects in some women. 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. For example, in one recent NIA-supported study, researchers found that the hormone progesterone enhanced memory consolidation in aged female mice. While the study did not address the more relevant concern of women on menopausal hormone therapy—i.e., long-term progesterone use—the findings do provide important initial confirmation of the role of progesterone in memory consolidation in an animal model.

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; 1 in every 2 women over age 50 will have an osteoporosis-related fracture in her lifetime. Treatment options for women have most often included menopausal hormone therapy involving estrogen; however, recent clinical evidence has indicated that

such therapy may have undesired side effects on other organs.

Investigators with the Study of Women's Health Across the Nation have studied the rate of change in bone mineral density in women across the menopausal transition and found the following:

- Typically, women experience little or no bone loss in pre- and early perimenopause.
- Rates of both lumbar spine and total hip bone loss accelerate substantially in late perimenopause and continue at a similar pace in the early postmenopausal years.
- Body weight is a major determinant of the rate of bone loss during the menopause transition, with women of lower body weight losing bone more rapidly.
- Observed ethnic differences in rates of menopausal bone loss are largely explained by differences in body weight.

Use of antidepressant medication is linked with increased risk for osteoporosis.

Treatment with SSRIs account for over 60 percent of prescriptions for depression—particularly in the elderly, due to the drugs' better safety profile for cardiovascular disease. However, recent findings from two large cohort studies, the Osteoporotic Fractures in Men (Mr. OS) Study and the Study of Osteoporotic Fractures (SOF), suggest a deleterious effect of SSRIs on bone in both older men and women. Results of Mr. OS and SOF indicate that use of SSRIs is associated with reductions in bone mineral density among men and an increased rate of bone loss at the hip in women.

Because bone loss is common among older people, with the most severe loss generally seen among post-menopausal women, the finding that SSRIs may be a significant contributing factor to osteoporosis could have significant public health implications and may suggest the need for changes in the way depression is managed in middle-aged and older individuals. For example, even if treatment with SSRIs appears to be clinically appropriate in a given case, measures to forestall bone loss may also be indicated. However, further research is needed to confirm these findings and to determine the best interventions to ameliorate depressive symptoms without compromising bone health among older Americans.

Bone mass regulation: A gut feeling.

Throughout life, bone is constantly renewed through a complex process known as bone remodeling, which consists of two phases: resorption of old bone by specialized cells called osteoclasts, and formation of new bone by other specialized cells known as osteoblasts. Among the many molecular and systemic factors that regulate this process, the protein Lrp5 is particularly important. When Lrp5 function is compromised, osteoporosis results, while overactive Lrp5 is associated with high bone mass syndromes in humans. Scientists have long believed that Lrp5 controls bone mass primarily through signaling in the Wnt pathway in osteoblasts. However, a new and surprising finding challenges this theory.

NIH-supported investigators found that in mice, Lrp5 inhibits expression of Tph1, an enzyme involved in synthesis of the hormone serotonin in the small intestine. The resulting decrease in serotonin production was associated with an increase in bone mass in the mice. Conversely, mice deficient in Lrp5 produced an excess of gut serotonin, and were also prone to low bone mass. When the researchers "turned off" Lrp5 activity in the gut, bone mass was decreased, whereas turning off Lrp5 in osteoblasts had no effect on bone mass, suggesting that Lrp5 exerts its effects through the gut and not the bone. The researchers also demonstrated that serotonin acts directly on osteoblasts to decrease bone formation.

These findings suggest that Lrp5 regulates bone formation through serotonin synthesis in the gut and not directly through the bone, as was previously believed. Furthermore, the finding that serotonin inhibits osteoblast activity may help explain the recent finding that individuals who take SSRIs for the treatment of depression or related conditions may be prone to reduced bone mass. Overall, this study broadens our understanding of bone remodeling and suggests new therapeutic approaches to increase bone mass.

Other Research Accomplishments

Preventive Health Care for Older Women

More data on the benefits and risks of many health promotion measures for women aged 80 and older are needed to help target use to women most likely to benefit. NIA-supported investigators identified factors important to mammography screening decisions among older women; the results indicated that while a doctor's recommendation is the vital factor influencing elderly women's mammography screening decisions, habit and reassurance also strongly influence decision-making. In addition, in a comprehensive review of preventive health measures for elderly women, the investigators found that most women in poor health were screened for cancer, but not for other common health problems, such as depression; nor were they counseled about exercise, falls, or incontinence, thus indicating a need to improve delivery of preventive health care to older women.

A Potential Treatment Target for Preeclampsia

Although preeclampsia (PE) is a major cause of maternal and fetal mortality, its pathogenesis is not fully understood. Compounds known as endogenous digitalis-like cardiotonic steroids (CTS) are implicated in the pathophysiology of PE. Recently, NIA intramural investigators reported that plasma levels of marinobufagenin (MBG), a type of CTS, are increased four-fold in patients with severe PE. More recently, they found that levels of MBG are significantly elevated in the preeclamptic placenta, and that a monoclonal anti-MBG antibody reduces blood pressure in experimental PE, indicating that MBG is a potential treatment target in patients with PE.

Education and Outreach

Menopause: Time for a Change

When a woman nears menopause, she may wonder about unfamiliar changes in her body. What are the signs of the menopausal transition? What can she do to ease her hot flashes and other uncomfortable symptoms? What are some health concerns she may face in the future? NIA's Menopause: Time for a Change can help answer these questions. This booklet, developed in consultation with scientific experts, provides a lively, easy-to-read overview of the menopausal transition, including a description of some of the common signs that the transition is underway, along with information about handling bothersome symptoms; a discussion of some health problems that become more common after menopause; suggestions for staying healthy; and a resource list for more information.

Exercise & Physical Activity: Your Everyday Guide from the National Institute on Aging

This completely updated, 120-page book for older adults provides tips for getting started, including how to set goals and measure progress, and offers helpful worksheets. Sample exercises—to improve endurance, strength, balance, and flexibility—include easy directions and colorful photos to help readers do them safely. Developed under the guidance of the NIA Exercise and Physical Activity Task Force, the guide also offers a chapter on healthy eating, 20 frequently asked questions with answers, a list of more than 30 organizations to contact for other resources, and a tear-out card to order an official NIA physical activity certificate.

Both publications are distributed free of charge and are available on the NIA Web site (http://www.nia.nih.gov/HealthInformation/Publications/; click on "Women's Health").

Gender Analyses

Females generally have lower mortality than males at every age. The magnitude, however, of the male disadvantage varies depending on environmental, social, and economic conditions. In fact, the male disadvantage in infant mortality underwent a surprising rise and fall in the 20th century. In a recent study of 15 developed countries, investigators found that, as infant mortality declined over two centuries, the excess male mortality increased. The research purports that the worsening male disadvantage from 1751 until 1970 may be due to differential changes in cause-specific

infant mortality by sex, such that declines in infant mortality from infections and the shift of deaths to perinatal conditions favored females. The observed reduction in male excess infant mortality after 1970 can be attributed to improved obstetric practices and neonatal care. Overall, this analysis provides evidence of marked changes in the sex ratio of mortality at an age when behavioral differences should be minimal.

During 2007–2008, NIA supported a number of research projects aimed at identifying and explaining sex and gender differences in a variety of health-related areas. Representative projects include:

- A study of sex differences in bone loss and incident fractures
- A study of sex differences in apoptosis and stem cell function
- A study of the influences of gender, age, and ethnicity in the management of chronic illness

Conferences and Workshops

A symposium on "Estrogen, Menopause, and the Aging Brain: How Basic Neuroscience Can Inform Hormone Therapy in Women" was held at the 36th Annual Meeting of the Society for Neuroscience in October 2006. The symposium highlighted the work of NIH-supported investigators who described their work on hypothalamic control of reproductive aging; synaptic effects of estrogen in hippocampus and prefrontal cortex and implications for cognitive aging; and strategies for predicting clinical outcomes in women and development of therapies based on steroid hormone mechanism of action.

Initiatives

Requests for Applications (RFAs)

NIA, in collaboration with NICHD, NCCAM, and ORWH, has established the Menopause Strategies: Finding Lasting Answers for Symptoms and Health initiative, a multisite research network to conduct randomized clinical trials of promising treatments for the most common symptoms of the menopausal transition. The initiative was established in 2008 in response to recommendations from the 2005 NIH State of the Science Conference on the Management of Menopause-Related Symptoms and is projected to run for 5 years. (RFA AG08-004)

The MsFLASH network is composed of five clinical research centers and a Data Coordinating Center. Different approaches will be studied for efficacy against hot flashes and night sweats in diverse groups of women in trials with either placebo or usual-care control groups. Investigators will also look at possible effects on other symptoms at middle age, including sleep disturbance, mood disorder, vaginal dryness, and sexual function. A number of different treatment strategies are under consideration. Possible treatments to be studied during the 5-year project period include the following:

- Antidepressants such as paroxetine (Paxil®) or escitalopram (Lexapro®)
- Paced respiration (slow deep breathing; also known as relaxation breathing)
- Yoga
- Low-dose estradiol patch and low-dose estradiol gel
- Exercise programs, both moderate and vigorous

Ongoing Research Initiatives

▶ **The Study of Women's Health Across the Nation.**
This ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to post-menopause is of high relevance to understanding healthy aging in midlife women and beyond. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in Caucasian, African-American, Chinese, Japanese, and Hispanic women. Funded initially in 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center, an advisory

panel, and a repository of blood, urine, and DNA specimens. The study is supported by NIA, the National Institute of Nursing Research, and ORWH.

- **The SWAN Sleep Study**
  SWAN investigators from four sites are examining sleep patterns and factors that may affect sleep during the menopausal transition. Although sleep disruptions, insomnia, and breathing-related sleep disorders increase as women age, little is known about how their sleep changes as women progress through the menopausal transition. The goals of Sleep I, the baseline phase, were to (1) characterize sleep disturbances in a large, multiethnic sample of midlife women; (2) characterize relationships among menopausal characteristics (e.g., vasomotor symptoms and bleeding) and sleep disturbances; (3) evaluate the influence of psychobiological factors on the sleep–menopause relationship; and (4) establish baseline data for Sleep II, the longitudinal phase of this research study. The major goals of Sleep II, currently in progress, are to identify (1) potential predisposing, precipitating, and perpetuating factors for chronic sleep disturbances during the menopausal transition, and (2) adverse effects of sleep disturbances on subsequent health status during early postmenopause.

- **The Women's Health Initiative Study of Cognitive Aging**
  WHISCA investigates both on-trial and long-term, posttrial effects of exposure to menopausal hormone therapy on cognitive aging within the context of the Women's Health Initiative Memory Study and the Women's Health Initiative more generally. While WHIMS focuses on the effects of menopausal hormone therapy on the risk and progression of Alzheimer's disease and other dementias, WHISCA assesses the effects of hormone treatment on memory, cognition, and mood in nondemented WHIMS volunteers age 65 and older who had been randomized to hormone therapy or placebo within the WHI trial. More than 12,000 longitudinal assessments have been performed for 2,302 WHISCA participants. In addition to allowing assessment of hormonal effects on cognitive aging, this database also allows more general investigation of risk and protective factors for cognitive decline in older women. Since almost half of the women have also participated in the WHIMS-magnetic resonance imaging (MRI) study, this database also allows investigation of variation in brain volumes and brain lesion burden in relation to cognitive change.

  A new study involving the WHISCA cohort has just begun to probe the complexity between genetic background and cognitive decline as an intermediate phenotype of dementia. The study will also examine how cognitive decline is modified by hormone therapy. The study will measure variations in candidate genes with known involvement in certain aspects of cognition, and will explore the relationship between these candidate genes and incidence of MCI and dementia. Secondary analysis will examine the relationship between candidate gene variants and cognitive decline as a function of hormone therapy, and volumetric brain changes as an intermediate phenotype in the gene-to-behavior pathway.

- **Estrogen, Menopause, and the Aging Brain: How Basic Neuroscience Can Inform Menopausal Hormone Therapy Use in Women**
  Several large studies on steroid hormone neurobiology may provide insights into the basis of disparities between basic science outcomes and clinical trial outcomes in hormone therapy regimens, and thereby lay the groundwork for more informed approaches to hormone use in humans in order to help promote successful brain aging. These studies include the following:

  - *Estrogen and the Aging Brain*
    The goal of this study is to elucidate the interactions between the brain and female reproductive senescence, with particular attention to the impact of these events on cognitive function. The grant is studying the spectrum of mechanistic analyses from the in vitro cellular/molecular level to an in-depth structural and functional assessment of the effects of estrogen therapy and more physiological

forms of combined hormone therapy on behaviorally characterized nonhuman primates.

- *Progesterone in Brain Aging and Alzheimer's Disease*
  Investigators are working to enhance our knowledge of the neurobiology of progesterone action in brain regions required for cognition and are vulnerable to age-associated degenerative disease such as Alzheimer's. The hypothesis under study is that the sex steroid hormone progesterone promotes the brain's molecular, synaptic, cellular, and behavioral plasticity and reduces its vulnerability to the development of AD via direct effects mediated by progesterone receptors in the hippocampus and indirect effects via interaction with estrogen pathways.

- *Novel Mechanistic Targets of Steroid Hormones in the Brain*
  The overall goal of this study is to identify and characterize new and alternative targets by which estrogens and progestins are neuroprotective. Investigators will study a variety of receptors as potentially critical players in neuroprotection and neurogenesis.

▶ **Epidemiology of Menopause and Dementia in Down Syndrome**
Studies in the general population suggest that the dramatic decline in estrogen levels following menopause may play an important role in the etiology of Alzheimer's disease. Among women with Down Syndrome (DS), the average age at onset of menopause is 46 and the average age at onset of AD is 50–55. The short interval between menopause and AD in women with DS provides a unique opportunity to examine the influence of endogenous estrogen activity on disease risk in a prospective study. A longitudinal study in 336 women with DS, who were 40–59 years of age at the start of the analysis, is under way. The overall aim of this project is to investigate the contribution of small changes in genes (called polymorphisms) that influence endogenous estrogen levels or estrogen receptor function to the rate of cognitive decline and risk of AD in women with DS. Findings so far support the hypothesis that reductions in estrogen following menopause contribute to the cascade of pathological processes leading to AD. Some polymorphisms in the genes under study also may contribute to this cascade.

▶ **KEEPS Cognitive and Affective Study**
The KEEPS (Kronos Early Estrogen Prevention Study) Cognitive and Affective Study is the first multisite, randomized, placebo-controlled, double-blind, parallel-group design clinical study to address major issues related to use of menopausal hormone therapy raised by the Women's Health Initiative and the Women's Health Initiative Memory Study. Specifically, this study evaluates the differential efficacy of conjugated equine estrogen (CEE—e.g., Premarin) and transdermal 17 p-estradiol (tE2) on comprehensive measures of cognition and mood in perimenopausal women over an extended therapy of 4 years. Study participants will also be treated with progesterone to counteract overproliferation of endometrial tissue, which can be a side effect of menopausal hormone therapy. The goals of the study are (1) to characterize the potential differential efficacy and adverse effect profile of extended therapy with CEE and tE2 on cognitive function of perimenopausal women; (2) to identify the effects of micronized progesterone on the proposed battery of cognitive and affective tests in perimenopausal women; (3) to establish the relationship between estrogen-induced changes in markers of atherosclerosis, heart disease, and measures of mood and cognition; (4) to characterize the relationship between estrogen-related changes in proposed markers of inflammation, blood hypercoagulability, and tests of cognition and mood; and (5) to determine whether ApoE genotype will influence cognitive responsivity to menopausal hormone therapy.

▶ **Experience Corps**
NIA is funding a major community intervention designed to improve social, cognitive, and physical functioning among poor, inner-city elderly through the Experience Corps evaluation. Experience Corps recruits older people for cognitively challenging,

meaningful roles as volunteers in inner-city elementary schools. The program is active in 19 cities nationwide, and the majority of volunteers are women.

Selected Intramural Research Initiatives

- **Genes Associated With Ovarian Development and Premature Ovarian Failure**
  Because the pool of ovarian follicles is largely established during fetal life, the development of the ovary predetermines female reproductive lifespan, including the time of onset of menopause. NIA intramural investigators are studying the roles of several genes that are involved in ovarian development and premature ovarian failure, including Foxl2 (known to be mutated in some patients with premature menopause), Foxo3, and Wnt4. They have found that overall, Foxl2, Wnt4, and several other master genes are involved in establishing and maintaining the follicle pool in the ovary. By contrast, Foxo3 determines the rate at which the follicle pool is depleted by the growth and maturation of individual oocytes during the female reproductive lifespan.

- **Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR)**
  Co-STAR evaluates the effects of these selective estrogen receptor modulators (SERMs) on cognition and mood as an ancillary study to the Study of Tamoxifen and Raloxifene (STAR) breast cancer prevention trial. Co-STAR enrolled 1,532 participants ages 65 years and older who have been followed with annual assessments of global and domain-specific cognitive function. Since the unblinding of the main STAR trial on April 17, 2006, Co-STAR participants have received a final posttrial assessment, with assessments available for more than 1,000 participants. In addition to allowing assessment of the effects of these SERMs on cognitive aging in older women, this database also allows more general investigation of risk and protective factors for cognitive decline in older women.

- **Ovarian Cancer Pathogenesis and Drug Resistance**
  NIA intramural investigators are working to elucidate clues to the pathogenesis of ovarian cancer, one of the most common gynecological malignancies in women, with particular attention to a family of proteins known as claudins. Evidence is mounting that claudin-3 and claudin-4 may represent useful markers for the detection and diagnosis of ovarian cancer. The same research team is also identifying genes associated with resistance to drugs that are commonly used to treat ovarian cancer.

Health Disparities Among Special Populations of Women

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. NIA is committed to addressing health disparities, with many initiatives supported in partnership with the National Center on Minority Health and Health Disparities. Minority aging research is conducted throughout the Institute's programs, and much of this research has relevance to the health needs of minority women. Examples of current programs and projects include the following:

- The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, a community-based research effort designed to focus on evaluating health disparities in minority and socioeconomically diverse populations;
- A study of gender, age, and ethnicity in the management of chronic illness;
- A longitudinal study of urinary incontinence among participants in the SWAN study, including White, African-American, Hispanic, and Asian women;
- A study of genetic factors related to Alzheimer's disease among African-American men and women; and
- An investigation of barriers to preventive care use among unmarried Latinas, focusing on cancer screening.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Executive Summary

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) was created in 1971 by the U.S. Congress to serve as the focus for the Federal Government's efforts to prevent and reduce the enormous health, social, and economic consequences of alcohol abuse and alcoholism in the United States. As a central part of this mission, NIAAA supports a wide range of biomedical and behavioral research, ranging from the basic physiological mechanisms of alcohol's action to studies of the psychosocial and demographic correlates of its use to prevent and treat these significant public health problems. Untreated alcohol problems waste an estimated $184.6 billion per year in healthcare, business, and criminal justice costs, and they cause more than 100,000 deaths. Studies of the general population in the United States indicate that women consume lower levels of alcohol than men and are less likely than men to drink daily or to engage in binge patterns of use. However, women are more sensitive than men to the physiological effects of alcohol, reach higher blood alcohol concentrations, have a higher risk for the development of alcohol-related diseases, and show higher vulnerability to alcohol dependence. Complex biological and social factors underlie the differences in men's and women's drinking behaviors and related problems. NIAAA is committed to uncovering the foundations of these gender/sex differences and to devising effective strategies to treat and prevent female alcoholism.

Research advances that affect women can be found within many of the Institute's broad research categories and in each programmatic division of the Institute. In the past two fiscal years, the following scientific areas related to women's health and studies of sex/gender differences have undergone significant advances in knowledge: biological, psychosocial, and cultural bases for the differences in men's and women's drinking behavior and related problems; alcohol use and fetal alcohol spectrum disorders; the role of sex hormones on immune responses, tissue injuries, and neurobiology of alcohol dependence and withdrawal; and differences in alcohol metabolism between men and women.

NIAAA continues to expand its research portfolio on women's health by supporting both traditional and high-risk cutting-edge applications arising from the NIH Roadmap. Recognizing recent advances in molecular biology techniques coupled with progress in stem cell research and epigenetics, NIAAA, together with the Office of Research on Women's Health (ORWH) is currently supporting a study of alcohol's effects on conception and pregnancy via epigenetic modifications. This research will eventually help us to understand the molecular consequences of pregnancies influenced by alcohol. A wide effort to include female animals in basic science studies has led to significant advances in our knowledge about the mechanisms that underlie women's higher susceptibility to some of the negative medical consequences of alcohol use, such as digestive diseases, cirrhosis of the liver, cardiac disease, and cognitive impairments. The research findings of these projects have provided new therapeutic possibilities that would be helpful in the regeneration or inhibition of tissue damage in alcoholic patients.

Alcohol is now recognized as the leading teratogen to which the fetus is likely to be exposed. In the United States, an estimated 130,000 women per year expose their fetuses to high levels of alcohol, and the estimated associated costs are $4–$11 billion. Alcohol-induced birth defects are known as fetal alcohol spectrum disorders (FASD). Fetal alcohol syndrome (FAS) is the most clinically recognizable form of FASD. Studies have shown that FAS is completely preventable and that the consumption of alcohol during pregnancy can result in lifelong physical and mental impairments. One NIAAA-funded project aims to identify and test therapies that could protect the developing brain from ethanol injury and preserve cognitive functioning in children at risk for fetal alcohol spectrum disorders. One possible mechanism responsible for these learning and memory deficits is a defect in the signaling of gamma-aminobutyric acid (GABA), one of the major neurotransmitters

in the brain. A recent study found that during brain development, binge-like intoxication in rat pups distorted the maturation of GABA synapses in certain brain regions. This action could be largely prevented by finasteride, a drug that blocks the formation of GABA synapse modulators. This work has the potential to provide a model for testing interventions for preventing or limiting cognitive injury in children with FASD.

While the majority of FAS studies have been conducted in the United States, international collaborations provide a wealth of resources for the study of FAS. To take advantage of cross-cultural and cross-ethnic comparisons, NIAAA supports several collaborative research projects on the international scale, including the longest running U.S.–South African project and new U.S.–Russian study. In addition, a cooperative agreement was established jointly with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to conduct community-linked studies on the underlying causes of sudden infant death syndrome and adverse pregnancy outcomes, such as stillbirth and FAS, and the role of prenatal alcohol exposure. Multiple international sites with a high incidence of FAS and FASD are participating in this important study. The long-term goals of this initiative are to decrease fetal and infant mortality and improve child health in the affected communities.

Complex psychosocial determinants and environmental conditions are associated with alcohol intake in women, the understanding of which could lead to the development of gender-specific therapeutic interventions. Many studies have found that posttraumatic stress disorder, depression, violence, and unstable family life are risk factors for drinking problems in women. For example, a study using data collected from 1981 to 2001 from the National Study of Health and Life Experiences of Women (NSHLEW) found that different patterns of childhood sexual abuse (CSA) predict different long-term drinking outcomes. The effects of more severe CSA appeared to increase as women age, pointing to an important or delayed sleeper effect where continued or increased drinking may be attributable to unresolved psychological factors or trauma. Early identification and intervention among women at risk of developing alcohol problems may avert the more severe, adverse consequences of alcohol abuse and dependence, emphasizing the importance of screening and primary prevention work on alcohol issues. Alcohol-related health disparities in women have been recognized as an additional important factor in alcohol abuse and dependence. The findings from an ongoing randomized trial, Screening and Brief Intervention of Problem-Drinking Women, indicate that African-American women with a positive screening test for problem drinking consume significantly more drinks per drinking day than Asian and Caucasian women with a positive alcohol screening test. The basis of these differences is still poorly understood and needs to be addressed further.

NIAAA provides leadership in the important effort to ameliorate the alarming rise in binge drinking among college women by supporting research to design effective interventions that target this group. Findings from the "Heads UP! Women" cooperative agreement funded in NIAAA's Rapid Response to College Drinking Initiative demonstrate the high efficacy of a motivational interviewing-based intervention in the reduction of alcohol consumption among all participant groups, including freshman women, females sanctioned by the university's Judicial Affairs, and general members of the college campus community.

It has long been recognized that acting to support awareness, self-esteem, and decision-making among women provides a solid foundation for prevention of alcohol abuse. To raise awareness of the negative effects of alcohol consumption on the female body and to encourage a healthy lifestyle, NIAAA promotes prevention messages through the media. Two recent publications in an Alcohol Alert brochure discuss the potential harm posed by alcohol use during pregnancy, and they target women of childbearing age.

NIAAA participates in multiple scientific partnerships, meetings, and collaborative activities to benefit women with many Federal and non-Federal organizations. In addition to existing programs, NIAAA will cosponsor, with NICHD, the National Cancer Institute (NCI), and the National Center for Complementary

and Alternative Medicine (NCCAM), an initiative for a multicenter international research network designed to conduct randomized clinical trials of interventions to reduce the major risks to maternal, neonatal, infant, and early childhood health in resource-poor countries. NIAAA seeks to include alcohol screening and interventions in the health care of women in prenatal care and the screening of children from birth through early childhood for the disabilities that result from prenatal exposure to alcohol.

The current report highlights NIAAA's recent accomplishments in women's health research that promote our understanding of biological and psychosocial mechanisms of alcoholism and related diseases in women as we support the development of effective prevention, early intervention, and treatment of alcohol problems in women.

Accomplishments

Psychosocial Determinants of Drinking in Women

Trends in Women's Drinking Patterns

A study using data collected from 1981 to 2001 from the National Study of Health and Life Experiences of Women examined 12-month drinking trends among women and found (1) that different patterns of childhood sexual abuse (CSA) predict different long-term drinking outcomes, (2) that quantity-frequency methods of alcohol consumption may overestimate women's reports of alcohol use; (3) that recalled ages of drinking onset predict subsequent drinking and may have implications for prevention of early onset of drinking; and (4) a significant involvement of alcohol in the number of episodes as well as severity of physical partner aggression. The effects of more severe CSA appeared to increase as women aged, pointing to an important or delayed sleeper effect where continued or increased drinking may be attributable to unresolved psychological factors or trauma.

Interventions To Reduce Drinking-Related Harm in College Women

Heads UP! Women was a cooperative agreement project in NIAAA's Rapid Response to College Drinking Initiative that tested the efficacy of a multicomponent, motivational interviewing-based intervention for freshman women, females sanctioned by a university's Judicial Affairs, and general members of a college campus community. Findings from this cooperative agreement are notable as the intervention significantly reduced alcohol consumption, number of binge drinking episodes, and drinking-related consequences among all participant groups. In addition, the intervention effect was greatest among women with stronger social and enhancement motivations for drinking. This work has implications for designing effective interventions that target college women. Furthermore, booster or maintenance sessions may promote more enduring effects.

Effects of Service Agency Utilization and Drinking Trajectories

Preliminary findings from a longitudinal study of gender differences in drinking trajectories among treated vs. untreated dependent and problem drinkers found that recovery-oriented social networks, Alcoholics Anonymous (AA) attendance, and contact with the mental health system were significantly related to decreased consumption for both genders, with welfare contacts additionally related to less drinking for women only. This work has implications for service agencies that intervene and treat individuals with drinking problems.

Gender Analysis

Sex Differences in Alcohol Withdrawal

Clinical experience has shown that women alcoholics experience fewer alcohol withdrawal symptoms than men. NIAAA is supporting a research study, cofunded by ORWH through the Research Enhancement Awards Program (REAP) program, to establish mechanisms responsible for gender differences in the typical brain hyperexcitability that occurs during alcohol withdrawal. These neurochemical and behavioral studies are being conducted

in an animal model of chronic alcohol exposure, with the objective of examining the role of specific synaptic proteins involved in the sex differences. The primary hypothesis is that sex differences in recovery from ethanol withdrawal involve sex-selective changes in inhibitory (GABAergic) and excitatory (glutamatergic) neurotransmission that occur as a result of the differing hormonal milieu between males and females. The project has identified significant sex differences in withdrawal recovery, in the effectiveness of GABAergic neuroactive steroids to moderate withdrawal seizure risk, and in chronic ethanol-induced alterations of GABA receptor subunit levels. Findings generated from this proposal have important clinical implications, by predicting neurobiological differences in the sequelae of withdrawal between men and women. This information will also enable tailoring of treatments of alcoholics according to gender and hormonal status.

Sex-Selective Effects of Ethanol

A growing body of evidence suggests that men and women exhibit significant differences in alcohol dependence and withdrawal. In fact, research has shown that females may recover more quickly from withdrawal-induced seizures than males. However, the neurobiological basis for this phenomenon remains unclear. Recent findings from an NIAAA-funded research program demonstrate that differences between males and females in hormonal status as well as in brain structure, such as the sexually dimorphic areas of the hypothalamus, contribute to the sex differences in response to ethanol withdrawal. Several ongoing studies are examining sex differences in behavioral responses to ethanol withdrawal and hormonal treatments. They are also identifying sex differences in response to alcohol at the molecular level, including adaptations of neurotransmitter systems, signaling molecules, and receptor expression. In addition to providing the neurobiological basis for sex-selective effects of ethanol, the outcome of these studies may suggest ways that the treatment of alcohol withdrawal could be optimized by considering hormonal status.

Alcohol and Reward Mechanisms Are Different in Women Than in Men

Men and women show differences in response to alcohol, possibly due to sex hormones or other factors. These sex differences may extend to the mesolimbic dopamine system, a circuit in the brain that mediates reward and is involved in alcohol addiction. Recent research found decreased mesolimbic dopamine release in mice lacking the mu opioid receptor, a protein that conducts pleasure signals in the brain. The decrease in dopamine release was more marked in females than in males, however. This study demonstrates that there may be sex differences in ethanol reward mechanisms in the brain, which could partially explain why women may be affected by ethanol in different ways than men.

Sex-Specific Differences in Alcoholic Gut and Liver Injury

Women are at a greater risk for alcohol-induced liver injury than men, but underlying mechanisms are poorly understood. Many publications indicate that chronic alcohol consumption dramatically changes the hormonal milieu of both the blood and liver in both sexes. The liver is a key player in this scenario, because in addition to being the site of steroid hormone metabolism, the liver is responsive to sex hormones. One proposed link between female sex hormones and alcoholic liver injury is through gut-derived endotoxin, a component of the outer wall of Gram-negative bacteria that causes hepatic tissue injury. Estrogen enhances liver sensitivity to endotoxin and may therefore worsen liver injury, especially in alcoholics that show an elevated level of endotoxin. To understand the interactions among alcohol, gut-derived endotoxin, sex hormones, and liver injury, this project investigates sex-specific differences in alcoholic gut and liver injury. Successful completion would add important information on how hormones and alcohol interact.

Gender Differences in Inflammation May Mediate Susceptibility to Liver Injury

This project studies in an animal model a sexual dimorphism in expression of the interleukin-6 receptor (IL-6R) and regulation of the IL-6R and IL-6 signaling by ethanol. IL-6

is a pleiotropic cytokine that promotes inflammation and is a marker for alcohol-induced liver disease (ALD) in humans. Compared to male mice, after chronic alcohol administration, female mice have higher receptor levels—a finding that suggested greater inflammatory activity. After alcohol administration, compared to females, male rats also had higher levels of levels of NF-kappaB, an inhibitory signaling molecule thought to downregulate the expression or function of the IL-6R, thus resulting in dampened inflammatory activity. The research findings on this project not only help us understand the mechanism that underlies the gender difference in the development of ALD, but they will also provide some new therapeutic possibilities that would be helpful in the regeneration or inhibition of hepatic damage in alcoholics.

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 syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and 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 of the United States and in the Western Cape of South Africa, serving at-risk Native American Indian and Cape "colored" populations, respectively; a developmental biology and pathology center; a physiology assessment center; and a data-coordinating and -analysis center. Since FY 2007, the PASS Network has enrolled nearly 2,000 pregnant women (toward an enrollment goal of 12,000) in a comprehensive longitudinal cohort study in which their infants will be followed for up to 1 year. In parallel, the network also is recruiting known cases of SIDS and stillbirth for a retrospective study. Additionally, 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.

Alcohol's Effects on Conception and Pregnancy

Maternal alcohol consumption during pregnancy produces a variety of adverse pregnancy outcomes and birth defects. However, the effects of acute alcohol consumption near the time of conception are relatively unstudied. NIAAA, together with ORWH through the REAP program, is currently supporting a study of alcohol's effect on the oocyte-to-embryo transition, called periconception, which is a critical developmental period when the totipotent embryo generates the entire individual. Any epigenetic misprints occurring during this stage are inherited throughout the body. The goal of this research is to determine how alcohol exposure influences genomic modification and function during the oocyte-to-embryo transition and leads to susceptibility to disease. This project will identify candidate genes for which expression and epigenetic status are influenced by ethanol during the oocyte-to embryo transition. Previous studies have shown that mice oocytes exposed to alcohol during in vitro maturation develop into adults with a higher incidence of metabolic disease, such as obesity and diabetes. The investigators will first identify the critical genes altered by acute alcohol exposure during in vitro maturation in oocytes and embryos. Then they will test the effects of ethanol exposure on the establishment of initial epigenetic patterns in preimplantation embryos as a mechanism for altered gene expression. This initial in vitro work will provide the requisite foundation for future in vivo studies. This research will eventually help in understanding the molecular consequences of the pregnancies under the influence of alcohol.

Alcohol Effects on Human Breastfeeding and Lactation

The belief that drinking alcohol aids lactation is prevalent in many cultures, but there had been little scientific research to support this belief. One project is investigating the effects of drinking during breastfeeding on

alcohol pharmacokinetics and hormonal responses in the mother and on infant behavior and nutrition. Previous research found that infants, whose mothers drank moderate amounts of alcohol during lactation, had abnormal breastfeeding responses. These infants were less likely to breastfeed and sucked more intensely during the first few minutes of the nursing period. Recently published findings show that breast pumping after drinking alcohol slows the normal prolactin response during the next pumping session, indicating that alcohol interferes with the lactation process. In addition, new research indicates that the prolactin response to breast pumping is significantly slower in women with a positive family history of alcoholism compared to women with a negative family history, suggesting that genetic factors may be involved. These findings, that moderate drinking adversely affects milk production by mothers and milk intake by their infants, have important public health policy implications regarding moderate alcohol use in women who are nursing.

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 FASDs 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. In addition, some consortium members are developing animal models of FAS and FASD with aims of clarifying mechanisms, improving diagnostic methods, identifying genetic and molecular markers of these disorders, and testing potential interventions. 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.

Differences in the Serotonin System in Animals Exposed to Prenatal Ethanol

Prenatal ethanol exposure may affect an individual's brain function later in life, and some effects may be specific to females. NIAAA is funding a research program to investigate fetal programming of the stress and hormonal response after exposure to prenatal ethanol. Adult female rats, which were exposed to ethanol prenatally, show an altered stress hormone response to drugs that attach to the serotonin receptor in the brain. Males show no hormonal effect to these drugs. Publications from this research show that prenatal ethanol exposure has differential long-term effects on the brain stress system in males and females. The changes induced by prenatal ethanol exposure may alter the way women respond to stress later in life, and may have implications for depression and other related mental health disorders.

Neurocircuit Targets of In Utero Ethanol Intoxication and of Therapies for Fetal Alcohol Spectrum Disorders

There are currently no treatments to prevent or reverse cognitive deficits in children caused by ethanol intoxication during pregnancy. One NIAAA-funded project aims to identify and test therapies that could protect the developing brain from ethanol injury and preserve cognitive functioning in children at risk for fetal alcohol spectrum disorders. One possible mechanism for these learning and memory deficits is a defect in the signaling of GABA, one of the major neurotransmitters in the brain. A recent study found that during a period equivalent to human third-trimester brain development, binge-like intoxication in rat pups distorts maturation of GABA synapses in certain brain regions. This action could be largely prevented by finasteride, a drug that blocks formation of modulators of the GABA synapse. This work has the potential to provide a model for testing treatments aimed at offering hope for preventing or limiting cognitive injury in children with fetal alcohol spectrum disorders.

Alcohol's Effects on Teratogenesis

Women who consume alcohol during pregnancy place their offspring at risk for a number of teratogenic effects. In the United States, an estimated 130,000 women per year expose their fetuses to high levels of alcohol, and the estimated associated costs are $4–11 billion. Genetic factors, both maternal and fetal, are known to play a role in susceptibility to ethanol during teratogenesis. NIAAA currently supports a study on the genetic mechanisms mediating differential susceptibility to the teratogenic effects of ethanol. A maternal effect mediating different teratogenic outcomes following prenatal ethanol exposure has been identified in a mouse model. The study examined genomic imprinting as an epigenetic mechanism for the teratogenic effect. Following prenatal ethanol exposure, DNA methylation, histone modifications, and gene expression changes were found in embryos and placentas for several imprinted genes. The genes are known to play a role in growth and development. In addition, they examined global gene expression changes in fetuses exposed to alcohol in utero. These epigenetic modifications and/or gene expression changes identified in imprinted genes following prenatal alcohol exposure in mice can be potential targets for future human studies. The study of the methyl-supplementation diet on some of the teratogenic effects of ethanol may allow for the design of rational treatment, and ultimately, prevention strategies in the future.

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. Significantly more mothers of FASD children reported drinking before becoming pregnant than control mothers (92 percent versus 25 percent), and more FASD mothers continued to drink throughout all three trimesters of the index pregnancy. Although 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; and lower height, weight, 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

Effects of Alcohol on Cognition and Health in Postmenopausal Women

Postmenopausal women are not usually included in many research studies, and the effect of drinking alcohol in this population has not been well studied. Whether there are special risks to drinking in postmenopausal women or possible benefits is of interest for healthcare management and for understanding effects related to hormone replacement therapies. The NIAAA is funding a research study investigating the effects of drinking and estrogen replacement therapy on cognitive function and health in postmenopausal women, between 50 to 65 years of age, who are living in rural communities. Recently published findings from this study suggest that there appear to be no health benefits from moderate drinking in this population. While some studies in the general population have suggested beneficial cardiovascular effects from light to moderate drinking in older adults (e.g., lowered cholesterol levels), no beneficial effect was observed in the postmenopausal women studied. The use of estrogen replacement therapy was found to be a good predicator of performance on tests requiring episodic and knowledge-based memory whereas drinking was a weak predictor. This longitudinal study will track the relationship between alcohol use and health status and how this relation-

ship may change over time as postmenopausal women grew older.

Prenatal Drinking and Knowledge of Fetal Alcohol Syndrome: A Randomized Trial in Russia

The overarching aim of the study is to reduce risk for alcohol-exposed pregnancy (AEP) and Alcohol Related Neurodevelopmental Disorder/FASD by testing a prevention model specifically targeted to large numbers of women in Obstetrics/Gynecology (OB/GYN) clinics in Russia. The study will conduct a randomized trial to determine whether physicians, trained to conduct brief motivational interventions, can foster (1) changes in childbearing-aged Russian women's health beliefs regarding risk for AEP; and (2) greater reduction of women's AEP risk behaviors (e.g., through abstinence from alcohol use and consistent contraception use) compared to standard OB-GYN care. Preliminary studies have suggested that while many Russian women reduce alcohol consumption after pregnancy recognition, prior to the diagnosis of pregnancy, few women recognize the risks of combining alcohol use with the potential to become pregnant. Therefore, substantial numbers of children of women of childbearing age may be at high risk for fetal alcohol exposure during the early weeks of pregnancy.

The project has been approved to receive a supplemental award to recruit an additional 200 women who meet criteria as heavy drinkers and to conduct assessments of HIV/AIDS risk and treatment among this high-risk, understudied population. This would increase the number of subjects from 500 to 700. In addition, since American-based definitions of minority/ethnic group status are not comparable to Russian population subgroups, the research team will recruit minority participants who are specific to the Russian culture (e.g., Ukrainian, Tatar, Belarusian). Thus, the sampling plan will include recruitment of participants from different socioeconomic classes and geographical regions of Russia (i.e., rural—Nizhniy Novgorod, Central; and urban—St. Petersburg, Northwest). These locations will provide diversity across the sample of women in Russia with regard to ethnic, cultural, and sociodemographic backgrounds. Increasingly hazardous drinking in women indicates that prevention of alcohol-exposed pregnancies is an important public health issue in Russia. Effectiveness of this intervention across alcohol consumption levels will be explored and knowledge gained from the study can contribute to the FASD prevention research throughout the world.

Reducing Alcohol-Exposed Pregnancy Risk

While most women discontinue drinking after learning that they are pregnant, approximately one-half of all pregnancies are unplanned, and most women do not know they are pregnant until 4–6 weeks after conception. This means that, even among women who are inclined and able to discontinue drinking after learning they are pregnant, a high percentage of pregnancies are alcohol exposed. Thus, while it is known that approximately 15 percent of women continue to drink after learning they are pregnant, the actual percentage of alcohol-exposed pregnancies is probably significantly higher. One of the strongest predictors of substance use during pregnancy is substance use before pregnancy. In an ongoing behavior therapy development project, investigators are seeking to develop and test the feasibility and efficacy of a brief, theory-based intervention to reduce the risk of AEP in high-risk community women. The EARLY intervention is based on social learning theory, with counseling components including personalized feedback on risks related to drinking and ineffective contraception; health information; decisional balance exercises; discussion of readiness to change; eliciting of goal statements; and development of change plans. Participants are a high-risk community sample of women who drink frequently or who binge, and who use contraception ineffectively, drawn from sexually transmitted disease (STD) and public health clinics and alcohol/drug treatment settings. Investigators anticipate that women who receive the EARLY intervention will show a significantly greater reduction in high-risk behavior, including risky drinking and ineffective use of contraception, than women in the information/attention control group. The study includes analysis of correlates of change, including, among other factors, alcohol/drug

use and severity of use; psychiatric comorbidity; and motivation for change. This analysis aims to increase understanding of how the intervention works and what factors predict response. Findings from this study will inform the development of brief interventions that effectively reduce the risk behaviors for AEP and that may be transferred to a variety of public health treatment and intervention settings.

Screening and Brief Intervention of Problem-Drinking Women

Early identification and intervention among problem-drinking women may avert the more severe, adverse consequences of alcohol abuse and dependence. Among nonpregnant women of childbearing age, the use of alcohol and in particular the practices of frequent and binge drinking have not changed since 1995. An ongoing randomized trial is evaluating the effectiveness of screening and brief intervention in reducing risk drinking (exceeding NIAAA sensible drinking limits of seven drinks per week or one to two drinks per episode) by nonpregnant women with four specific medical problems exacerbated by excessive alcohol consumption: diabetes, hypertension, infertility, and osteoporosis. The investigators predict that significantly more women who receive the medically oriented brief intervention than who receive medical treatment as usual will achieve NIAAA sensible drinking limits in the 12 months following study enrollment. It is also anticipated that clinical outcomes related to the targeted medical conditions will be better among women who achieve NIAAA sensible drinking limits. Preliminary findings indicate that women who had the highest number of drinks per drinking day and who had a positive screening test for problem drinking had the lowest scores on measures of physical and mental well-being. There were also statistically significant differences in baseline drinking behavior by disease and race, with alcohol screen-positive women with diabetes consuming significantly more drinks per drinking day than those with infertility or osteoporosis. Preliminary results also indicate that African-American women with a positive screening test for problem drinking consumed significantly more drinks per drinking day than Asian and Caucasian women with a positive alcohol screening test. There were no differences by race among women with a negative screening test for problem drinking. Findings from this study will inform future recommendations regarding alcohol screening and interventions in general medical settings.

Reducing Alcohol and Risks Among Young Females

An ongoing intervention study is examining the combined effect of early alcohol use and risky behavior in a population of urban African-American and Latina adolescents who are at high risk for human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and other infections. Past research by the investigative team has documented that nearly 10 percent of females in their target population are at risk in 7th grade and more than half are at risk by the spring of 10th grade. This study, involving parents and their eighth-grade daughters, examines the effectiveness of an audio-CD intervention in promoting attitudes and behaviors associated with reduced alcohol consumption and sexual risk taking among adolescent girls. Investigators are also seeking to determine whether changes in the girls' attitudes and behaviors are mediated by changes in certain parenting practices, including parental monitoring, household rule setting, and communication. Preliminary results from the study indicate that girls who received the intervention reported fewer sexual risks and less drinking at followup than those in the control group. In addition, their parents reported greater self-efficacy to address alcohol use and sexual risk taking and more communication on these topics. Findings from this study have advanced understanding of the link between early alcohol initiation and risky sexual behavior, and they may have important implications for the design and implementation of school-based programs to reduce alcohol, drug, and HIV-related risks among adolescent girls.

Brief HIV and Alcohol Combined Interventions for Women

A recent randomized clinical trial focused on reducing HIV risk behaviors among women seeking help for alcohol problems. This study is evaluating the relative effectiveness of

Combined Behavioral Intervention (CBI), a state-of-the-art, empirically based treatment for addressing alcohol problems in dependent drinkers, followed by an HIV risk reduction intervention (HIV-RR) versus CBI followed by an intervention limited to dissemination of HIV information (HIV-I). Investigators had predicted that women who responded favorably to alcohol treatment and who received 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, would fare better than their counterparts in HIV-I. However, preliminary results indicate that by the last followup points, all participants, regardless of condition, improved across time on many sexual risk and substance use measures. The research team has hypothesized that, among other factors, these results may have been influenced by the severity of alcohol use disorders (high rate of alcohol dependence) among women in the study, the fact that women were seeking treatment for their alcohol and other drug use while not seeking to change sexual behavior, and the effect of reduced drinking on sexual risk. Thus, while it appears that there was a null result for the HIV risk-reduction intervention, these results may add to a growing body of evidence that alcohol and other substance use disorders are the most important drivers of the high-risk sexual behavior that is fueling the HIV epidemic, and that providing treatment for alcohol and substance use disorders is the key to reducing HIV risk related to both substance use and sexual behavior.

Behavioral Treatment for Alcohol-Dependent Women with Co-Occurring Depression

Co-occurring alcohol dependence and major depression is a serious and common public health problem, yet one that, for the most part, has not been addressed. Among alcohol-dependent individuals, co-occurring depression is associated with worse treatment outcomes, increased risk for relapse, worse long-term social and functional adjustment, and higher probability of dire outcomes such as suicide. In one ongoing study, investigators are testing the feasibility and acceptability of Interpersonal Psychotherapy (IPT) as an adjunct to standard therapy for mentally ill chemical abusers among alcohol-dependent women with major depression and comparing its effects with those of treatment-as-usual individual therapy. IPT seeks to enhance interpersonal skills in four areas (interpersonal conflict, loss/grief, role transitions, interpersonal sensitivity) as a way to decrease symptoms and improve functioning. Compared to treatment as usual, investigators expect IPT to lead to greater reductions in women's drinking frequency, drinking intensity, and depressive symptoms, and to improvements in interpersonal functioning. Findings from this study may lead to the development of a novel therapy for women with co-occurring alcohol dependence and major depression that will expand and enhance the range of treatment options for women in this understudied but very vulnerable group.

Alcohol and Psychiatric Comorbidity in HIV Positive Women

Alcohol, depression, and anxiety independently affect HIV disease progression. Importantly, alcohol use frequently co-occurs with depression and anxiety, particularly among women. Despite the relative frequency of co-occurrence, the impact of co-occurring alcohol use and depression/anxiety has not been evaluated among HIV positive women. An ongoing study is examining the effect of both co-occurring alcohol and depression and co-occurring alcohol and anxiety on HIV disease progression (i.e., HIV-RNA, adherence, quality of life, mortality) in HIV positive women and evaluating the effectiveness of brief alcohol interventions in HIV positive women with co-occurring disorders. In addition, the investigative team will conduct detailed psychological assessments of participants to examine the role of subthreshold psychiatric symptoms in alcohol use and HIV disease progression. This will mark the first time that subthreshold psychiatric symptoms have been explored within the contexts of alcohol use or HIV disease. Study findings will advance understanding of the relationship between mental health, drinking, and HIV disease progression among women, and inform the development of innova-

tive, women-focused interventions to reduce the impact of drinking among women with co-occurring HIV infection, alcohol use, and mental health disorders.

Testing Cognitive Behavioral Therapy (CBT) Models and Change Mechanisms for Alcohol-Dependent Women

There is limited research on alcohol-dependent women and, in particular, on the change mechanisms that enable them to reduce drinking and maintain sobriety. Furthermore, there is a paucity of clinical research to develop and test cost-effective group therapy models for alcohol-dependent women. One ongoing study is adapting an existing Individual Female Specific Cognitive Behavioral Therapy approach to treating women with alcohol dependence to a group format and comparing the relative efficacy of the two approaches. Both the group and individual treatments are abstinence based and include motivational enhancement, coping skills training, management of negative affect, skills to manage heavy drinkers in the social network, relapse prevention, and discussions of personal autonomy. In addition to determining their relative efficacy, investigators are examining hypothesized mechanisms of change in drinking that are common to both the group and individual treatments. The study is also examining the relative cost-effectiveness of the individual and group treatments in an effort to inform decisionmaking by health service policymakers and administrators. Consistent with a growing trend in alcohol treatment search, the research team has developed a plan for transdisciplinary collaboration to explore genetic and environmental interactions that may influence the course of alcohol dependence among women, as well as women's response to treatment.

Cooperative Projects Between the NIAAA and ORWH

Chronic fatigue syndrome (CFS) is a complex disorder occurring more often in women than men, characterized by fatigue, sensitivity to exercise, and immune suppression. The cause of CFS is unknown, but some evidence suggests that neuroimmune dysregulation is involved. Two exploratory projects were cofunded by NIAAA from 2006 to 2008 in response to an ORWH initiative (RFA-OD-06-002) to elucidate neuroimmune mechanisms involved in the pathogeneses of chronic fatigue syndrome.

Neuropeptide Y: A Potential Mediator of CFS

CFS is characterized by extreme fatigue, malaise, lowered mood, and sleep disruptions. Since abnormalities of the stress response are hypothesized to be associated with CFS, this study investigated neuropeptide Y (NPY) as a mediator of CFS and as a potential biomarker of the disease. NPY is released from sympathetic nerve terminals during the stress response, along with catecholamines norepinephrine and epinephrine. NPY release correlates with stress, negative mood, and impaired natural killer (NK) cell cytotoxicity. The aims of this study were to test for a correlation between NPY levels and the physical symptoms and immunological characteristics of CFS. The investigators have compared NPY and CD26 (an NPY-interacting molecule) levels in plasma from women and men suffering from CFS to a control population. Early analysis of the data showed a trend toward higher NPY levels and lower CD26 levels in CFS sufferers, although the differences were not significant. The investigators intend to correlate these parameters with the available clinical data, including gender. Future plans (using a no-cost extension) also include recruiting another patient set along with controls, for in vitro analysis of NK cell activity upon challenge with NPY. The latter aim will determine the relationship between NPY and NK cell cytotoxicity in CFS, in order to further characterize the immune dysfunction of CFS.

Role of Mast Cells in CFS Pathogenesis; Therapeutic Potential of Antidepressants

CFS has been considered, rightly or wrongly, a neuroimmmunopsychiatric disorder. While the physical symptoms of CFS are real, the altered mood is sometimes treated with cyclic antidepressants. The symptoms of irritable bowel syndrome, a stress-related disorder often comorbid with CFS, are relieved by treatment with antidepressants. In view of the association of mast cell activity with irritable bowel

syndrome, and other evidence for alteration of immune function by antidepressants, this project tested the hypothesis that antidepressants may lessen the severity of CFS by inhibiting the release of pro-inflammatory mediators from mast cells, especially in the brain. Four classes of antidepressants (a selective serotonin reuptake inhibitor, a selective norepinephrine reuptake inhibitor, a dopamine–norepinephrine reuptake inhibitor, and a tricyclic antidepressant) reduced the release of the pro-inflammatory cytokines IL-8, IL-6, and VEGF from stimulated mast cells. In contrast, only the tricyclic antidepressant reduced histamine release from stimulated mast cells, and only partially. These data support the hypothesis that neuroimmune dysfunction underlies CFS, and support the design of clinical trials for treating CFS with specific antidepressants.

Initiatives

Request for Applications (RFAs)

- **Alcohol, Puberty, and Adolescent Brain Development**
  NIAAA issued an RFA to support preclinical studies to increase our understanding of (1) the degree to which hormonal changes at puberty interact with neurodevelopmental processes to promote sex differences in alcohol use and misuse, and (2) the effects of adolescent alcohol exposure on these interactive processes. The use of a variety of cellular, molecular, neuropharmacological, and physiological tools was encouraged. Three applications were funded under this RFA to study the role of pubertal hormones in the emergence of sex-typical patterns of alcohol use and consequences and to determine whether alcohol effects sex-dependent changes in neurodevelopment (RFA-AA-07-007, RFA-AA-07-008).

- **Advancing Novel Science in Women's Health Research (ANSWHR)**
  NIAAA participated in this ORWH initiative. The overall purpose of ANSWHR is to stimulate and support innovative research that will advance new concepts in women's health research and the study of sex/gender differences (PAS-07-381, PAS-07-382).

- **Research on Causal Factors and Interventions That Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (R01)**
  NIAAA joined many National Institutes of Health (NIH) components in this ORWH-led initiative to support research on (1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering; and (2) the efficacy of programs designed to eliminate sex/gender disparities and promote the careers of women in these enterprises (RFA-GM-09-012).

Program Announcements (PAs)

- **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence**
  NIAAA participated with the National Institute on Drug Abuse (NIDA) in an initiative to promote research on women and sex/gender differences in drug/alcohol abuse and dependence. This initiative encourages research from basic studies of molecular genetics and neurotransmitters to studies of epidemiology, etiology, and prevention/treatment interventions that focus on sex/gender differences. Studies on sex/gender-based interventions related to HIV/AIDS and cross-cutting issues related to stages of the lifecycle, health disparities, methodological approaches, and gender-specific recruitment issues are also encouraged (PA-07-329, PA-07-330, PA-07-331).

- **Chronic Fatigue Syndrome: Pathophysiology and Treatment**
  NIAAA has a shared interest in two ORWH initiatives on pathophysiology and treatment of chronic fatigue syndrome. The objective of these program announcements is to encourage research into the etiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the lifespan, into the environmental and biological risk factors, the determinants of heterogeneity among patient populations, and the common mechanisms influencing the multiple body systems that are affected in CFS. Interdisciplinary research is highly encouraged (PA-08-246, PA-08-247).

Conferences and Workshops

- **Preventing Alcohol, Tobacco, and Other Substance-Exposed Pregnancies: A Community Affair Symposium**
  The symposium was held on September 23–24, 2008, in Rockville, MD. The primary objective of the symposium was to explore approaches to changing the popular perception that the use of alcohol, tobacco, and certain other drugs during pregnancy is safe. Specifically, it focused on getting the message out about the potential adverse consequences of risky drinking and other substance use during the childbearing years, and, in particular, the importance of abstaining from any and all drinking and smoking during pregnancy.

- **Sex Differences in the Causes and Consequences of Drug Abuse**
  Dr. Ellen Witt (NIAAA) and Dr. Cora Wetherington (NIDA) cochaired this meeting at the Second Annual Meeting of the Organization for the Study of Sex Differences. The purpose of this symposium was to present data on the role of gonadal and stress hormones in sex differences in the etiology and consequences of drug and alcohol abuse. The talks covered the age range from adolescents to adults, and used different approaches, including animal behavioral models, neuroimaging, and clinical assessments in humans.

- **First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators (PIs)**
  In June of 2008, a group of PIs that had been funded by a 2006 RFA on CFS met to present results and discuss tools and techniques to advance the CFS field. The meeting was organized by ORWH, while the travel funds had been allotted in the grant budgets. The two NIAAA cofunded investigators participated.

Outreach Publications

- The NIH Publications on Women's Health Issues booklet (updated version)
- The Embryo and Fetus: Focus on Fetal Alcohol Spectrum Disorder (FASD) (Alcohol Alert No. 74: Alcohol Research: A Lifespan Perspective (2008))
- Fetal Alcohol Syndrome (FAS) (Alcohol Alert No. 74: Alcohol Research: A Lifespan Perspective (2008))

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated diseases, including diseases that affect the health of women and girls. NIAID involves women in many of its clinical studies on treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and sexually transmitted infections (STIs). 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 in women's health research. Investigators engage in basic research, preclinical research, and clinical research in an effort to better understand how women and girls are preferentially susceptible to particular infectious or immune-mediated diseases. Accomplishments include the sponsorship of clinical trials that test possible antiretroviral drugs or topical microbicides to prevent the transmission of HIV to women or their partners; epidemiological studies to explore the cardiovascular health of women infected with HIV; therapeutic studies to examine the effects of antiretroviral drugs, such as protease inhibitors, during pregnancy; basic research on proteins found in the thymus that are known to cause broad autoimmunity against many organs and tissue; as well as preclinical vaccine research for the herpes simplex virus. A breadth of research sponsored by NIAID is aimed at improving and protecting the lives of women and girls in the United States and globally.

The overview of selected NIAID-sponsored women's health activities, as well as scientific advances, is presented here in two separate focus areas: scientific accomplishments and related accomplishments in women's health research. The first section includes accomplishments in research on HIV/AIDS, STIs, and immunology and immune-mediated diseases. Related accomplishments in women's health research include research training and the women's health research work group. Also included is a section on initiatives, which includes program announcements, requests for applications, contracts, and conferences. Sex/gender analysis studies and research on health disparities in special populations are highlighted.

Accomplishments

HIV/AIDS

United Nations Joint Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO) statistics estimate that 33 million people worldwide are infected with HIV. Women face a greater risk than men of acquiring HIV due to substantial mucosal exposure to seminal fluids, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners. Most women are infected with HIV through sex with men or through injection drug use.

Over the past 2 years, the number of women and girls infected with HIV has increased in every region of the world, with rates rising particularly rapidly in Eastern Europe, Asia, and Latin America. At the end of 2007, women accounted for 50 percent of all adults living with HIV worldwide, and for 60 percent in sub-Saharan Africa. The U.S. Centers for Disease Control and Prevention (CDC) found that women accounted for over 26 percent of all new AIDS cases reported in the United States in 2005, an increase from 11 percent in 1990.

In addition to the well-known complications of AIDS that are not specific to one gender, infected women also suffer gender-specific manifestations of HIV disease such as recurrent vaginal yeast infections, pelvic inflammatory disease (PID), genital ulcer disease, severe herpes infections, pathologies related to infection with human papillomavirus (HPV), as well as vulvar and vaginal carcinomas. Drug metabolism also differs in women as compared to men, potentially resulting in differential responses to antiretroviral (ARV) 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.

NIAID is supporting investigations of the course of HIV/AIDS in women through multiple initiatives, including intramural studies; unsolicited research; the Women's Interagency HIV Study (WIHS), a long-term cohort study; the Centers for AIDS Research (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 (MTN), the AIDS Clinical Trials Group (ACTG), the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), and the International Network for Strategic Initiatives in Global HIV Trials.

Epidemiological Research

NIAID supports epidemiological research on the following:

- The long-term natural and treatment history of HIV infection in women; in particular, research that evaluates the impact of ARV therapy on the clinical course of HIV disease
- The effect of hormonal, endocrine, and local factors on HIV viral load and sexual transmission
- Studies of older populations of HIV-infected women to investigate what pathogenic processes are related to HIV, ARV therapy, and/or the aging process

- Characterization of acute clinical events and coinfections and their impact on HIV disease progression
- Studies of the female genital tract, including the microenvironment, HIV virology, and immunology of the female genital tract as compared to blood

▶ **Women's Interagency HIV Study**
WIHS is the largest observational study of HIV-infected women and includes participants living in six U.S. metropolitan areas. The majority of the more than 3,500 women enrolled in the study are African-American and Latina women living in urban areas. The size of the study, the number of recently diagnosed patients, and the availability of stored biospecimens allow the evaluation of clinical outcomes in the era of highly active antiretroviral therapy (HAART). Researchers are investigating factors such as the development of AIDS, drug resistance, coinfections, therapy use and treatment effects, metabolic abnormalities and toxicities, hormonal factors, aging, neurocognitive functioning, and physical impairment. This study has yielded major discoveries that have led to a better understanding of how HIV is spread, how HIV disease progresses, and how it can best be treated. More information is available at: http://statepiaps.jhsph.edu/wihs/.

▶ **The Risk of Cardiovascular Disease (CVD) Among Women in the WIHS Study Initiating Abacavir**
This NIAID-funded study is designed to analyze specimens and associated data from the WIHS biorepository to study risk factors for the development of CVD in women infected with HIV who are taking the ARV abacavir. Earlier research has shown that women infected with HIV tend to have a higher underlying risk for CVD compared to the general population, partly due to HIV-specific factors. For example, use of ARV drugs may increase the risk for myocardial infarction, possibly in association with inflammation and subclinical atherosclerosis. Investigators will evaluate biomarkers associated with these pathologies in WIHS participants initiating abacavir- and non-abacavir-containing ARV regimens. They will also evaluate the cardiovascular outcomes among women by abacavir treatment history. Investigators also will test samples from the Multicenter AIDS Cohort Study (MACS) biorepository to identify potential gender-specific differences in abacavir response.

Scientific Advances

▶ **Risk Factors for Carotid Lesions in Women and Men Taking HAART**
WIHS and the National Institutes of Health (NIH) collaborators explored the risk factors for the development of carotid lesions, a sign of early-stage atherosclerosis, in individuals infected by HIV. In 2008, they reported that the immune suppression associated with HIV infection may significantly increase the risk for carotid lesions in women and men. However, the use of HAART was not consistently associated with carotid atherosclerosis, especially in women. Furthermore, the risk for carotid atherosclerosis was not significantly associated with either HIV viral load or a history of clinical AIDS. The findings suggest that maintaining adequate levels of CD4 T-cells, a type of immune cell, may reduce the risk of CVD among HIV-positive individuals (*AIDS* 22(13):1615-1624, 2008).

▶ **Other WIHS Research Findings**
WIHS reports in 2008 addressed topics such as the relationship of HAART adherence in women with adverse treatment effects (*Clinical Infectious Diseases* 45:1377-1385, 2007); perception of body fat changes (*AIDS and Behavior* Epub ahead of print, 2008); presence of children in the household (*AIDS Patient Care and STDs* In press, 2008; *Pediatrics* 121:e787-e793, 2008); and illegal drug use (*American Journal of Drug and Alcohol Abuse* 34:161-170, 2008). Other reports dealt with the relationship between HIV progression and variables such as illegal drug use (*AIDS* 22:1344-1363, 2008) and insulin-like growth factor (*Journal of Infectious Diseases* 197:319-327, 2008. The importance of illegal drug use in recent WIHS findings (*American Journal of Drug and Alcohol Abuse* 34:161-170, 2008; *Journal of Acquired Immune Deficiency Syndromes*

In press, 2008; *AIDS* 22:1625-1627, 2008: *Drug and Alcohol Dependence* 89:74-81, 2007) reflects the fact that about one-third of WIHS participants were infected via shared needles and are also infected with hepatitis C virus.

Prevention Research

Seroincidence Study

▶ **The Women's HIV SeroIncidence Study (ISIS) (HPTN064)**
ISIS is part of the HPTN, a worldwide collaborative clinical trials network that develops and tests the safety and efficacy primarily of nonvaccine interventions for the prevention of HIV. ISIS is a multisite, observational study that will estimate the overall HIV-1 incidence in women at high risk for HIV acquisition in the United States. Investigators will also evaluate laboratory assays for HIV-1; estimate study recruitment and retention rates; describe sexual behaviors, alcohol and drug use, prevalence of domestic violence, and mental health indicators of women at risk for HIV; assess women's preferred recruitment and retention strategies for future studies; describe social, structural, and contextual factors to inform future intervention studies; and explore facilitators and barriers to HIV testing among men residing in high-risk areas. In 2009, the HPTN study will begin enrollment of 2,000 women from 10 geographically distinct high-risk areas of the United States. Investigators will follow all participants for 6 to 12 months. More information on this and other HPTN research is available at: http://www.hptn.org/research_studies.asp.

Topical Microbicides

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.

NIAID-sponsored research goals support the development of a topical microbicide that—

- Prevents HIV infection and/or viral replication
- Is safe and noninflammatory (causes no irritation to the vaginal/cervical/urethral/rectal epithelium)
- Reduces transmission and acquisition, including reducing potentiation of HIV acquisition by other STIs

Scientific Advances

▶ **Use of Tenofovir for Simian Immunodeficiency Virus Prevention in a Nonhuman Primate Model**
Research in a nonhuman primate model suggests that the vaginally formulated microbicide tenofovir (TFV) gel may help prevent rectal transmission of HIV. The investigators evaluated the efficacy of the gel applied rectally prior to rectal exposure with simian immunodeficiency virus (SIV) in rhesus macaques. Eight of nine macaques in the study were protected from infection. This nonhuman primate study provides the first evidence that an ARV-based, vaginally formulated topical microbicide may protect against rectal transmission of HIV. The data also suggest that TFV drug levels in the blood may serve as surrogate markers in clinical trials of microbicide efficacy. Furthermore, the finding suggests the possibility of a novel pathway for using microbicides to induce a protective immune response similar to that of a vaccine (*PLoS Medicine* 5(8):e157, 2008).

Clinical Trials

▶ **Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5 percent PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women**
Initiated in 2005, HPTN 035 is a Phase II/IIb trial to evaluate the safety and efficacy of the microbicides BufferGel and 0.5 percent PRO2000/5 Gel (P) when applied vaginally by women at risk for sexually transmitted HIV infection. This study enrolled more than 3,000 women at sites in the United States, Malawi, Zimbabwe, Zambia, and South Africa. More information on this and other HPTN research is available at: http://www.hptn.org/research_studies.asp (HPTN 035).

Note: The results of this trial were presented in February 2009 at the Conference on Retroviruses and Opportunistic Infections in Montreal, while this report was being drafted. The data showed that the microbicide gel known as PRO2000 (Indevus Pharmaceuticals, Inc.) was safe and approximately 30 percent effective (33 percent effectiveness would have been considered statistically significant). BufferGel had no detectable preventive effect on HIV infection. While additional research is needed, this is the first human clinical study to suggest that a microbicide may prevent male-to-female sexual transmission of HIV infection.

- **Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1 percent Tenofovir Gel**
  This study will assess the safety of TFV gel for vaginal use in HIV-uninfected women when used once daily or prior to intercourse. Enrollment in this HPTN clinical trial set in New York, NY, Birmingham, AL, and Pune, India, is complete and followup is ongoing (HPTN 059).

- **Phase I Study of the Safety and Acceptability of 3 percent w/w SPL7013 Gel (VivaGel™) Applied Vaginally in Sexually Active Young Women**
  The MTN uses a focused microbicide research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. This MTN clinical trial is ongoing at two study sites, one in Tampa, FL, and one in San Juan, PR. Both sites are part of the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD)-funded Adolescent Trials Network. This study will evaluate the safety of VivaGel applied twice daily for 2 weeks in sexually active 18- to 24-year-old women. Study investigators plan to enroll a total of 60 women. More information on this and other MTN research is available at http://www.mtnstopshiv.org/node/studies (MTN-004).

- **Phase II Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir**
  This MTN clinical trial will enroll 144 women at seven clinical sites in the United States and Africa to examine adherence and acceptability of 6 weeks each of oral, vaginal, and dual use of tenofovir. The trial will include pharmacokinetic studies (MTN-001).

- **Phase IIB Safety and Effectiveness Study of Tenofovir 1 percent Gel, Tenofovir Disoproxil Fumarate (DF) Tablet, and Tenofovir DF-Emtricitabine Tablet for the Prevention of HIV Infection in Women**
  The MTN is planning this clinical trial, also known as the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial. Beginning in early 2009, investigators expect to begin enrollment of 4,200 women in Africa to test a preexposure prophylaxis (PrEP) approach to HIV prevention, especially in heterosexual sub-Saharan African women. VOICE is the only PrEP study to focus exclusively on women. This large randomized clinical trial will compare the safety and effectiveness of two approaches to HIV prevention: (1) use of an oral ARV pill (either TFV or Truvada®) once a day, and (2) use of an ARV-based vaginal microbicide TFV gel on a daily basis. VOICE will also evaluate the potential for and prevalence of drug resistance in women who acquire HIV while participating in the study. Two substudies will examine bone mineral density (VOICE B) and the impact of individual and community factors on trial retention and on treatment adherence (VOICE C). This is the first study to evaluate the effectiveness and acceptability of oral and vaginal forms of PrEP in the same study (MTN-003).

- **The Sexually Transmitted Infections Clinical Trials Group (STI CTG)**
  The STI CTG has completed enrollment in a Phase I trial to evaluate the safety of a twice daily, vaginally applied microbicide gel (SPL 7013). This topical microbicide is designed to prevent STIs, including genital herpes and HIV. More information on this and other STI CTG trials is available at: http://www.stictg.org/protocols.html.

- **Integrated Preclinical/Clinical Program—HIV Topical Microbicides Awards**
  Several studies funded through this award program were developed, initiated, and/or completed in 2008. They include an ongoing trial of rectal health, behaviors, and microbicide acceptability; a safety and acceptability study of UC-781, a vaginal microbicide gel for rectal application in individuals not infected with HIV-1; a study of the pharmacokinetics and pharmacodistribution of oral TFV and vaginally formulated TFV gel used rectally; and a comparative study of the mucosal toxicity, colorectal distribution, and participant acceptability of three different preparatory enemas. More information is available at: http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/funding.htm.

- **Investigator-Initiated Microbicide Clinical Trials**
  NIAID also funds microbicide trials through investigator-initiated awards. Various studies are investigating the safety and persistence of 0.1 percent UC-781 vaginal gel in HIV-1-negative women; the effect of repeated applications of TFV gel on mucosal mediators of immunity; utility of optical coherence tomography as a safety imaging system for microbicide use; intrinsic antimicrobial activity of cervicovaginal secretions in women at low risk for HIV-1 infection; and postcoital antiviral activity of cervicovaginal secretions following vaginal application of the microbicide 0.5 percent PRO 2000/5 Gel (P).

Vaccine Research

Vaccines contain killed or modified microorganisms or parts of microorganisms that can stimulate an immune response in the body to prevent future infection with the same or similar microorganisms. Despite extraordinary advances in understanding both HIV and the human immune system, an effective HIV vaccine continues to elude researchers. NIAID conducts and supports basic research in areas such as infectious diseases, microbiology, and immunology to generate the knowledge essential for developing safe and effective vaccines for the prevention of HIV infection.

Clinical Trials

- **Longitudinal Studies of Women at High Risk for HIV-1 Infection To Inform HIV Vaccine Trial Participation**
  The NIAID-funded HVTN is planning two studies on the feasibility of recruiting and retaining women at high risk for HIV infection for participation in vaccine trials. HVTN 906 will enroll women who reside in areas of high HIV prevalence or who engage in high-risk behavior in New York, Philadelphia, and Chicago. Investigators will also enroll women who are partners of men from subgroups with a high prevalence of HIV. HVTN 907 will enroll women living in the Caribbean (Haiti, Dominican Republic, and Puerto Rico) and will focus on female commercial sex workers with demographic, behavioral, or other social factors associated with high prevalence of HIV. Investigators will also assess HIV prevalence in both studies. More information on HVTN research is available at: http://www.hvtn.org/index.html (HVTN 906, HVTN 907).

Prevention of HIV in Individuals Infected with Herpes Simplex Virus Type 2 (HSV-2)

Scientific Advances

- **Tests of Acyclovir for HIV Prevention in Women and Men Infected with HSV-2**
  Research suggests that HSV-2 infections are associated with an increased risk for HIV infection. This HPTN study investigated whether suppression of HSV-2 with the antiviral drug acyclovir would reduce the risk of HIV-1 acquisition in HSV-2-positive women and men who have sex with men. The researchers reported that suppressive therapy with standard doses of acyclovir did not reduce HIV acquisition in this population. This study and other research emphasize the need for novel strategies to interrupt interactions between HSV-2 and HIV-1 (*Lancet*: 371:2109-2119, 2008).

Clinical Trials

▶ **Effectiveness of Acyclovir in Suppressing HIV Viral Load in Women Coinfected With HIV and HSV-2**
Scientists are analyzing data from this NIAID-supported study conducted by the Comprehensive International Program for Research on AIDS (CIPRA) Peru Project. This study examined the use of acyclovir for the suppression of HIV viral load, and mucosal shedding in women coinfected with HIV and HSV. The results of this analysis are expected in early 2009. More information is available at: http://clinicaltrials.gov/show/NCT00371592.

Prevention of Mother-to-Child Transmission (PMTCT) of HIV

According to WHO, the vast majority of all HIV-infected infants and children acquire the virus from their mothers before or during birth or through breastfeeding. Most mother-to-child-transmission (MTCT) occurs late in pregnancy or during birth. Currently, the United Nations Children's Fund (UNICEF)/WHO recommends that infants born to HIV-infected mothers who do not have access to acceptable, feasible, affordable, sustainable, and safe (AFASS) replacement feeding should be exclusively breastfed for at least 6 months. NIAID is conducting studies on the safety and pharmacology of potent drug combinations for PMTCT in HIV-infected pregnant women. NIAID-sponsored research goals on PMTCT focus on the following:

- 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 ARV strategies to prevent mother-to-infant HIV infection through clinical trials in the United States and international settings
- Developing interventions for prevention of HIV transmission via breastmilk in settings where breastfeeding is the best assurance for infant nutrition

Scientific Advances

▶ **Use of Nevirapine To Decrease HIV Transmission Through Breastfeeding**
Three coordinated studies in Ethiopia, India, and Uganda assessed whether giving daily nevirapine (NVP) to breastfed infants through 6 weeks of age can decrease HIV transmission. Overall, these studies showed that this treatment regimen significantly reduced risk of HIV transmission at 6 weeks of age; the reduction at 6 months of age was not statistically significant. The data suggest the need for a longer course of daily NVP to prevent HIV transmission via breastmilk through 6 months of age in settings where AFASS criteria are not met. These findings provide key guidance for designing extended treatment trials (*Lancet* 372(9635):300-313, 2008).

Clinical Trials

▶ **The Effects of Single-Dose Nevirapine (SD NVP) on Future Treatment Options for Women and Children**
The ACTG and IMPAACT are cooperating with the HPTN and Department of Defense to conduct clinical trials on this topic. "Optimal Combined Therapy after Nevirapine (NVP) Exposure" (ACTG 5208), a randomized clinical trial set mainly in Africa, is evaluating the effects of exposure to SD NVP on HAART treatment outcomes. A parallel study (PACTG 1060) will investigate the effects of SD NVP on ARV therapy treatment outcomes in infants. A study (ACTG 5207) conducted in Africa, India, and Haiti and one in Thailand (PACTG 1032) will explore strategies to minimize viral resistance to ARV therapy and assess the impacts of viral resistance after SD NVP. Another study (ACTG 5227) will examine whether the impact of HAART in women for treatment of HIV is affected by prior exposure to HAART for PMTCT. More information on ACTG research is available at: http://www.aactg.org/.

Therapeutics Research

Scientific Advances

- **The Safety of Depot Medroxyprogesterone in HIV-Positive Women on ARV Therapy**
  ACTG investigators reported findings from a clinical trial examining the safety of the contraceptive depot medroxyprogesterone (DMPA) when used with ARV therapy regimens. They showed that DMPA-related adverse events in ARV-treated women who are infected with HIV-1 were similar to adverse events reported in women not infected with HIV. There were no differences in adverse events observed among the women in the different treatment regimens, indicating that concomitant use of ARV therapy and DMPA in this population is safe (*Contraception* 77(2):84-90, 2008; Epub 2007 Dec 21).

- **The Effects of Protease Inhibitors in Pregnancy**
  An ACTG study recently showed that use of protease inhibitors (PIs), a type of ARV, do not increase risk of glucose intolerance or insulin resistance among pregnant women infected with HIV. This multicenter, prospective, observational study found that body mass index, Hispanic ethnicity, and maternal age, but not PIs, were associated with glucose intolerance. Use of PIs was not associated with any differences in insulin resistance or pancreatic beta-cell function. (*American Journal of Obstetrics and Gynecology* 196(4):331.e1-7, 2007).

  The same study showed that pregnancy outcomes were not different between women taking HAART regimens containing PIs compared with non-PI-containing HAART regimens. The data did show increases in total cholesterol and triglycerides in the women receiving PI-containing HAART, and higher triglyceride levels were associated with lower birthweights of infants. Overall, these data support the continued use of PIs during pregnancy. Further study is needed on the clinical importance of the lipid changes and their impact on birth outcomes (*Obstetrics and Gynecology* 110(2 Pt 1):391-397, 2007).

Clinical Trials

- **Clinical Trials of ARV Therapy During Pregnancy**
  Ongoing and planned ACTG and IMPAACT treatment trials include a study of the pharmacokinetics of the ARV Efavirenz in the last trimester of pregnancy; a study of the pharmacokinetics of contraceptives used in conjunction with newer ARV drugs; an assessment of gender differences in HAART responses evaluated in large naïve treatment trials (ACTG 5095, ACTG 5142, and ACTG 5202); and an investigation of the toxicities and complications of the use of an HPV vaccine in HIV-infected girls (PACTG 1047) and women (ACTG 5240).

- **Osteoporosis in HIV-Infected Postmenopausal Women**
  This ongoing investigator-initiated clinical trial is examining the impact of traditional risk factors for osteoporosis as well as characteristics of HIV infection and ARV therapy on the prevalence of osteoporosis and the rate of bone loss in HIV-infected postmenopausal African-American and Hispanic women (R01 AI 065200).

- **Sex and Disease-Dependent Nucleoside Analog Toxicity**
  This investigator-initiated clinical trial will compare concentrations of nucleosides in the cells of men and women on nucleoside analog-containing ARV therapy regimens. This study seeks to explain gender differences in adverse events such as localized loss of fat tissue and fat accumulation. Investigators will also evaluate gender differences in the effects of nucleoside analogs on the mitochondria, which are cellular organelles involved in energy production (R01 AI 064029).

The Centers for AIDS Research

CFAR is a unique program that provides infrastructure to support multidisciplinary peer-reviewed HIV/AIDS research in an environment that coordinates studies, promotes communication, provides shared services/expertise, and funds short-term feasibility studies that cannot be funded easily by other mechanisms.

Several pilot projects were funded through the CFAR Developmental Core. The "Pilot Study of HIV in Women Attending a Women's Health Clinic in Mumbai, India" will gather data on HIV prevalence; risk behavior; and knowledge, attitudes, and beliefs about HIV-infection. "HIV Prevention in Xhosa Women" will test an HIV intervention tool adapted for Xhosa-speaking women in South Africa. "HIV Prevention for Women: Barriers, Facilitators, and the Media's Role" will examine sociocultural factors of the HIV epidemic in African-American women in Boston. Other projects include "Genotypic Resistance After Pregnancy-Limited Combination Antiretroviral Therapy" and "Exploring the Immunologic and Virologic Differences Between Pre- and Postmenopausal HIV-Positive Women." More information on CFAR research is available at: http://www3.niaid.nih.gov/research/cfar/.

Sexually Transmitted Infections

The prevention and treatment of STIs are critical global and national health priorities because of their disproportionate and devastating impact on women and infants and their interrelationships with HIV/AIDS. The CDC reported in 2006 that about 19 million new STIs occur in the United States each year at a cost of nearly $15 billion. The CDC report, Sexually Transmitted Disease Surveillance 2007, shows persistent racial disparities in the cases of chlamydia and gonorrhea and a particular burden of diseases among women in the United States.

NIAID supports a broad array of biomedical research for more effective prevention and treatment approaches to control STIs. This includes the following:

- Research for safe and effective vaccines, topical microbicides, therapeutics, and strategies for preventing and treating STIs and resulting conditions
- Basic research on pathogenesis, immunity, and molecular and structural biology of sexually transmitted pathogens and the impact of STIs in various populations
- Development of better and more rapid diagnostics

Human Papillomavirus

HPV is a group of viruses that includes more than 100 different strains. HPV is of clinical and public health importance because persistent infection with certain oncogenic types can lead to cervical cancer, which is one of the most common cancers in women worldwide. In 2006, the Food and Drug Administration (FDA) licensed an HPV vaccine, Gardasil®, for use in females ages 9–26 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. The CDC recently reported that approximately 25 percent of adolescent females aged 13 to 17 years old in the United States initiated the vaccine series in 2007 (*MMWR* 57:1100-1103).

Trichomoniasis

Trichomoniasis is one of the most common STIs. An estimated 7.4 million new cases of trichomoniasis occur each year in men and women in the United States. 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 have an increased susceptibility to HIV infection and many 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.

SCIENTIFIC ADVANCES

▶ **Scientists Sequence Genome of Parasite Responsible for Trichomoniasis**
NIAID-sponsored researchers have decoded the genetic makeup of the parasite that causes trichomoniasis, revealing potential clues as to why the parasite has become increasingly drug resistant and suggesting possible pathways for new treatments, diagnostics, and a potential vaccine strategy (*Science* 315:207-212, 2007).

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 than in men. 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.

Scientific Advances

- **Preclinical Research on Genital HSV-2 Vaccines**
  NIAID has supported testing of several vaccines for the prevention or reduction of genital HSV-2, including a vaccine containing a single protein from HSV-2 (HSV-2 glycoprotein D). Two randomized, controlled clinical trials of this vaccine demonstrated a lower rate of HSV-2 infection in women who were not previously infected with HSV-1. However, the vaccine was not effective in men or in women who were previously infected with HSV-1. NIAID scientists also are evaluating two recently developed candidate HSV-2 vaccines that performed well in preclinical testing. The demonstrated safety of one of these vaccines in highly immunocompromised animals makes it an excellent candidate for studies in humans (*Vaccine* 26:4034-4040, 2008).

Clinical Trials

- **Herpevac Clinical Trial for Women**
  This pivotal Phase III clinical efficacy trial of a vaccine for the prevention of genital herpes has enrolled over 8,300 women at approximately 50 sites in the United States and Canada. This study is a public–private partnership with GlaxoSmithKline. More information is available at: http://www.niaid.nih.gov/dmid/stds/herpevac.

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.

Scientific Advances

- **Discovery of DNA Transfer in *Chlamydia trachomatis***
  Basic research studies on *C. trachomatis* are hampered by the fact that it grows exclusively in mammalian cells and has proven resistant to transformation, a cornerstone molecular biology research technique in which foreign DNA is inserted into bacteria to cause the bacteria to produce the proteins encoded by the foreign genes. NIAID-supported researchers are conducting laboratory studies to determine whether transformation will be possible in *C. trachomatis*. Their research may lead to discovery of a way to accomplish successful transformation in *C. trachomatis* and thus advance this important area of research (*Journal of Bacteriology* 189:991-1003, 2007).

- **Toward the Goal of an Attenuated Chlamydia Vaccine**
  Reproductive tract complications of *C. trachomatis* infection are caused by an aggressive immune response that damages the reproductive tract, but leaves the bacteria unharmed. Scientists have long known that a related bacterium, *C. muridarum*, causes a similar disease in mice, including reproductive tract pathology. NIAID-supported researchers recently noticed that most strains of both *C. trachomatis* and *C. muridarum* contain an extra piece of DNA known as a plasmid. Furthermore, they discovered that removal of the plasmid DNA from the *C. muridarum* bacteria made the bacteria less virulent and the plasmid-free strain did not cause reproductive tract pathology in the mice. In addition, infection with the plasmid-free strain protected mice from subsequent infection with the virulent, plasmid-containing strain. Future

research will determine whether a plasmid-free strain of *C. trachomatis* could be used to create an attenuated chlamydia vaccine for humans (*Journal of Immunology* 179:4027-4034, 2007).

- **Cost Effectiveness of Chlamydia Screening in STI Clinics**
  NIAID collaborated with the University of Massachusetts Medical School and The Johns Hopkins University to compare the cost-effectiveness of chlamydia screening strategies in an STI clinic setting. They reported that self-collected vaginal swabs tested by nucleic acid amplification tests (NAATs) were the least expensive and most cost-effective screening method. Nearly half of the women in the study preferred self-vaginal sampling, almost 30 percent preferred physician-collected cervical sampling, and 25 percent preferred self-collected urine sampling. The study also showed that limiting speculum exams to women who require a Pap smear or who present with symptoms, especially abdominal pain, results in substantial healthcare savings while detecting 97.2 percent of infections. Researchers concluded that providing women with noninvasive screening not only respects the desires of many patients to avoid a speculum exam, but is also cost effective (*Sexually Transmitted Diseases* 35:649-655, 2008).

Immunology and Immune-Mediated Diseases

NIAID supports investigations of immunology and immune-mediated diseases and their effect on women's health. The goal of this research is to increase the health and well-being of women by developing new methods to prevent and treat autoimmune diseases, enhance graft survival in women, and prevent the immunologic causes of infertility.

Autoimmune Diseases

Multiple Sclerosis

About 250,000 to 350,000 Americans have multiple sclerosis (MS), and women are affected almost twice as often as men. MS is characterized by scarring of the myelin in the brain and spinal cord, causing varying degrees of neurological impairment depending on the location and extent of the scarring. Although the cause of MS is unknown, scientific evidence increasingly suggests that genetics may play a role in determining a person's susceptibility to MS. There are several treatments to alleviate the symptoms of MS, but no cure.

SCIENTIFIC ADVANCES

- **Risk Alleles for MS Identified by a Genome-Wide Study**
  Scientists who analyzed the genomes of patients with MS and their family members have identified several genes associated with inherited risk for developing MS. Some of these genes help the body to distinguish between self and non-self and others help to control inflammation. These results enhance the understanding of the causes of MS and may suggest avenues for treatment of MS and other autoimmune diseases (*New England Journal of Medicine* 357:851-862, 2007).

- **Proteomic Analysis of Active MS Lesions Reveals Therapeutic Targets**
  Current treatments for MS involve broad suppression of the autoimmune response. The development of more targeted treatments will require a better understanding of the mechanisms of the disease. In this study, investigators examined MS lesions in brain tissue taken at autopsy and identified a set of proteins unique to individuals with chronic active MS lesions, including five proteins known to play a role in blood coagulation. The researchers also discovered that substances that inhibit the activity of these five proteins lessened symptoms in a mouse model of MS. This research provides potential biomarkers for MS diagnosis and suggests that personalized, targeted interventions in early-stage disease may help prevent further damage to the nervous system (*Nature* 451:1076-1081, 2008).

- **Copaxone® for Modulation of Central Nervous System Autoimmune Disease**
  NIAID-supported scientists used an MS mouse model to explore how the FDA-approved drug Glatiramer acetate (Copaxone®) reduces the symptoms of MS. They

showed that Copaxone® promoted the development of a specific type of anti-inflammatory immune cell, called type II monocytes. These cells, in turn, modified their output of inflammatory molecules, which led to the generation of T regulatory cells, a type of immune cell that can ameliorate MS-like symptoms and central nervous system inflammation. This improved understanding of how Copaxone® works may lead to the development of new and more effective forms of this drug (*Natural Medicine* 13:935-943, 2007).

- **Role of the Aryl Hydrocarbon Receptor in Autoimmune Disease**
  Research has shown that a relative imbalance in two types of immune cells, T regulatory cells (Tregs) and another type of T cell called TH17 cells, may be involved in autoimmune disease. TH17 cells cause inflammation, while Treg cells have the opposite effect of dampening the immune response. Therefore, when TH17 cells are overly active and/or Treg cells are underactive, autoimmune symptoms may develop. NIAID-supported researchers recently showed in a mouse model of MS that a protein called aryl hydrocarbon receptor (AHR), which is present in both types of T cells, can interact with two different molecules that cause opposing effects, and helps control the balance between Treg and TH17. This research has identified the AHR protein as a possible target for therapeutic drugs for MS (*Nature* 453:65-71, 2008).

Lupus

Systemic Lupus Erythematosus (SLE), more commonly known as lupus, is a chronic inflammatory autoimmune disease. Inflammation caused by lupus can affect many body systems, including the joints, skin, kidneys, blood cells, heart, and lungs. Lupus affects approximately 239,000 Americans and occurs more frequently in women than men. African-American women are affected more often than Caucasian women.

Scientific Advances

- **The Role of B Cell Maturation in SLE**
  NIAID-supported investigators identified a new "checkpoint" in the maturation of B cells, which are a type of immune cell. They studied a mouse model in which the lack of two proteins, located on the surface of the B cell, leads to the development of lupus. They showed that the absence of these proteins, called Cbl and Cbl-b, led to a faster rate of B-cell maturation and made the B cells less tolerant of self-proteins. These findings provide a new target for designing therapeutic intervention against autoimmune diseases such as SLE (*Immunity* 26:578-578, 2007).

Systemic Sclerosis

Systemic sclerosis (or scleroderma) is a group of autoimmune diseases in which the immune system is thought to stimulate cells called fibroblasts, which then produce too much collagen. Systemic scleroderma is the form of the disease that not only includes the skin, but also involves the tissues beneath, the blood vessels, and the major organs. The excess collagen forms thick connective tissue that can interfere with the function of affected organs. An estimated 40,000 to 165,000 people in the United States have this disease, and women—especially middle-aged and African-American women—are affected more than men.

Clinical Trials

- **High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Severe Systemic Sclerosis: Long-Term Followup of the U.S. Multicenter Pilot Study**
  This study is assessing the safety and potential usefulness of a therapy for systemic sclerosis that destroys the malfunctioning immune system and replaces it with immature immune cells, which develop into a healthy immune system. Preliminary results show improved overall function and general stability of organ function over a period of approximately 4 years (*Blood* 110:1388-1396, 2007).

Understanding the Causes of Autoimmune Diseases

NIAID supports research to elucidate the causes of autoimmune diseases. This research

is critical to inform the development of interventions to prevent, diagnose, and treat these illnesses.

SCIENTIFIC ADVANCES

- **Role of Extra-Thymic AIRE-Expressing Cells in Autoimmune Disease**
  Researchers recently discovered that a protein known as AIRE, which was thought to be located only in the thymus, also occurs in other parts of the body in mice. In the thymus, AIRE plays a key role in the removal of immune T cells that can recognize self-proteins. Mutations in thymus AIRE protein are known to cause broad autoimmunity against many organs and tissues. In this research, investigators found AIRE protein in cells in the spleen, lymph nodes, and Peyer's patches (lymph nodes found in the gut) that recognize additional proteins from the self. Their findings suggest that these cells may also be involved in the development of autoimmunity and may provide new therapeutic approaches for autoimmune diseases (*Science* 321:843-847, 2008).

- **Preventing Immune-Mediated Pregnancy Complications**
  Even though a fetus expresses both maternal (self) and paternal (nonself) genes, the fetus normally does not elicit an immune response from the mother, allowing it to develop through gestation until birth. Failure to develop this immune tolerance is a possible cause for recurrent miscarriages, high mortality and morbidity rates at birth, as well as long-term developmental delays and metabolic disorders during adult life.

- **Maternal Immune Response to Fetal Tissue**
  Researchers used a mouse model to explore the mechanisms used by the maternal immune system to recognize fetal tissue. They found that cells of the fetus did not make a set of proteins, called major histocompatibility class I proteins. Because these proteins were absent, the maternal immune cells did not recognize the fetus as foreign, and therefore did not mount an immune attack against the fetus. These findings improve the understanding of the immunology of pregnancy and early pregnancy failure, and potentially of transplantation and autoimmune disease (*Journal of Clinical Investigation* 117(5):1399-1411, 2007).

Related Accomplishments in Women's Health Research

Research Training and Career Development

- **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 has provided funds to eight international sites conducting innovative HIV research on women and children in Kenya, Mozambique, and Peru. Studies include investigation of MTCT and HAART research, microbicide and prevention research, and vaginal infection research.

- **Mentoring International Investigators on HIV Research and Women's Health**
  The NIAID-sponsored HIV and Women's Core grant at the Tufts University and Brown University CFAR provides mentoring to international investigators conducting research related to HIV and women. The 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

The Trans-NIAID Women's Health Research Workgroup focuses on women's health and gender-based research activities that advance the mission and research priorities of NIAID, identifies gaps in research, and provides recommendations for future women's health research opportunities. The Workgroup—

- Advises NIAID on the coordination of women and gender-based research across the Institute
- Develops a common framework for identifying and assessing women and gender-based research

- Encourages trans-NIAID and trans-NIH collaborations on women- and gender-based research activities
- Coordinates a seminar series highlighting issues and advances in women's health research

Initiatives

Initiatives in HIV Pathogenesis Research

Program Announcements

▶ **Transmission and Pathogenesis of HIV in Women**
NIAID released this program announcement (PA) in June 2008 to enhance the knowledge of transmission and pathogenesis of HIV infection in women through the study of biologic mechanisms that impact HIV transmission, acquisition, progression, and manifestations in women. The first round of awards is expected to be made in early 2009 (PAR-08-170).

Initiatives in Topical Microbicide Research

Request for Applications

▶ **Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM)**
This request for applications (RFA), sponsored by NIAID and the National Institute of Mental Health (NIMH), was issued in 2007 and 2008 to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The revised RFA is harmonized with the Microbicide Innovation Program (MIP). New awards will examine activity and pharmacodynamics of long-acting acceptable microbicides; support basic and comparative studies of inhibition of the HIV-related protein CCR5 to prevent HIV transmission; and pursue development of a practical microbicide based on HIV entry inhibitors (RFA-AI-08-057).

▶ **Microbicide Innovation Program**
NIAID supports MIP in coordination with the Office of AIDS Research (OAR) and the NIH Office of Research on Women's Health (ORWH). MIP supports research to advance the development of new microbicide approaches through preclinical and basic research; discovery and exploration of microbicides (singly or in combination) to prevent HIV or STIs that increase risk for HIV acquisition; emerging technologies or models to improve assessment of microbicide safety, efficacy, and acceptability; and exploration of complex prevention strategies that use microbicides in combination with other prevention strategies (RFA-AI-08-016).

Initiatives in STI Research

Request for Applications

▶ **Partnerships for Point-of-Care (POC) Diagnostic Technologies for Nontraditional Healthcare Settings (U01)**
In FY 2008, NIAID released an RFA calling for applications targeting product development activities that will lead to new or improved POC diagnostic technologies for infectious disease-causing pathogens or toxins in nontraditional healthcare settings. The definition of "nontraditional healthcare settings" includes the home, rural, and urban community public healthcare clinics, and temporary healthcare clinics established in response to a natural or manmade disaster. NIAID expects to make awards in FY 2009 (RFA-AI-08-003).

Research Enhancement Awards Program (REAP)

▶ **Biochemical Analysis of Papillomavirus Replication**
This investigation of papillomavirus genome replication received an ORWH REAP award in 2007 and is now funded by NIAID. The investigators are using genetic, biochemical, and structural analyses of the viral proteins and DNA segments called sequence elements that are required for viral DNA replication. Papillomaviruses are very important causative agents of human

disease, including cervical cancer. A deeper understanding of the lifecycle in general, and DNA replication in particular, is critical to the understanding of this disease, its transmission, and ultimately for the development of effective therapeutic measures. The viral DNA replication machinery to be elucidated in this research presents one of the few potential targets for drug therapy (1 R01 AI072345-01A2).

Initiatives in Autoimmune Disease

Program Announcements

- **Advancing Novel Science in Women's Health Research**
  NIAID is a cosponsor of this ORWH-led initiative. In 2008, this initiative funded a team of scientists to investigate whether estrogen receptors in key immune regulatory cells may mediate sex bias in lupus. Specifically, the investigators will develop a novel mouse model to explore how estrogens and their receptors regulate the function of two types of immune cells, B cells and dendritic cells, in lupus. These immune cells are known to express estrogen receptors and have been implicated in the pathogenesis of lupus. This research will advance scientific understanding of why lupus and other autoimmune diseases preferentially affect women (PAS-07-381).

Request for Applications

- **Autoimmunity Centers of Excellence (ACEs)**
  The nine ACEs conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials of drugs called immune modulators that act on the immune system. The Centers support close interaction between clinicians and basic researchers to facilitate identification of effective strategies for inducing immune tolerance and developing immune modulation strategies to treat or prevent disease. This interaction also accelerates the translation of scientific advances to the clinic. Completed, ongoing, and planned clinical trials address lupus, Sjögren's syndrome, rheumatoid arthritis (RA), MS, ulcerative colitis, scleroderma, pemphigus, and type 1 diabetes. The ACEs are currently cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH ORWH. The program will be renewed in FY 2009 with the additional cosponsorship of the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Neurological Disorders and Stroke (NINDS). More information is available at www.autoimmunitycenters.org (RFA-AI-08-010).

Initiatives on Sex-Based Differences in the Immune Response

Request for Applications

- **Immune Defense Mechanisms at the Mucosa**
  In January 2008, NIAID held a workshop to discuss recent research advances in immune defense mechanisms at mucosal surfaces, including the female genital tract. NIAID created the initiative "Immune Defense Mechanisms at the Mucosa" to address research gaps identified at the workshop (RFA-AI-08-020).

Conferences and Workshops

- **NIAID Women's Health Research Seminar Series 2008**
  The NIAID Women's Health Research Working Group launched its quarterly women's health seminar series in 2008. The goal of the series is to highlight research in infectious and immune-mediated research that advances women's health research. Presentations in 2008 addressed sex differences in HIV and outcomes in HAART; the need for a new strategy to understand how HIV-1 infects women, including the role of the mucosal immune response to HIV in the female genital tract; and sex differences that increase women's risk for lupus and other autoimmune diseases.

- **Workshop on Advances and Challenges in STI Microbicide Research**
  This workshop was held in April 2008, in Chapel Hill, NC, to review the ongoing research on microbicides to prevent transmission of sexually transmitted pathogens. The workshop provided an overview of the opportunities and challenges for STI microbicide research, development, and evaluation. Topics included microbicide safety and clinical trials.

- **Joint Symposium on HIV Research in Women**
  CFAR sponsored the first annual University of Washington–University of California at San Francisco Symposium on HIV in women in September 2008 in Seattle. The purpose of these symposiums is to mutually develop interdisciplinary projects and approaches to research in women, establish standardized definitions for variables pertinent to research in women, and generate synergy between institutions and individuals dedicated to HIV research in women. The theme of the 2008 symposium was "AIDS 2031: Looking Back to Look Forward." More than 100 attendees from a variety of scientific disciplines discussed the need for partnering with the aids2031 (www.aids2031.org) group to critically examine the past 25 years of the AIDS epidemic to inform the future research agenda for women. Symposium topics included HIV risk, prevention, and treatment in girls, adolescents, and women; women's participation in biomedical research trials; women's reproductive biology; immunology; and gender differences in HIV and comorbidities.

- **Workshop on Bacterial Vaginosis: Identifying Research Gaps**
  NIAID held this workshop in November 2008 in Bethesda, MD, to discuss three areas of research: (1) molecular methods for characterizing the vaginal microbiota, (2) the diagnosis and clinical definitions of bacterial vaginosis, and (3) the role of vaginal bacteria in adverse health events associated with bacterial vaginosis. Attendees participated in an active dialogue that may lead to future collaborations.

- **Scientific Symposium on Women and AIDS Research**
  In August 2007, NIAID convened the "Demystifying Women and AIDS Research" symposium at the National Minority Women's Health Summit, which was sponsored by the Secretary's Office on Women's Health. The presenters provided recent research findings on NIAID-sponsored epidemiological, microbicidal, and therapeutics research. More than 100 people attended the symposium, including Federal officials, women's health advocates, and health professionals.

Gender Analysis

NIAID supports research to analyze sex/gender differences in disease susceptibility, pathology, or response to prevention or treatment strategies. The following scientific advances and ongoing and planned activities are highlighted in this report:

- The Risk of CVD Among Women in the WIHS Study Initiating Abacavir
- Sex and Disease-Dependent Nucleoside Analog Toxicity
- Preclinical Research on Genital HSV-2 Vaccines
- Trans-NIAID Women's Health Research Workgroup
- NIAID Women's Health Research Seminar Series 2008
- Joint Symposium on HIV Research in Women

Health Disparities Among Special Populations of Women

NIAID supports research to understand and eliminate health disparities among special populations, including minorities, rural women, lesbians, women of lower socioeconomic status, women with disabilities, etc. The following scientific advances and ongoing and planned activities are highlighted in this report:

- WIHS
- Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and

0.5 percent PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women

- Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1 percent Tenofovir Gel
- Phase I Study of the Safety and Acceptability of 3 percent w/w SPL7013 Gel (VivaGel™) Applied Vaginally in Sexually Active Young Women
- Phase II Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir
- Phase IIB Safety and Effectiveness Study of Tenofovir 1 percent Gel, Tenofovir Disoproxil Fumarate (DF) Tablet, and Tenofovir DF-Emtricitabine Tablet for the Prevention of HIV Infection in Women
- Longitudinal Studies of Women at High Risk for HIV-1 Infection To Inform HIV Vaccine Trial Participation
- Use of Nevirapine To Decrease HIV Transmission Through Breastfeeding
- The Effects of Single-Dose Nevirapine (SD NVP) on Future Treatment Options for Women and Children
- The Effects of Protease Inhibitors in Pregnancy
- Osteoporosis in HIV-Infected Postmenopausal Women
- Strengthening International AIDS Research on Women and Children
- Mentoring International Investigators on HIV Research and Women's Health
- Partnerships for Point-of-Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Executive Summary

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. NIAMS funds studies on a number of diseases that affect women disproportionately, including osteoarthritis, osteoporosis, rheumatoid arthritis, 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.

Program Highlights

The anticipated increase in the United States' elderly population will probably be accompanied by a larger group of osteoporosis patients. New diagnostic methods are being developed to assess bone quality, and predict its impact on individuals' health status, in order to prevent morbidity from osteoporosis. These approaches include monitoring bone mineral density and bone microstructure. As well, there is an active pipeline of basic and translational research to develop drugs that improve bone quality.

Lately, research has led to a new understanding of rheumatoid arthritis, and has increased the likelihood that, in time, scientists will find even better ways to treat the disease. Several genetic and molecular components have been identified that may become useful therapeutic targets. Immune-modulating agents have been adopted for management of many rheumatoid arthritis cases, but recent investigations have pursued the unanticipated sequelae of these treatments, such as infections from immune suppression.

Linkage association and genome-wide association studies (GWAS) have yielded important results for complex rheumatic disorders, such as rheumatoid arthritis and lupus. This research has identified potential risk genes and pathogenic pathways for targeted drug development. Very large cohorts are needed for GWAS in order to see subtle genetic differences across patients' entire genomes, relative to control populations without the disease. Reaching this goal has been aided by the persistence of research networks in collecting a substantial number of patient samples over many years, and collaborations between U.S. and non-U.S. researchers, supported by government agencies, private foundations, and industry.

Accomplishments

Musculoskeletal Disorders

The Effects of Knee Laxity on Risk of Anterior Cruciate Ligament Injury in Young Female Athletes

Anterior cruciate ligament (ACL) injuries are common, with 200,000 injuries occurring in the United States each year, and half of these patients undergo surgical reconstruction. Women who participate in high-risk sports, such as soccer and basketball, suffer ACL injuries at a four- to six-fold greater rate than men. This increased risk involves many anatomic, physical, and psychological factors. Investigators showed that mild side-to-side looseness of the tibiofemoral (knee) joint and knee hyperextension may contribute to the increased ACL injury risk seen in female athletes. The validated injury risk testing method described in the study could be combined with other measures as a highly accurate and useful screening tool to identify high-risk athletes, especially young women. Susceptible individuals could undergo specific neuromuscular training to prevent these injuries.

Osteoarthritis

Osteoarthritis, or degenerative joint disease, is the most common form of arthritis. Nearly 27 million Americans, age 25 and older, have osteoarthritis. Although it is more common in older people, younger people can develop it—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 Provides a Wealth of Clinical Data to the Research Community

The Osteoarthritis Initiative (OAI), a prospective, natural history cohort established to improve diagnosis and monitoring of osteoarthritis and foster development of new treatments, has collected biological specimens (blood, urine, and DNA); images (x-rays and magnetic resonance scans); and clinical data such as dietary intake, medication use and pain, function, and general health assessments, from nearly 5,000 participants, age 45 to 79, 58.5 percent female. Women constitute 50–59 percent of all groups, including minorities, so the cohort is well powered for any analysis of gender differences in the onset and progression of osteoarthritis. This anonymous information is available to researchers worldwide, to expedite the pace of scientific studies and identification of biological and structural markers (biomarkers) for osteoarthritis. There are over 1,000 online users registered to obtain these clinical data. More than 2,500 datasets have been downloaded, and 135 imaging sets have been distributed. The OAI is a public–private partnership composed of five contracts funded by the NIAMS, National Institute on Aging (NIA), National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Center on Minority Health and Health Disparities (NCMHD), and National Center for Complementary and Alternative Medicine (NCCAM). Private-sector funding from Merck Research Laboratories, Novartis Pharmaceuticals Corporation, GlaxoSmithKline, and Pfizer, Inc., is managed by the Foundation for the National Institutes of Health.

Osteoporosis

Osteoporosis is a disease that alters the mechanical strength of bone, leading to increased risk for fracture. In the United States today, 10 million individuals already have osteoporosis and 34 million more have low bone mass, placing them at increased risk for this disease.

Fractures Due to High Trauma Are Associated with Low Bone Density and Predict Future Fractures

Researchers now have direct evidence that patients older than 64 years who seek treatment for broken bones should be screened for osteoporosis, even if the fracture occurred because of a highly traumatic injury that could hurt even a younger, healthy person. Although clinicians are quick to recognize osteoporosis as the cause of fractures resulting from minimal insult, breaks related to more substantial injury are rarely attributed to underlying bone disease. The latest findings from the long-standing, NIAMS-funded Study of Osteoporotic Fractures and Osteoporotic Fractures in Men Study revealed that older people who suffer high-trauma fractures are likely to have low bone mineral density and are at increased risk for subsequent fractures. The investigators support recommendations in the 2004 Surgeon General's Report on Bone Health and Osteoporosis, that fracture patients over 50 years of age should be tested for osteoporosis, and that those with low bone mass should take steps to protect their bones.

Findings Raise Concerns About Effects of Popular Antidepressants on Bone Health

Increasingly, elderly patients are being treated for depression, and selective serotonin reuptake inhibitors, or SSRIs, are often the first antidepressants prescribed. SSRIs work by blocking the action of serotonin transporters in the brain, but these transporter molecules are also present in bone cells, leading to investigation of the effects of SSRIs on bone health. Data from two large, ongoing osteoporosis studies showed a greater annual loss of bone mineral density (0.82 percent) in the hip bones of women age 65 and older taking SSRIs, in comparison with women from the same age group taking another type of antidepressant or no antidepressants (0.42 percent). Men taking SSRIs had lower bone mineral density in the hip (3.9 percent) and spine (5.6 percent) in comparison with participants taking other antidepressants or no antidepressants. These analyses, which were jointly funded by NIAMS and NIA, do not identify a direct link between bone loss and SSRIs, but they invite further investigation of this observation.

Bone Mineralization Is a Strong Predictor of Bone Strength and Is Maintained with a Single Intravenous Dose of Bisphosphonates in Aged, Estrogen-Deficient Rats

People who have low bone mineral density can make lifestyle changes and take bone-active drugs to protect their bone health. Bone mineral architecture, composition, distribution, and crystal structure are other properties affecting bone durability that may be influenced by the drugs. Choosing among the many treatments for postmenopausal osteoporosis in women is a great challenge in current clinical practice, and it is unclear which might be most effective in addressing estrogen-related bone loss. The medical community acknowledges a lack of correlation between changes in fracture rates and bone mineral density in women being treated for osteoporosis. Some of these questions about human bone health can be pursued with animal models. Recent experiments in an estrogen-deficient rat model demonstrated that a single intravenous dose of risedronate or zolendronic acid (members of a class of drugs called bisphosphonates) prevented loss of trabecular bone, which commonly deteriorates with age. These drugs also preserved the bone density and mineral content, and the ability of bone to tolerate compression stress; more modest results were seen in the rats with oral doses of raloxifene, a selective estrogen receptor modulator (SERM). Understanding the drugs' mechanisms of action will improve physicians' ability to treat postmenopausal osteoporosis effectively, and may contribute to tailored treatments for individual patients.

Low Levels of Vitamin D Associated With an Increase in Hip Fracture

Results continue to emerge from the 15-year NIH Women's Health Initiative. The latest findings confirm the association between low blood levels of vitamin D and hip fractures, independent of falls and measures of fragility. Although studies have largely failed to reduce the risk of hip or other fractures with vitamin D supplements alone, the finding provides one more clue to help physicians identify patients who are at risk for fractures, so that they may encourage them to take steps to protect their bones.

Bone Biology

A Piece of a Human Hormone Molecule Stimulates Bone Formation, Despite Promoting Cell Death

In 2002, recombinant human parathyroid hormone (1-34) [hPTH(1-34), a bioactive fragment of the human parathyroid hormone molecule] was approved to treat women with osteoporosis, for its action on osteoblasts to stimulate new bone growth and improve bone density. Unlike other antiresorptive drugs, that prevent further bone loss, hPTH(1-34) may have the potential to replace depleted bone stores; it is considered to be the first anabolic drug for osteoporosis. In post-menopausal women with osteoporosis receiving 1 month of hPTH(1-34) therapy, analysis of a spongy, highly porous section of their hip bones showed new growth on the inner (endocortical) and outer (periosteal) surfaces of denser (cortical) bone. During aging, the increase in the outer diameter of bone through periosteal apposition is one way that humans compensate for decreases in bone mass/density. Thus, PTH may contribute to bone strength by adding mass, as well as changing the geometry of bone: a tube-like bone with a larger outside diameter is stronger. A technique called histomorphometry enabled measurement of the amount of new bone, and a determination of bone areas that were already being rebuilt by osteoblasts or were not actively being remodeled. A four-fold increase in the bone formation rate on the outer, periosteal surface was detected, leading to speculation that improvements attributed to hPTH(1-34) therapy may be, in part, due to increased bone diameter. Previously, hPTH(1-34) was thought to improve bone health by increasing the functional lifespan of bone-forming osteoblasts. However, these recent results demonstrated that the bone formation rate was correlated with osteoblast apoptosis (a tightly controlled process that leads to cell death), which supports an alternative hypothesis that hPTH(1-34) therapy enhances osteoblast turnover, thereby making room for fresh, more effective, bone-forming cells. Because hPTH(1-34) loses its effectiveness with time of use (which is limited to 2 years), new information on its activity may help efforts to enhance its potential as a bone-building drug.

Identifying a Critical Molecular Link Between Mechanical Loading and Bone Formation

Mechanical loading on the skeleton, even at the level of normal daily activities, stimulates formation of new bone. Understanding the molecular mechanisms that mediate this response could lead to new drugs or other treatments that could reverse bone loss. Considerable evidence indicates that cells called osteocytes, which are embedded within the bone, detect loading and somehow communicate the presence or absence of load to the osteoblasts on the bone surface that make new bone. In the past decade, researchers studying diseases in which excessive bone formation occurs identified a protein called sclerostin, which normally suppresses bone formation, to keep it within healthy limits. Sclerostin is made mostly by osteocytes. Investigators have shown that mechanical loading of bone in mice and rats, which was already known to induce new bone formation, markedly decreases the amount of sclerostin produced by osteocytes. These results identify sclerostin as a critical molecular link between mechanical loading and bone formation. This finding opens a new avenue for developing drugs to prevent osteoporotic fractures because the most popular and convenient therapies for osteoporosis today block bone breakdown, but do little to restore bone that has already been lost.

Muscle Biology

Female Cells Build Muscle Better Than Male Cells

Promoting regeneration of muscle mass and function by transplanting stem cells from mature, healthy muscle into the defective tissue is one possible strategy for restoring muscle function to patients with muscular dystrophy or other muscle disorders. The healthy cells could potentially correct gene defects by fusing with existing muscle fibers and supplying them with functional proteins, which are missing in the diseased muscle. In pursuit of potential stem cell therapies for muscle, investigators searched for stem cell traits that would predict effective muscle regeneration. Of four characteristics studied, only cell sex correlated with the ability of muscle-derived stem cells' ability to produce dystrophin-positive muscle fibers in a mouse model of Duchenne muscular dystrophy (which fails to express the dystrophin protein). Transplantation of female cells into female mice yielded the most efficient regeneration, followed by female cells transplanted into male mice, in comparison with male cells transplanted into animals of either sex. This study has significant implications for stem cell biology and regenerative medicine, and may cause other investigators to consider the sex of the stem cells used in their research.

Sex-Related Difference in Gene Expression in Human Skeletal Muscle

On average, human males have greater muscle mass than females. A better understanding of the normal physiological mechanisms that regulate muscle protein synthesis and degradation, which determines muscle mass in humans, could lead to safe and effective approaches to treat conditions associated with abnormal loss of muscle mass. Such conditions include cancer cachexia, disuse atrophy, and age-associated sarcopenia. Studies from animal models have characterized several growth factors and their downstream signaling pathways that can modulate muscle mass during development and in adults. Insulin-like growth factor 1 (IGF-1) levels increase in response to exercise, and can boost protein synthesis, leading to a gain in muscle mass. Myostatin naturally limits muscle growth. Researchers found two proteins involved in regulating muscle mass that are produced at levels approximately two-fold higher in female muscles than in male muscles. Growth factor receptor bound 10 (GRB10) may interfere with IGF-1-mediated muscle growth, in response to exercise and other stimuli. Activin A receptor IIB (ACVR2B) is a receptor for myostatin. Because myostatin negatively regulates muscle growth, higher production of this receptor in women may limit muscle size. Some drugs currently in clinical trials for the treatment of muscular dystrophies act on signaling pathways involving GRB10 and ACVR2B. These drugs are designed to increase or maintain muscle mass. If they are found to be safe and efficacious in the dystrophies, they will likely be tested for the treatment of other, more common, conditions. Furthermore, similar approaches to modulate muscle mass and other characteristics of muscle physiology could be used to enhance athletes' physical performance.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) affects an estimated 2.1 million Americans. It is a debilitating autoimmune disease, characterized by chronic joint inflammation, in which the body's natural defense system attacks its own tissues.

Oral Contraceptive Use Is Associated with Decreased Biomarker Levels and Occurrence of Rheumatoid Arthritis

The blood test for the biomarker, rheumatoid factor (RF), is often used in the diagnosis and prognosis of rheumatoid arthritis. The appearance of RF precedes onset of rheumatoid arthritis, and stable increases in RF are associated with an increased incidence of rheumatoid arthritis. A protective effect of oral contraceptives in rheumatoid arthritis, and stimulatory effects of smoking and rheumatoid arthritis, have been observed. Recent research investigated the possible correlation of this biomarker with these external factors among mothers of children in a diabetes risk factor study (diabetes and RA share some susceptibility genes) who had no signs of rheumatoid arthritis. Their history of smoking and oral

contraceptive use was incorporated into the analysis of their RF blood tests. Women who had used oral contraceptives at any time in their lives were less likely to be RF positive than women who had never used oral contraceptives. Women who had a history of heavy smoking were more likely to be RF positive than women who had never smoked (or had smoked less than 100 cigarettes in their lives). This cross-sectional study of healthy women supports the hypothesis that oral contraceptive use is potentially protective against the development of RF and, subsequently, rheumatoid arthritis. These exogenous hormones may affect the early development of immune dysregulation in rheumatoid arthritis.

New Rheumatoid Arthritis Treatments Increase Risk of Serious Bacterial Infection

Rheumatoid arthritis is frequently difficult to treat, in part, because many anti-inflammatory therapies are very general. They can affect many organ systems, leading to unwanted side effects. Immunosuppressive treatments have also been employed, to reduce the immune reaction to autoantigens—the body's molecules that stimulate the aberrant immune reaction to its own tissues. Many new biologic immunosuppressive therapies have emerged for rheumatoid arthritis and other inflammatory, autoimmune diseases. They have greater specificity and, potentially, fewer side effects, such as inhibitors of tumor necrosis factor (TNF), a molecular messenger, or cytokine, which promotes inflammation, and is implicated in the pathogenesis of rheumatoid arthritis. While there is still no cure for rheumatoid arthritis, TNF-blockade improves clinical symptoms of rheumatoid arthritis dramatically, indicating TNF's central role in rheumatoid arthritis. However, ongoing research has raised concerns about side effects from these biologic immunosuppressive treatments, such as an increased risk of serious bacterial infections. Medical records of RA patients in a large healthcare organization were analyzed according to their treatment with biologic TNF inhibitors or methotrexate (MTX), a chemical immunosuppressive drug that is a widely used rheumatoid arthritis treatment. Over a median 17-month observation period, serious bacterial infections requiring hospitalization were more frequent in patients receiving TNF inhibitors than patients treated with MTX (2.7 percent vs. 2.0 percent). After adjustments for conditions unrelated to rheumatoid arthritis, treatments, and bacterial infections, the patients receiving TNF inhibitors had almost a two-fold increased risk of developing severe bacterial infections, compared to those who received only MTX. This retrospective study of rheumatoid arthritis patients in a large healthcare organization suggests that rheumatoid arthritis patients treated with anti-TNF therapy are at an increased risk of serious bacterial infections in comparison with patients receiving MTX, particularly shortly after treatment initiation. These results also bring attention to the risks of anti-TNF treatment for other inflammatory diseases.

Newly Identified Cadherin Molecule Implicated in Joint Damage in Rheumatoid Arthritis

Researchers hypothesize that rheumatoid arthritis arises from the body's normally protective immune system mistakenly attacking the synovium, the thin membrane that lines joints. In healthy joints, the synovium secretes a fluid that nourishes and lubricates the joint. In rheumatoid arthritis, T cells (a type of immune cell) infiltrate the synovium and drive inflammation, accompanied by overgrowth of the synovium. This overgrown membrane can attach abnormally to cartilage and bone, which can lead to erosion of these tissues, and subsequent joint damage and malformation. Investigators found an adhesion molecule on synoviocytes (cells of the synovium), called cadherin-11. At normal levels, cadherin-11 allows individual cells to stick together to form the synovium. But, when overgrowth of the synovium occurs, cadherin-11 plays a key role in its destructive behavior; namely, eroding the cartilage, which causes permanent destruction to the joint. To confirm the role of cadherin-11 in rheumatoid arthritis, the researchers genetically engineered rheumatoid arthritis-prone mice to eliminate the adhesion molecule. These mice failed to develop arthritis, or they developed only very mild disease. Rheumatoid arthritis-prone mice with intact cadherin-11 were similarly

protected from rheumatoid arthritis when treated with agents that blocked the adhesion molecule's activity, which prevented the aberrant attachment of the overactive synovium to the cartilage. This discovery may lead to safer, more specific rheumatoid arthritis treatments than those in current use, which suppress the immune system and leave patients vulnerable to infections.

Researchers Identify Genes That Increase Rheumatoid Arthritis Risk

A collaborative project of U.S. and Swedish investigators, including members of the NIAMS Intramural Research Program, applied whole-genome screening in the investigation of genetic differences between blood samples from rheumatoid arthritis patients and healthy controls. The U.S. researchers used rheumatoid arthritis patient samples collected by the North American Rheumatoid Arthritis Consortium (NARAC). The search led to a region on chromosome 9 associated with two genes relevant to chronic inflammation: TRAF 1 (encoding tumor necrosis factor receptor-associated factor 1) and C5 (encoding complement component 5). These are some of the first chromosomal susceptibility regions linked to rheumatoid arthritis, and may yield useful therapeutic targets.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (lupus) is a common autoimmune disease. Nine out of 10 people who have lupus are women. African-American women are three times more likely to get lupus than Caucasian women, and it is also more common in Hispanic/Latino, Asian, and American Indian women.

Association of STAT4 with Severe Manifestations of Lupus, Including Kidney Disorders

Lupus is heterogeneous and can cause a wide variety of clinical manifestations, including kidney disease and skin disorders. Prognosis varies greatly depending on the clinical features. For example, development of lupus-associated kidney disease is closely linked to mortality and morbidity. NARAC investigators, including the NIAMS intramural researchers and some of their U.S. collaborators involved in the TRAF 1-C5 study (mentioned above), identified gene variants that were common to rheumatoid arthritis and lupus patients, but were not found in healthy controls. Several of these small differences, called single-nucleotide polymorphisms, or SNPs, occurred in the gene for a protein critical to regulation of some immune cells, STAT4. These findings reveal the possibility that the two inflammatory, autoimmune diseases share a pathway for pathogenesis, and that these STAT4 gene variants increase the risk of developing these disorders. Further analysis established that the STAT4 gene variant associated with lupus susceptibility is more specifically associated with disease that is characterized by severe symptoms, such as disorders of the kidney. The frequency at which the STAT4 variant was identified was higher in the subset of lupus cases with kidney involvement (34.3 percent), and was even higher in cases with severe kidney disease (38.1 percent). This suggests that the variant predisposes patients more directly to lupus-associated kidney disease. Similarly, the variant frequency was found to be increased in cases with a disease onset at less than 30 years of age (33.8 percent), and in cases with autoantibodies to double-stranded DNA (35.1 percent). These observations suggest that the variant more strongly contributes to disease with these features. Kidney involvement, early disease onset, and autoantibodies to double-stranded DNA are all correlated disease features, and are associated with a poor clinical prognosis. Conversely, the STAT4 variant was not associated with disease in the subset of cases with skin disease manifestations, such as oral ulcers, which often occur in lupus, in the absence of more severe disease manifestations. Discovering that the disease-associated STAT4 variant is more specifically associated with severe lupus disease may allow physicians to assess the likelihood of developing acute disease manifestations in newly diagnosed patients. Although it is not yet known how this gene variant promotes disease, unraveling its molecular mechanisms may reveal novel therapeutic targets, which would be especially valuable for the individuals most likely to develop serious, lupus-associated morbidities.

More Discoveries in Lupus Genetic Susceptibility

Research advances identifying genetic susceptibility markers for rheumatic diseases reached a fever pitch at the beginning of 2008, with the refinement of tools for genome-wide association and genetic linkage studies. Several articles about genetic associations with lupus were published in high-profile journals, such as the *New England Journal of Medicine* and *Nature Genetics*, in January 2008. Genome-wide association, linkage analysis, and direct sequencing were utilized in large, case-controlled studies, and several findings were replicated in distinct racial or ethnic populations. Many SNPs confirmed previously identified SNPs associated with immune function, such as histocompatibility molecules, STAT4, and interferon regulatory factor 5. New SNPs from these reports occurred in molecules involved in vascular cell adhesion, clearance of immune complexes, and immune cell development and maturation. Disease-associated alterations in the gene products may contribute to vascular complications, persistence of inflammatory stimuli, and impaired tolerance mechanisms, leading to autoimmunity. As noted in an accompanying editorial in the *New England Journal of Medicine*, a critical factor in these and future studies is the collaboration between U.S. and European researchers, who are supported by government agencies, private foundations, and industry.

The X Factor: Unraveling Female Preponderance in Autoimmune Disease

In 2008, two major papers were published on the relationship between sex chromosomes and the risk of developing autoimmune diseases. One group of researchers used mouse models to see if there was a contribution of sex chromosomes to autoimmune disease susceptibility. In a unique model system, the testis-determining gene Sry, which normally resides on the Y chromosome, was either deleted from the Y (male) chromosome or "moved" from the Y chromosome to one of the non-sex chromosomes. This approach allowed the investigators to assess the effect of sex chromosomes in a female hormonal background. Likewise, mice with male hormonal backgrounds, but differing sex chromosome pairs, could be compared. Using separate mouse models for lupus and multiple sclerosis, the researchers found that normal female mice or male mice with an extra X chromosome (plus the Sry gene) experience more severe autoimmune disease in comparison with mice with one X and one Y chromosome (including females lacking the Sry gene). These are the first studies to describe a sex chromosome effect that is consistent with the known female sex bias present across distinct autoimmune diseases.

Another research group recommended that it is important for clinicians to maintain diagnostic vigilance for Klinefelter's syndrome when seeing male patients with lupus. This proposal is based on their research findings, which show that the occurrence of Klinefelter's syndrome (in which men have an extra X chromosome) shares a similar prevalence of lupus. Because this predilection is found in the environment of female (XX women), as well as male (XXY Klinefelter's men), sex hormones, the gene dosage from two X chromosomes may be significant in this disease. These recent studies support the influence of X chromosome genes on autoimmune diseases, and may lead to novel and valuable treatment targets for these diseases.

A Modular View of Gene Expression Profiles of Lupus Patients

Lupus is characterized by periods of illness (flares), alternating with remission. The wide spectrum of clinical manifestations and abnormal laboratory test results displayed by individual lupus patients creates a significant disease assessment challenge for clinicians. Currently, there are at least six different measures of global lupus disease activity. Each aggregates many (24 or more) different clinical and laboratory parameters, including "predictors" of flares, which may lead to organ damage. DNA microarray, a powerful, high-throughput technology, has been adopted by clinical researchers to gain insight into molecular mechanisms underlying disease pathogenesis, and to detect changes in the expression of thousands of genes very rapidly from a large number of patient samples. Using microarray analyses of blood samples from lupus patients, researchers have revealed dysregulation of many inflammatory and cell signaling

molecules in the immune pathways that can be used as signatures of lupus disease activity. In 2008, researchers reported the successful implementation of a novel strategy that uses gene groups, or modules, as the basic building blocks for microarray analysis of lupus patient blood samples. With the modular approach, the investigators observed disease-specific gene expression variations in 11 out of 28 different gene groups, in comparison with healthy controls. The patient gene expression profiles detected in the 11 modules correlated with disease activity, as determined by the Lupus Disease Activity Index (LUPUSDAI), the most widely used measure of disease activity. The researchers used the modular approach to reduce distinct gene expression patterns, associated with lupus pathogenesis, to a unique score that correlated with disease activity. This score has the potential to be a better measure for biomarker changes and disease progression, in comparison with current tools, such as the LUPUSDAI. Characterization of individualized measures of organ-specific damage could lead to the identification of lupus flare "predictors," to implement earlier therapeutic interventions and prevent irreversible damage. The development of an effective gene expression assay, to assess global and organ-specific disease activity in lupus patients, could be of great value in clinical settings to improve the management of patient care. It would also constitute an effective tool for the monitoring of drug efficacy and safety in clinical trials.

Potential Molecular Markers for Monitoring Lupus Disease and Therapies

Finding marker molecules in serum that allow monitoring of disease activity and indicate the effectiveness of a treatment is an important goal for understanding many diseases, including lupus. Certain products, or intermediates, of oxygen (superoxide) and nitrogen (nitric oxide—NO) are highly reactive and damaging to the body. These reactive oxygen and nitrogen intermediates (RONI) are formed in response to microbial factors. In mouse models of lupus, NO production correlates with kidney disease. In these animal models, studies with drugs that can inhibit the enzyme, inducible NO synthase (iNOS), have reduced production of these reactive intermediates significantly. Observational studies in human lupus also suggest that NO production is important in both systemic and local disease activity. Serum nitrate plus nitrite (NOx) is a marker of systemic NO production. By conducting long-term evaluations in patients with controlled dietary intakes of nitrates, researchers discovered that NOx levels were higher in patients with lupus than in healthy controls. Also, lupus patients who had evidence of kidney disease had higher levels of NOx than patients without kidney involvement, which is consistent with prior animal studies. These results suggest that NOx plays a significant role in disease activity in lupus, especially in those patients with kidney disease. This clinical study is an important illustration of investigations that translate animal results into better ways to diagnose and treat lupus. It has implications regarding mechanisms of kidney injury, and suggests that NOx and the enzymes involved in their production, such as iNOS, are therapeutic targets. Further research will be necessary to determine if the results of pharmacologic inhibition of iNOS in animal models, which significantly reduces NOx and renal damage, will translate into clinical benefit for lupus patients.

Researchers Correlate Clinical Criteria and Associated Antibodies in Lupus Patients

Antiphospholipid antibodies (APLs) are autoantibodies that recognize complexes of proteins and other molecules (phospholipids). They occur in a small percentage of the general population, but more commonly in lupus patients. In the absence of underlying connective tissue disease, their persistent appearance is strongly associated with early fetal loss and blood clots, in the condition known as primary antiphospholipid syndrome. Preliminary observations of associated heart valve problems and atherosclerosis led to investigation of the specific nature and association of APL and cardiovascular disease in lupus patients. Ultrasonographic studies were conducted to measure the function and dimensions of specific arteries and regions of the heart. Laboratory assessments were also conducted to determine the presence or absence of APL, along with lipids and molecular markers of

inflammation. APL-positive patients were more likely to be Caucasian, with some history of smoking, and they had more active disease. However, equivalent numbers of APL-positive and APL-negative patients displayed atherosclerosis-related arterial measurements, and had experienced cardiovascular disease, such as arteriosclerosis, stroke, or heart attack. The most significant difference was a three-times higher prevalence of mitral valve nodules in APL-positive patients than in APL-negative patients (the mitral valve separates the left upper chamber of the heart from the left lower chamber). Mitral dysfunction, or regurgitation, was also higher in APL-positive patients; this is also a predominant defect in antiphospholipid syndrome.

Lupus Disease Onset and Course Are Not the Same in Children and Adults

Differences in childhood- and adult-onset lupus have been observed over the years, but new availability of standardized clinical measures of lupus disease and damage have allowed direct comparison of their distinctive disease courses. A recent study confirms that children with lupus have more active disease than adults at the time of diagnosis. As well, pediatric lupus patients have more aggressive and severe disease than adult lupus patients, over time. In particular, renal disease in pediatric lupus occurs at a higher frequency, and damage appears to develop more rapidly. Furthermore, potent medications (steroids and immunosuppressive drugs) are required more often in children than adults, and are associated with more damage (eye and hip disease) in children than adults. To the extent lupus and its treatment are not the same in these populations, further studies need to focus on childhood lupus directly; management of pediatric lupus should not rely solely on therapeutic regimens and approaches that have been studied primarily in adult lupus patients.

Scleroderma

Scleroderma is a disabling, autoimmune disease, characterized by fibrosis and hardening of tissues, with an unknown cause, no cure, and few effective treatments. Systemic sclerosis (SSc) is one form of scleroderma and affects many parts of the body, such as skin, internal organs, and blood vessels.

Treatment Improves Quality of Life for Scleroderma Patients

Approximately 40 percent of scleroderma patients experience breathing impairment, which is often the subsequent cause of death. The Scleroderma Lung Study, sponsored by the NIH, was a double-blind, randomized, placebo-controlled trial of the immunosuppressive drug cyclophosphamide (CYC), for patients with scleroderma-related lung diseases. The trial demonstrated that oral administration of the drug for 12 months modestly improved pulmonary function. Trial participants also provided patient-reported outcomes on health-related quality-of-life (HRQOL) topics. The investigators utilized an estimation of minimum clinically important difference (MCID), a relatively new measurement in HRQOL, to detect the smallest improvements in patient-reported outcomes that might lead to changes in disease management. Detailed analysis of the HRQOL results from this study revealed that, on average, participants rated their physical and mental health below that of the general U.S. population. Surveys at regular intervals during the 12-month treatment period were linked to physiological measures as well, such as lung function and skin scores. At the end of the trial, a greater proportion of participants in the CYC-treated group reported improvement in their health (47 percent), compared with the placebo group (12 percent). Fewer (24.2 percent) of the participants in the CYC-treated group said that their health was worse at the end of the trial than the placebo group (38.7 percent). There was a modest correlation between the clinical measurements of breathing ability and participant-reported outcomes, linking improvement in lung function and other physical conditions with enhanced mental well-being. The information provided by the analysis of outcomes, such as those used in this study, will allow future trials in scleroderma to evaluate the effects of new drugs on health preferences, decision, and risk assessment—all critical outcomes in patients with chronic conditions.

Fibromyalgia

Fibromyalgia syndrome (FMS) is a chronic disorder, characterized by widespread pain and tenderness. It is frequently accompanied by other symptoms, such as fatigue, insomnia, depression, and anxiety. FMS affects approximately 2 percent of the U.S. population; it is much more common in women than men, and it is associated with substantial morbidity and disability. The precise cause of FMS is not known, but research suggests that it is related to a problem with the central nervous system's processing of pain. As with some other chronic pain conditions, people with FMS often develop a heightened response to stimuli, experiencing pain that would not cause problems in other people.

Tailoring Psychological Treatments to FMS Patients

Psychological processes are thought to contribute to the physical functioning, poor coping ability, and overt expressions of pain ("pain behaviors") of FMS patients. Psychological treatments, such as cognitive-behavioral therapy (CBT) and operant-behavioral therapy (OBT), have shown effectiveness in treating FMS patients. CBT has been proposed as a component of FMS clinical practice guidelines; it focuses on thought processes to modify awareness, assumptions, beliefs, and behaviors, in order to influence emotions. OBT stresses the importance of antecedents and consequences of behavior, such as rewards for positive behavior. Results from these approaches have measured different variables, making it difficult to establish effectiveness, and a large proportion of patients have not reported clinically significant outcomes. In a clinical study, FMS patients received CBT, OBT, or "attention placebo" (AP) treatment, in which the control group participated in general, therapist-guided discussions about medical and psychosocial problems, with no intervention. CBT involved problem solving, pain coping strategies, and relaxation. OBT utilized role playing to reduce pain behaviors and increase healthy behaviors. Twelve months after treatment, more patients treated with CBT or OBT reported significant decreases in pain, as well as decreases in physical impairment, in comparison with the AP group. Many patients in the control group had increased pain and physical impairment, suggesting that the discussions, without intervention, may have reinforced negative behaviors. Pain behaviors were the most important predictors that differentiated the three treatment groups; patients most responsive to CBT showed low pain behaviors, while patients who responded to OBT showed high pain behaviors. Pretreatment patient characteristics may serve as important predictors of response to psychological therapies, and allow matching of specific treatments to the appropriate person. With further outcomes research, it may be possible to tailor psychological and drug-related treatments to the individual with FMS, which should lead to better, and more predictable, outcomes for FMS patients.

Gabapentin Shown Effective for FMS Pain

In early 2007, researchers reported that the anticonvulsant medication gabapentin, which is used for certain types of seizures, can be an effective treatment for the pain and other symptoms associated with FMS. Although gabapentin has little, if any, effect on acute pain, it has shown a robust effect on pain caused by a heightened response to stimuli related to inflammation or nerve injury in animal models of chronic pain syndromes. Researchers have suspected that it might have the same effect in people with FMS. In a randomized, double-blind clinical trial of 150 women (90 percent) and men with the condition, those taking gabapentin at dosages of 1,200 to 2,400 mg daily for 12 weeks displayed significantly less pain than those taking a placebo. Patients taking gabapentin also reported significantly better sleep and less fatigue. For the majority of participants, the drug was well tolerated. The most common side effects included dizziness and sedation, which were mild to moderate in severity in most cases. The drug received approval from the Food and Drug Administration in June 2007 for treatment of FMS.

Health Disparities Among Special Populations of Women

Research Characterizes Factors Influencing Decisions About Total Knee Replacement Procedures

Total knee replacement (TKR) is a highly successful treatment for end-stage osteoarthritis of the knee joint, when other treatments have failed to alleviate pain and improve or maintain function. Large disparities with regard to race and ethnicity in the use of TKR in the United States have been well documented. Analysis of Medicare data from 27.5 million Americans in 2000 revealed that the osteoarthritis prevalence is similar across socioeconomic groups, although the prevalence of osteoarthritis was higher among African-American men and women than Caucasian men and women. However, non-Caucasian patients were less likely to undergo TKR than their White counterparts. In designing programs to improve access to care across American society, these findings suggest that the healthcare system should use culturally and ethnically sensitive decision aids to help patients make well-informed decisions about the risks and benefits of TKR surgery.

Scientists Predict That 3 Million People in the United States Will Suffer from Osteoporosis-Related Fractures in 2025, at a Cost of $25.3 Billion

Current health data indicate that 1.5–2.1 million people break a bone because of osteoporosis each year, and healthcare costs due to osteoporosis fractures have been estimated at $13.7–20.3 billion annually. The number of Americans over 50 years old is expected to increase more than 40 percent from 2005 to 2025, and, without intervention, both the prevalence of osteoporosis and associated costs are expected to increase dramatically in the next two decades. Researchers projected that the annual cost of osteoporosis-related fractures in the United States is likely to grow to $25.3 billion, an almost 50 percent increase from the 2005 estimated cost of $17 billion, without adjusting for price inflation. Unlike previous analyses of the burden of osteoporosis, this research reflects healthcare costs due to fractures in bones, in addition to the traditional osteoporosis sites (i.e., the hip, spine, and wrist), and accounts for anticipated growth in the aging and minority populations in the United States over the next 20 years. This concurs with the 2004 Surgeon General's Report on Bone Health and Osteoporosis, which stated that interventions and education will need to target populations with growing and unrecognized needs, such as minorities.

Despite Decrease in Disease Activity, Workforce Dropout Rate in Women With Rheumatoid Arthritis Remains High

In two groups of women with rheumatoid arthritis studied 11 years apart, researchers found that the rate at which women left the workforce did not fall significantly, despite decreased disease activity. In both cohorts, more than a quarter of the women stopped working within 4 years after being diagnosed with rheumatoid arthritis. The researchers hypothesized that the rate of stopping work would be lower in the 1998 cohort than in the 1987 cohort because of improvements in disease management and advances in pharmaceutical therapies. However, the difference (31 percent in the 1987 cohort and 26 percent in the 1998 cohort) was not statistically significant. Disease activity, as measured by the severity of patients' malformations, decreased; 39.6 percent of women in the 1987 cohort had malformations in at least one joint group within the first year of diagnosis, compared with 22 percent in the 1998 cohort. Researchers concluded that more women left work in 1998 for reasons other than increased disease activity, which may have included the period's economic climate. Most participants in both cohorts were Caucasian, married, and older than age 50. The only significant demographic difference was that the 1998 cohort was more affluent, adjusting to 1998 dollars. Another similarity between cohorts was that married women had a greater tendency to leave the workforce, in comparison with those who were unmarried. Researchers noted that this tendency could be related to the financial assistance that a spouse provides, or to the greater physical and social demands placed on married women with families.

Study Indicates Significant Work Loss Associated with Lupus

Research on work loss associated with lupus estimated that almost three-quarters of the study's 982 participants (age 18–64) would stop working before the usual age of retirement, and that half of those who had jobs when they were diagnosed (with an average age of about 35) would no longer be working by age 50. In addition to evaluating work loss by age/time frames, the scientists examined risk factors for job loss, including demographics (age, sex, and education), socioeconomic status, disease status, general health, functional status (how well the individual is able to function and carry on typical daily activities), mental/cognitive status, healthcare use, and employment information. The data analysis tools (the Kaplan-Meier method and the Cox model) allowed the scientists to evaluate data collected over 2 years and to reliably estimate long-term patterns of work loss. The researchers determined that demographics and work characteristics (the physical and psychological demands of jobs, and the degree of control over assignments and work environment) had the greatest impact on work loss.

Information Dissemination

- **Bone Health Information for You and Your Patients (CD-ROM):** http://www.niams.nih.gov/News_and_Events/Announcements/2007/bone_cd.asp
  This CD-ROM guide provides the latest information on bone health and diseases, and treatment options for many bone diseases. It is intended primarily for health professionals and the general public, and includes PDFs of patient education brochures and professional education resources.

- **Bone Health for Life:** http://www.niams.nih.gov/Health_Info/Bone/Bone_Health/bone_health_for_life.asp
  This publication is geared for patients and families, and has easy-to-read information on bone health, including osteoporosis and preventive health strategies.

Initiatives

The NIAMS participated in the following Funding Opportunity Announcements:

- **PA-08-246, Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01); PA-08-247, Chronic Fatigue Syndrome: Pathophysiology and Treatment (R21) (fibromyalgia comorbidity)**
  This ORWH-led solicitation was created to stimulate research on the epidemiology, diagnosis, pathophysiology, and treatment of Chronic Fatigue Syndrome (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.

- **PAS-07-381, Advancing Novel Science in Women's Health Research (R21), PAS-07-382, Advancing Novel Science in Women's Health Research (R03)**
  Another funding announcement led by ORWH emphasized support of pilot or small, self-contained projects that promoted innovative, interdisciplinary research to advance new concepts in women's health research and research in sex/gender differences.

NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

Executive Summary

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) was established by law in December 2000. NIBIB received its first appropriation and grant funding authority in fiscal year FY 2002. As NIBIB continues to mature and establish programs, funding opportunities have been developed to support a variety of scientific areas, including programs aimed at fostering women's health research.

NIBIB serves as the hub within the NIH for coordination of biomedical imaging and bioengineering efforts. 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 symposiums, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. During FYs 2007 and 2008, 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 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 prevent bone resorption for women suffering from osteoporosis.

During FYs 2007 and 2008, NIBIB supported research on women's health in the following disease areas: factors that influence careers of women in science and engineering; technologies to reduce health disparities; and the topic areas of aging, autoimmune disease, breast cancer, cervical cancer, reproduction, diabetes, obesity, epilepsy, HIV/AIDS, heart disease, osteoporosis, and temporomandibular joint (TMJ) disease.

NIBIB Report on Women's Health Research

Dr. Roderic Pettigrew, the first Director of NIBIB, began his tenure at the National Institutes of Health (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 NIBIB.

In December 2004, Dr. Anthony Demsey joined NIBIB as the Director of the Office of Extramural Policy and subsequently of the Office of Research Administration. Under his purview, Dr. Demsey has the overall responsibility of managing and monitoring all 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 NIBIB, and has direct day-to-day responsibility for women's health research oversight. In addition, Drs. Demsey and Gordon direct the efforts of NIBIB to support research on women's health by serving as NIBIB representatives to the Coordinating Committee on Research on Women's Health.

Accomplishments

Highlighted below are significant NIBIB research accomplishments related to women's health.

Breast Cancer

Breast Cancer Diagnosis by Electrical Impedance Imaging

The long-term goal of this project is to develop a new technology to improve the screening for and diagnosis of breast cancer. Noninvasive electrical impedance measurements made with a handheld probe have been shown to improve the specificity and sensitivity of mammography for breast tumor diagnosis in patients with ambiguous mammograms. 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 noninvasive 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) are predicted to assist doctors'

efforts to evaluate and treat cancer patients. Researchers are leading an effort to explore the medical applications of quantum dots that are manufactured to emit light at specific wavelengths in response to illumination. When injected near a tumor in an animal, the dots quickly reveal the sentinel lymph node closest to the tumor. The researchers believe that someday the dots 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. The 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 they recruited 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.

MRI Evaluation of Tumor Growth and Treatment Response

This project addresses the quantitative evaluation of tumor growth and treatment response by MRI by integrating dynamic contrast-enhanced MRI (DCE-MRI) measurements with quantitative metrics derived from other imaging modalities such as diffusion-weighted MRI (DW-MRI), fluorodeoxyglucose positron emission tomography (FDG-PET), computed tomography (CT), and optical methods. The performance of these methods in serving as reporters on tumor growth and treatment response will be evaluated when used separately or in combination to evaluate human breast cancer treatment response.

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 of the first-line combination therapies are regarded as equally efficacious and have a 60 percent response rate. A team of investigators 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.

Speckle-Free Transmission Ultrasound for Breast Imaging

The goals of this project are as follows: the development and implementation of a Breast Ultrasound Fluoroscopy System (BUFS), which includes image acquisition and post-processing for the C-scan ultrasound images; the generation of preliminary tests with 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. Scientists and engineers successfully built a higher dynamic range CMOS-base ultrasound sensor. 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" Breast Ultrasound Fluoroscopy System prototype 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.

Highly Fluorescent Magnetic Nanoprobes for Enhanced Cancer Imaging and Therapy

The broad objective of this proposal is to develop new multifunctional nanoprobes with superior optical and magnetic properties for enhanced molecular cancer imaging and therapy. An electromagnetic device for producing a controllable magnetic field gradient will be designed and used in the guiding of the nanoprobes to target cells. The targeting efficacy of the fluorescent nanoprobes (also incorporating drug load) will be evaluated in the imaging and treatment of breast cancer in model systems.

Breast CT Scanner for Earlier Cancer Detection

Breast cancer is a disease with high incidence in the United States and elsewhere, and population-level methods of fighting this disease are aimed primarily at using mammography screening for early detection. While breast CT would probably improve cancer detection in all women, some women may have risk factors (dense breasts, genetic markers, etc.) that require additional screening using breast CT. In this research project, a team composed of medical physicists, physicians, mechanical and electrical engineers, and breast cancer advocates collaborated on the design of the dedicated breast CT scanner. The scanner has been built, is operational, and has been evaluated with 139 women. The second phase of the project included noise-reduction techniques in the preprocessing of the images, and also included computer-aided diagnosis (CAD) tools. Using computer-based observer performance methods, lesion detection performance was also tested and showed that anatomical noise for breast CT was greatly reduced. In addition, a second, more sophisticated breast CT scanner has been designed and constructed, which includes other modalities, such as PET and robotic biopsy guidance and initial imaging studies. Based on initial tests, breast CT has demonstrated enormous potential to detect breast cancer early and lead to more timely treatments for breast cancer patients.

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. 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 (the fraction of positive cases that are properly identified) and specificity (the fraction of negative cases that

are properly identified). These analysis methods have the potential to improve the accuracy and reliability of breast cancer detection. One project is focused on developing innovative statistical methods for the evaluation and validation of new and low-cost diagnostic modalities. These researchers are evaluating statistical methods developed in two areas of high importance to women's health: breast cancer prediction and assessment of osteoporotic fracture risk. A second project is designed to determine whether detection methods optimized in the laboratory can be expected to exhibit the same level of sensitivity in the clinical environment.

Magnetic Resonance Elastography

The goal of this research is to develop, validate, explore, and identify high-impact applications of a new diagnostic imaging technology for quantitatively assessing the mechanical properties of tissues: Magnetic Resonance Elastography (MRE). Mechanical waves are generated in tissue and a remarkably sensitive phase-contrast MRI technique, using synchronous motion-sensitizing gradients, is used to directly image the pattern of wave propagation. Specially developed mathematical algorithms are used to analyze the wave images and to generate quantitative images depicting the stiffness and other mechanical properties of tissue. Using magnetic resonance to palpate tissues will allow clinicians to identify breast lesions and will distinguish benign lesions from malignant ones.

Advanced High-Resolution, Two-Dimensional X-Ray Detector for Mammography

The goal of this project is to improve the image quality and reduce the cost of digital mammography. The research team will develop a computed radiography (CR) system for mammography based on novel glass ceramic materials. These glass materials will be used to develop a transparent phosphor material that is less expensive and can attain better performance than existing phosphor materials. Because they are transparent, they do not suffer from loss of resolution and increase in noise due to light scattering from grain boundaries, as do polycrystalline materials. Specifically, the investigators plan to (1) perform structural investigations; (2) optimize the transparent phosphor material for the application in CR mammography; (3) design and construct a readout system for transparent phosphor material; and (4) characterize and benchmark the new computed radiography.

Near-Infrared Diffused-Light Imaging With Ultrasound Guidance

The goals of this project are to explore the utility of a novel hybrid ultrasound/optical imaging technique for (1) accurate diagnosis of breast lesions that could result in a reduction in benign biopsies; and (2) assessment of chemotherapy response and evaluation of treatment efficacy. The hybrid technique is implemented by simultaneous use of near-infrared optical sensors and a commercial ultrasound transducer mounted on a handheld probe, and utilizing coregistered lesion structure information provided by ultrasound to improve the inverse optical tomography reconstruction. As a result, the optical tomography overcomes problems associated with intense light scattering and has provided reliable tumor angiogenesis distributions. Initial tests on a group of biopsied patients have shown that early-stage invasive cancers may be distinguished by an average of twofold greater total hemoglobin concentration when compared to fibroadenomas and other benign lesions. Also, early results obtained from advanced cancers have shown that the angiogenesis distribution is highly distorted and heterogeneous, and the distorted distributions correlate with histological microvessel counts and can be used to assess chemotherapy response. Going forward, the research team plans larger scale clinical studies to further validate these initial results in assessing chemotherapy response and evaluating treatment efficacy.

Robotic Haptic Feedback System for Bx/RFA of Breast Tumor Under Continuous MRI

This project proposes to develop an image-guided robotic system that will be able to perform breast biopsy and deliver radiofrequency ablation (RFA) at the site of the breast tumor. The investigators will incorporate continuous MRI during the procedure so that

sampling errors will be minimized during the biopsy. Furthermore, the haptics in the teleoperated robotic system will provide force feedback to the clinicians to guide the biopsy and RFA needle with wider areas of access to various regions of the breast.

Aging, Osteoporosis

Biomaterials (Mg/Zn/F-BCPs) 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), and F (fluoride) ions in a calcium (Ca) phosphate system (Mg/Zn/F-BCP). Separately, these ions have been associated with bone formation, biomineralization, and 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. An osteoblast-like cell line was used for screening Mg/Zn/F-BCP compounds to measure in vitro cell response (principally, proliferative capacity). The data indicate that all the preparations tested (about 40) show significantly higher proliferative capacity (from 1.5 to 4 fold) compared to controls.

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 of this has been the reliable detection of fetal ST segments, obtained from an electrocardiogram (ECG), which is potentially valuable because 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 f-fMRI. These techniques involve novel approaches for reducing the field of view of the MRI image, and they 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 nonspecific, and 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 the use of MRI data with US 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 to US data alone.

Development of Spatial-Temporal Analysis Tools for Uterine Biomagnetic Signals

The proposed study will record the magnetic field corresponding to the electrical activity of uterine contraction and will provide requisite spatial-temporal information. To take advantage of the spatial-temporal resolution in uterine magnetomyographic (MMG) signals, the investigators will further enhance computational and analysis tools and will develop this system as a clinical device to predict

the onset of labor both in term and preterm patients. The goal is to develop techniques to improve the extraction, recognition, and validation process of uterine magnetomyographic activity. This ability would be of great clinical benefit for the management of the term patient and especially for the management of patients at high risk for premature delivery.

Development of Analysis Tools To Enhance Fetal Neurological Assessment

The ultimate goal of this proposal is to develop a clinical neurological assessment tool for the developing fetus. This proposal has two specific aims. One is to improve fetal spontaneous MEG (magnetoencephalography) signal extraction by using advance spatial filter processing methods, and the other is to apply this technology to assess the spontaneous brain activity in a specific group of fetuses who are at risk for developing neurological problems. The investigators will specifically investigate IUGR fetuses because their compromised intrauterine environment affects potential growth and brain development. The spontaneous brain activity characteristics of IUGR fetuses will be compared to fetuses with normal growth.

Temporomandibular Joint Disorder

Tissue Engineering TMJ Articular Fibrocartilage

Temporomandibular joint (TMJ) disorders are painful conditions that disproportionately affect women and for which there are few (if any) successful treatments. The TMJ is the small, complex joint that forms the articulation of the lower and upper jaws, and it is characterized by an unusual hybrid-type of cartilage. Several major technical hurdles have barred the development of clinically useful engineered cartilage, particularly optimization of mechanical properties, and obtaining an appropriate cell source. These investigators plan to utilize recent advances (cell sourcing, bioreactor growth systems, scaffolds with functional tensile strength) to generate TMJ articular cartilage appropriate for implantation and repair of the TMJ. These studies will lead to translational research, where these tissue-engineered constructs will be assessed in preclinical models.

Initiatives

In FY 2007–2008, the NIBIB participated in initiatives that addressed areas relevant to women's health.

Joint Initiatives

- **Research on Causal Factors and Interventions That Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering**
  NIBIB participated in a trans-NIH Funding Opportunity for research on (1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering and variation across different subgroups, and (2) the efficacy of programs designed to eliminate sex/gender disparities and promote the careers of women in these enterprises. This program is designed to better understand the factors that influence existing outcomes; to identify new principles to inform the development and adaptation of existing intervention strategies; to analyze differences in the career activities of men and women scientists and engineers that may inform the development of interventions for remediation; and to analyze career patterns to further support new programs (RFA-GM-09-012, R01).

- **Advancing Novel Science in Women's Health Research (ANSWHR)**
  With the Office of Research on Women's Health (ORWH), NIBIB cosponsored a trans-NIH investigator-initiated exploratory developmental program designed to promote innovative, interdisciplinary research to advance new concepts in women's health research and the study of sex/gender differences. Published research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. The ANSWHR program is focused on stimulating and supporting innovative research that will advance new concepts in

women's health research and the study of sex/gender differences (PAS-07-381, R21).

- **Advancing Novel Science in Women's Health Research**
  With ORWH, NIBIB cosponsored a trans-NIH investigator-initiated small grants program designed to stimulate and support innovative research that will advance new concepts in women's health research and the study of sex/gender differences (PAS-07-382, R03).

NIBIB Initiatives

- **Development and Translation of Medical Technologies That Reduce Health Disparities**
  NIBIB sponsored a Funding Opportunity focused on reducing health disparities through the development and translation of appropriate medical technologies, new or existing, that can have a significant impact on healthcare access and health outcomes for health disparities in populations. The RFA supports a wide range of research, aimed at the development of innovative diagnostics, treatments, and preventative strategies to reduce, and eventually eliminate, health disparities (RFA-EB-09-001, SBIR [R43/R44]).

- **Development and Implementation of Innovative Ultrasound Therapy Technologies**
  NIBIB sponsored a Funding Opportunity to solicit projects that develop and accelerate the implementation of innovative, disruptive, noninvasive, or minimally invasive ultrasound technologies that produce or enhance interventional therapies in humans. Ultrasound has long been considered a diagnostic imaging modality. There is increasing evidence from in vitro, animal, and human subject studies that application of ultrasound to certain conditions in the body can produce effective therapy, and that, when used as an adjunct to existing therapies and agents, ultrasound can significantly improve the effectiveness of the existing therapy. Research projects must demonstrate the identification and resolution of critical basic or technical problems that presently exist, and which have prevented the proposed ultrasound-based interventional application technology from being implemented in safe clinical use in humans (RFA-EB-07-004, R01).

Health Disparities Among Special Populations of Women

Nanodevice for Digital Imaging of Palpable Structure at Human-Finger Resolution for Breast Cancer Detection

The investigators propose to develop an inexpensive, noninvasive, handheld screening tool for early detection of breast cancer that can image the palpability of a tumor and the nature of its attachment to surrounding tissue. The overall goal of this research is to develop a thin-film nanodevice, that is, electronic skin, that will convert the pressure distribution on physical contact to light that can be imaged directly on a digital camera at a resolution on par with the human finger (~20 μm). This tool will enable family physicians and other clinicians to screen patients who do not have access to the more expensive screening tools and avoid unnecessary exposure to radiation used in mammography.

The NIBIB is continuing to develop and support a research portfolio that pursues cutting-edge science in the area of women's health research. The NIBIB increased its commitment to women's health research from $7–8 million in 2005–2006 to more than $10 million in 2008.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Executive Summary

On December 21, 2007, the National Institute of Child Health and Human Development was renamed the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in recognition of Mrs. Shriver's vision and dedication, not only in helping to establish the Institute, but also

in leading continued efforts to advance the mission of the NICHD. The Institute's mission is to ensure that every child is born healthy and wanted; to ensure that women suffer no harmful effects from reproductive processes; to ensure that all children can achieve their full potential for healthy and productive lives, free from disease or disability; and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation. As indicated in the mission statement, the NICHD plays a unique role in women's health research, aiming to overcome many of the complex challenges that women encounter over their lifetimes, including challenges that affect the health of their children and families. Not only does the Institute support research on women's health, but it also conducts outreach and dissemination activities and develops press releases and publications to share information with the general public.

The NICHD supports a wide-ranging research portfolio in women's health, including research on oogenesis, ovarian failure, uterine fibroids, pelvic floor disorders, endometriosis, vulvodynia, infertility, contraception, HIV, menopause, violence, preconception care, obstetrical pharmacology, preterm birth, stillbirth, and many other aspects of women's health to improve the lives of women around the world. The NICHD's research efforts in women's health focus on understanding these and other conditions and how they affect women. The Institute also develops and evaluates different treatments for conditions and disorders affecting women's health. In addition, to maintain a cadre of researchers who focus on pressing women's health issues, the NICHD supports several research training and career development programs. Given that women's health issues may be related to a variety of other research areas, the Institute partners with many NIH Institutes, Centers, and Offices, as well as other Federal agencies to support its women's health research, training, and outreach activities.

NICHD research advances in women's health include, among others, reassuring millions of women with HIV worldwide that they can safely use an effective hormonal contraceptive while taking antiretroviral drugs. In fact, in another study, researchers showed that some common contraceptives do not appear to increase the risk of HIV infection in women. For women with polycystic ovary syndrome (PCOS) who are ready to have children and are seeking treatment for PCOS-induced infertility, NICHD-supported researchers have shown that the existing standard of treatment resulted in more pregnancies than a promising drug that is typically used to treat diabetes. In another study, investigators reported that gene variations in women with PCOS also affect how these women may respond to the promising drug.

Among its efforts to share the latest research findings in women's health and to include communities in research activities, the Institute continues to support outreach activities across the Nation and worldwide. Such efforts include addressing the impact of pregnancy on maternal obesity, preventing maternal mortality in developing countries, and preventing HIV transmission during pregnancy. The Institute also continues to partner with Federal, non-Federal, and community organizations to promote research and dissemination activities related to women's health. For instance, in recognition of the Institute's longstanding efforts to address the prevention and treatment of preterm birth, the Office of the Surgeon General selected the NICHD to lead the "Surgeon General's Conference on the Prevention of Preterm Birth." The 2-day conference convened on June 16, 2008, and resulted in a national action plan designed to prevent preterm birth in the United States.

The NICHD's women's health research accomplishments are wide ranging and address conditions across the life stages. Highlighted in this report are just some of the NICHD's recent activities related to women's health. The report is organized (1) to briefly summarize the NICHD organizations that focus on women's health, (2) to highlight some of the Institute's recent accomplishments and activities, across categories affecting women's health such as training and special populations, and (3) to list and briefly describe initiatives and conferences related to women's health, again across categories. By organizing the report in this manner, some information may be found in more than one section. Outreach and dissemination activities are also included throughout

the report. When available, hyperlinks are included for more information about specific activities. Additional information about the Institute's research on women's health is also available on the NICHD Web site at: http://www.nichd.nih.gov/womenshealth/womenshealth.cfm.

NICHD Organizational Components Focusing on Women's Health Research

The NICHD supports research and activities that promote women's health across its six major research components and through the NICHD Office of the Director (http://www.nichd.nih.gov/about/org/orgchart/).

The NICHD Office of the Director provides leadership for the scientific direction of the Institute. The NICHD Director and Deputy Director are committed to improving the lives of women, children, and families and have launched multiple initiatives dedicated to improving women's health. For instance, in 2007, to address the growing epidemic of maternal obesity, the Obesity Research Strategic Core was created to reduce maternal and childhood obesity. In addition, the NICHD Community Ambassadors partnership was established to increase minority patient recruitment and to identify community research interests. The partnership resulted in the successful recruitment of African-American women for an NICHD intramural study on fibroids. The Public Information and Communications Branch, housed in the Office of the Director, continues to conduct outreach efforts and to share information concerning women's health issues with the public. For example, for women's health month in May 2008, an NICHD Spotlight was developed to highlight the Institute's women's health research (http://www.nichd.nih.gov/news/resources/spotlight/052308_Womens_Health_Research.cfm).

The Center for Developmental Biology and Perinatal Medicine supports a broad range of research to advance fundamental and clinical knowledge about maternal health and problems of child development. Research efforts include studies on the factors that affect pregnant women and their unborn infants, such as the causes and consequences of fetal growth restriction, preterm labor and birth, and stillbirth. In 2007, the Center led the development of an international stillbirth classification system necessary for uniformity in reporting research results. The Center also supports a program on intellectual and developmental disabilities, which has partnered with other NICHD research programs to expand the portfolio of Fragile X research to study the associations between premature ovarian failure and Fragile X premutation carriers (http://www.nichd.nih.gov/about/org/cdbpm/).

The Center for Population Research supports a diverse range of population studies to understand reproductive health and biology, with the goal of alleviating human infertility and reproductive disorders. Reproductive sciences research includes studies 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 Center also continues to support a research network on pelvic floor disorders and created new funding opportunities to study chronic pelvic pain, including vulvodynia. In addition, a research program on contraception and reproductive health supports the development of a variety of contraceptive methods that are safe and effective, inexpensive and readily available, preferably reversible, and meet the diverse needs of women throughout their reproductive lives, including the need to prevent the spread of sexually transmitted diseases. In 2007, the Center renewed funding for a multicenter program to help translate basic research findings into clinical investigations that address important problems in reproductive medicine, including infertility. The center also supports demographic and behavioral sciences research to examine reproductive health issues (http://www.nichd.nih.gov/about/org/cpr/).

The Center for Research for Mothers and Children supports a vast array of maternal and child health research, including gestational diabetes; obesity; and HIV/AIDS in children, adolescents, and women. The Center also funds research that examines the mechanisms of cognitive, social, emotional, and neurobiological development, as well as the influences

of genetics, nutrition, the environment, and life experiences on overall physical growth and the development of health promotion and disease prevention strategies. Such research may show gender differences during development. The Center is home to unique clinical networks that include research specifically targeting obstetrical pharmacology. Also critical in protecting women's health is a program that supports research in the epidemiology, natural history, pathogenesis, transmission, and treatment of HIV infection and disease in women of childbearing age and pregnant women, as well as in infants, children, adolescents, and families (http://www.nichd.nih.gov/about/org/crmc/).

The NICHD Division of Epidemiology, Statistics & 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 factors that increase risks of motor vehicle crashes for girls and boys, and coping with such diseases as diabetes in a family context (http://www.nichd.nih.gov/about/org/despr/).

The NICHD Division of Intramural Research conducts interdisciplinary and interactive research to answer basic biomedical research questions and solve difficult clinical problems in female reproduction and development. This includes research in genetics, genomics (the study of how genes function), and epigenetics (DNA-associated, heritable switches that can affect gene function) and how these influence normal and abnormal development. The intramural program also studies the basic biophysical mechanisms underlying cell and tissue function, early development, and the prevention and treatment of conditions of female reproduction, through innovative diagnostics and therapies. In 2007, the intramural program completed its reorganization to enhance efficiency and collaborations between clinical and "bench" scientists and to stimulate closer interaction between scientists with diverse backgrounds. This included creating a new program focusing on women's health issues, such as ovarian function and processes that lead to successful fertilization and infertility treatment. The Program in Reproductive and Adult Endocrinology examines research areas such as endometriosis, fibroids, infertility, and endocrine aspects of disease—both basic and clinical. More information about the studies being conducted in this and other women's health-related research programs is available at the NICHD Division of Intramural Research Web page (http://dir.nichd.nih.gov/dirweb/home.html).

Accomplishments

Pelvic Floor Disorders

One-Quarter of U.S. Women Affected by Pelvic Floor Disorders

In the first nationally representative sample, NICHD researchers found that 24 percent of U.S. women are affected by one or more pelvic floor disorders, which are a cluster of health problems that cause physical discomfort and limit activity, including some serious health issues. Pelvic floor disorders—urinary incontinence, fecal incontinence, and pelvic organ prolapse—occurs when the muscles and connective tissue within the pelvic cavity holding the bladder, uterus, bowel, and rectum weaken or are injured. Pressure and protrusion of the pelvic organs through the vaginal canal may make physical activity difficult, and may interfere with sexual functioning. Researchers found an increase in frequency of pelvic floor disorders with older age, higher body mass index (BMI), and greater number of times a woman had given birth. They did not find any differences in pelvic floor disorders based on race, ethnicity, or level of education achieved. The current treatment for pelvic floor disorders varies with the severity of symptoms. Treatment may involve behavioral therapies, exercises to strengthen muscles, vaginal devices to hold up the bladder or other pelvic organs, medications, or surgery. Funding for this study was provided by the NICHD, National Institute of Diabetes and Digestive and Kidney Diseases,

and NIH Office of Research on Women's Health (ORWH), and by the National Center for Health Statistics of the Centers for Disease Control and Prevention (http://www.nichd.nih.gov/news/releases/sep091608_PFV.cfm).

Polycystic Ovary Syndrome

Gene Variation Predicts Response to Treatment in Common Infertility Disorder—Polycystic Ovary Syndrome

PCOS is the leading cause of infertility in women, affecting 8 to 15 percent of American women of reproductive age. Along with infertility and cyst-like structures in the ovaries, women with PCOS are at higher risk for diabetes, heart disease, high blood pressure, excess hair growth, and acne. Obese women are more likely to develop the condition. Metformin is a new, promising drug treatment for some women with the condition and the drug is thought to increase fertility by increasing ovulation patterns. NICHD-supported researchers discovered that women with PCOS are less likely to ovulate in response to metformin if they have a variation in the gene involved in controlling blood sugar levels, STK (serine-threonine kinase) 11. Researchers found that metformin lowers blood sugar levels and may be used as a treatment for PCOS; however, the study results also showed that women's response was dependent on how many copies of the variant gene they possessed. The next step for the researchers is to conduct a genetic analysis on a large sample of women to try to find out how frequently the gene variant occurs in the population and to distinguish women who would be unlikely to ovulate in response to metformin from those likely to ovulate. Funding for the study was provided by the NICHD and the National Center for Research Resources (http://www.nichd.nih.gov/news/releases/gene_variation_040108.cfm).

Standard Therapy More Effective Than Diabetes Drug for Achieving Pregnancy in Polycystic Ovary Syndrome

For women with PCOS who are seeking to have children, treatments have been limited to metformin and clomiphene. Women with PCOS frequently experience insulin resistance, and metformin is thought to make the body more sensitive to insulin, therefore increasing ovulation. Clomiphene fosters ovulation by stimulating the release of hormones needed for ovulation, resulting in multiple mature ovarian follicles. NICHD researchers conducted the largest, most comprehensive effort yet to compare metformin and clomiphene in helping women with PCOS achieve successful pregnancy. Researchers randomly assigned infertile women with PCOS for 6 months to one of three groups: (1) clomiphene and a placebo, (2) metformin and a placebo, and (3) both metformin and clomiphene. Researchers found that fewer women in the metformin-only group had given birth than had women in either of the clomiphene groups. Women in the combination therapy group ovulated more frequently than did the women in either the clomiphene-alone or the metformin-alone groups. However, the tendency to ovulate more frequently did not translate into a significantly greater number of pregnancies for the combination group. Women who ovulated while taking clomiphene were twice as likely to become pregnant than a woman ovulating on metformin. Women in the clomiphene groups had more occurrences of multiple pregnancies because of stimulation of multiple ovarian follicles. The study results support the use of clomiphene citrate alone as first-line therapy for infertility in women with PCOS. The NICHD and the National Center for Research Resources supported the study (http://www.nichd.nih.gov/news/releases/pcos_treatments.cfm).

Polycystic Ovary Syndrome (PCOS): Beyond Infertility Booklet

The NICHD created a 32-page booklet describing the common symptoms, features, and other disorders associated with PCOS, the most common cause of infertility in the United States. The booklet also describes some of the ongoing research conducted and supported by the NICHD on PCOS and provides contact information for organizations that can provide additional information, services, and support to women affected by PCOS and their families (http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5699).

Pregnancy

Maternal Diabetes in a Mouse Model Affects Egg Quality and Can Lead to Developmental Malformations

Diabetes is a chronic disease that can lead to complications throughout the body and its effects can even be seen in birth outcomes. Types 1 and 2 diabetic women are three to four times more likely to have children with neural tube, skeletal, and cardiovascular defects than nondiabetic women even with close monitoring and glucose control. Researchers hypothesize that diabetes may affect the quality of a woman's eggs prior to or around the time of fertilization, just as diabetes has an effect on a wide variety of cells and organs throughout the body. NICHD-supported scientists induced diabetes in female mice to expose the ovaries and their eggs to a diabetic environment immediately preceding and at the time of fertilization. The newly fertilized eggs were removed and transferred to nondiabetic surrogate female mice. The developing fetuses were then examined and found to have higher rates of growth retardation and malformations such as neural tube closure defects and abdominal wall and limb deformities, compared to those that had not been exposed to a diabetic environment. These findings are the first to show that acute exposure to a diabetic environment in vivo, limited only to the egg stage, can lead to abnormalities during fetal development. The findings raise the question, in humans, of what impact long-term maternal diabetes may have on egg quality, in addition to its effects on fetal development. Even more stringent control and management of diabetes over a longer period of time before pregnancy may be needed to lessen the effects that diabetes can have on egg quality. One-cell zygote transfer from diabetic to nondiabetic mouse results in congenital malformations and growth retardation in offspring (Wyman, A. et al. *Endocrinology* 149: 466-469, 2008).

Mothers' High Normal Blood Sugar Levels Place Infants at Risk

Diabetes occurs in roughly 5 percent of all pregnancies in the United States. Babies born to mothers with diabetes are at higher risk of prenatal complications and for obesity, high blood pressure, and heart disease when they reach adulthood. Until now, physicians were not certain at which point elevated maternal blood sugar posed a risk for the baby. NICHD-supported researchers have conducted the first study to document that the higher the blood sugar levels (even if they are not high enough to be considered diabetes), the greater the risks for both mother and baby. Mothers with higher blood sugar levels were more likely to have infants with high insulin levels and low blood sugar levels at birth. Moreover, the higher the mother's blood sugar levels, the higher the risk for preeclampsia, preterm birth, and shoulder dystocia (a condition occurring during birth, in which an infant's shoulder becomes lodged inside the mother's body, effectively halting the birth process). Researchers were unable to identify a precise level where an elevation in blood sugar increased the risk for any of the outcomes observed in the study. Rather, the chances for the observed outcomes increased gradually, corresponding with increases in the women's blood sugar levels. The increased risks due to higher blood sugar levels existed even when researchers controlled for other potential causes of risks, including older maternal age, obesity, and high blood pressure. Funding for this study was provided by the NICHD, National Institute of Diabetes and Digestive and Kidney Diseases, National Center for Research Resources, and the American Diabetes Association (http://www.nichd.nih.gov/news/releases/may072008-highBloodSugar.cfm).

Older Mothers More Likely Than Younger Mothers To Deliver by Cesarean

The National Center for Health Statistics report that, between 1980 and 2004, the number of women in the United States giving birth at age 30 or older doubled, at age 35 and older tripled, and at age 40 or older nearly quadrupled. The risk of delivery complications increases with the mother's age, as does the risk of premature birth and infant death. Such complications include excessive bleeding during labor, prolonged labor lasting more than 20 hours, and dysfunctional labor that does not advance to the next stage. It has long been speculated that older women undergo cesarean section at higher rates than younger

women. NICHD-supported researchers examined over 8 million U.S. birth certificates and discovered that overall, pregnant women over age 35, despite race and smoking status, were at higher risk for complications during pregnancy and delivery and more likely to undergo cesarean delivery than were mothers who were younger. Whether or not the women had previously given birth also affected their risk of certain complications. Regardless of age, women giving birth for the first time were much more likely to deliver by cesarean section, even when their pregnancies were low risk (full-term infants without birth defects, with a normal, head-down presentation, and in the absence of any bleeding complications). Women over 40 were also at greatest risk for excessive bleeding during labor, premature delivery, and cesarean delivery. Plus, women giving birth at age 45 or older were most likely to have high blood pressure and diabetes while pregnant. The researchers concluded that the chance of cesarean delivery in all pregnancies increased with women's age and include even pregnancies deemed low risk (http://www.nichd.nih.gov/news/releases/caesarean_release_030807.cfm).

Experimental Vaccine Given During Pregnancy Reduces Stillbirths from Common Virus—Cytomegalovirus (CMV)

NICHD researchers have developed an experimental vaccine that reduces stillbirths among rodents born to females infected with CMV. CMV is a common viral infection in the human population. It is present in bodily secretions and spread through close personal contact. It can cause mental retardation and hearing loss in newborn children who were infected in early fetal life. Estimates place the number of U.S. children born with CMV each year at about 40,000, and there is no vaccine or treatment for pregnant women who have the infection. Researchers found 10 to 15 percent of babies with congenital CMV have a long-term disability such as mental retardation, cerebral palsy, and hearing loss. The virus can also damage the placenta, leading to pregnancy loss. The experimental CMV vaccine prototype differs from traditional vaccines, which are made from a whole killed virus. Called a vector vaccine, the experimental vaccine uses an altered virus to deliver one gene from the viral DNA to the animal's cells. The cells then begin manufacturing the viral protein. Cells of the rodent's immune system detect the viral protein and launch an attack against it. In so doing, they learn to recognize CMV. The young female rodents in the study were vaccinated three times at 2-month intervals before they became pregnant and were injected with the rodent form of CMV early in their third trimester. Tests showed that the rodents given the experimental vaccine had acquired immunity to rodent CMV because they produced antibodies to the virus. Female rodents given the CMV vaccine before becoming pregnant gave birth to fewer dead pups (13 percent versus 57 percent mortality rate) and were less likely to transmit the infection to their offspring than were female rodents that did not receive the vaccine. Researchers also found that the surviving pups weighed more than the pups of mothers that did not receive the CMV vaccination before becoming pregnant. Further research is needed to identify potential uses for human benefit (http://www.nichd.nih.gov/news/releases/experimental_vaccine_during_pregnancy.cfm).

Preterm Birth

The Surgeon General's Conference on the Prevention of Preterm Birth

The NICHD led this conference and convened leaders in the field of preterm birth on June 16–17, 2008, in Rockville, MD. Congress directed the Office of the Surgeon General to hold a conference that would establish an agenda "for activities in both the public and private sectors that will speed the identification of, and treatments for, the causes of and risk factors for preterm labor and delivery." The agenda called for a national system to better understand the occurrence of preterm birth and a national education program to help women reduce their chances of giving birth prematurely. Conference participants established an agenda that covered six general topic areas: biomedical research, epidemiological research, psychosocial and behavioral considerations, professional education and training, public communications and outreach, and quality of health care and health services.

The Office of the Surgeon General will examine the conferees' findings to determine how to best move forward and consider how these findings relate to ongoing efforts in the field. In addition to the NICHD and the Office of the Surgeon General, the ORWH, the Office on Women's Health at the Department of Health and Human Services (HHS), and other professional and community organizations provided support for the conference (http://www.nichd.nih.gov/news/releases/june192008_Surgeon_Generals_Agenda.cfm).

Common Treatment (Magnesium Sulfate) To Delay Labor Also Decreases the Risk for Cerebral Palsy in Preterm Infants

Cerebral palsy is a group of neurological disorders affecting control of movement and posture. Almost one-third of children with cerebral palsy are born preterm. It has long been theorized that magnesium sulfate, when given to pregnant women delivering prematurely, might help protect preterm infants from cerebral palsy by stabilizing blood vessels, preventing damage from oxygen depletion, and avoiding injury from swelling and inflammation. To rigorously evaluate whether the magnesium sulfate treatment could prevent cerebral palsy in preterm infants, researchers conducted a randomized clinical trial through the NICHD Maternal Fetal Medicine Units (MFMU) Network, which included 20 centers across the United States. The women were from 24 to 31 weeks pregnant and at risk for preterm delivery. When the women went into labor, they were assigned at random to receive either magnesium sulfate or a placebo. Researchers found that a higher proportion of children born to mothers in the placebo group had cerebral palsy than did children born to mothers who received magnesium sulfate. Death rates occurring in the magnesium sulfate group did not differ significantly from those in the placebo group. The study findings showed that preterm infants born to mothers receiving intravenous magnesium sulfate—a common and inexpensive treatment to delay labor—are less likely to develop cerebral palsy than are preterm infants whose mothers do not receive it. The study findings may help reduce the number of children born with cerebral palsy, a condition that leaves individuals with serious lifelong disabilities. The NICHD and the National Institute of Neurological Disorders and Stroke supported this study (http://www.nichd.nih.gov/news/releases/aug272008_magnesium_sulfate.cfm).

Progesterone Treatment Does Not Prevent Preterm Birth in Twin Pregnancy

Women pregnant with twins are at higher risk for preterm birth than are other pregnant women, with more than half delivering prematurely. Researchers at the NICHD MFMU Network reported in 2003 that weekly injections of progesterone reduced the risk of preterm birth by 34 percent among pregnant women who had given birth prematurely in an earlier pregnancy. Many physicians then began prescribing the therapy for pregnant women with twins without evidence that progesterone treatment was effective in these groups. MFMU Network researchers have now shown that progesterone therapy does not reduce the chances of preterm birth in women pregnant with twins. The study included 655 pregnant women with twins who were randomly assigned to receive weekly injections (from 16 weeks to 35 weeks) of a placebo or progesterone known as 17-alpha hydroxyprogesterone caproate (17-OHPC). The use of progesterone did not reduce premature birth in twin pregnancies when compared with the placebo group. However, the study could not determine whether progesterone therapy could potentially reduce the chances of preterm birth in women pregnant with twins who had delivered prematurely in a previous pregnancy. The findings indicate that progesterone therapy is not effective for all women who are at risk for giving birth prematurely. Additional studies are needed to test progesterone in other groups of women who are at risk for preterm birth, such as women with shortened cervixes and women pregnant with triplets (http://www.nichd.nih.gov/news/releases/prevent_preterm_birth_080207.cfm).

Obesity

Excess Fat Around Waist May Increase Risk of Death for Women

Researchers found that women who carry excess fat around their waists were at greater

risk of dying early from cancer or heart disease than were women with smaller waistlines, even if they were of normal weight. In 2004, over one-half of U.S. adults had abdominal obesity (over 35 inches for women, over 40 inches for men). Previous studies have shown that the tendency to deposit fat around the waist increases the risk for health problems. NICHD researchers conducted the largest, most comprehensive study of its kind, analyzing data from more than 44,000 women in the Nurses' Health study, which followed the health history of thousands of registered nurses in 11 States. At the beginning of the study, the women were asked to measure their waists and hips. Every 2 years, the women completed questionnaires about their health, providing information about their age, activity level, smoking status, diet, blood pressure, and cholesterol levels. Researchers examined the cause of death for all women who died over the course of the study. In total, 3,507 deaths occurred—of these, 1,748 were due to cancer and 751 were due to heart disease. Women with a waist size equal to or greater than 35 inches were approximately twice as likely to die of heart disease and of cancer as were women with a waist size of less than 28 inches, regardless of their body mass index (BMI). The researchers also examined the waist-to-hip ratios and found it to be as strongly associated with risk of early death as the measurement of waist size alone. Because the majority of the women who took part in the study were White, researchers do not know if their findings pertain to other groups of women or to men and they call for future studies to investigate abdominal obesity and the risk of death in other ethnic groups and in men. Funding for the study was provided by the NICHD, National Institute of Diabetes and Digestive and Kidney Diseases, and National Cancer Institute. The Nurse's Health Study was supported by the National Heart, Lung, and Blood Institute (http://www.nichd.nih.gov/news/releases/april07_2008.cfm?from=women).

Obesity Strategic Research Core

The NICHD is leading the way to develop and implement a multilevel public health approach to address the issue of maternal as well as childhood obesity that encompasses new research directions, new training activities, and new partnerships and alliances with domestic and global organizations that share the same cause. To increase the NICHD's visibility in the fight against childhood and maternal obesity and to provide the Institute with greater opportunity to move the field ahead, the Institute created the NICHD Obesity Research Strategic Core (ORSC) in the Office of the Director. The ORSC will (1) lead a multilevel, integrative approach to childhood and maternal obesity by coalescing obesity research and translation activities across the NICHD; (2) serve as an advisory body on future directions of obesity-related activities; (3) coordinate and facilitate the implementation of an agenda with broad domestic and international impact on childhood obesity; and (4) serve as a resource for cross-disciplinary, systems research on complex public health issues.

HIV/AIDS

Women's Response to Anti-HIV Therapy Improved If Treatment Began 6 Months After an Earlier Preventive Regimen

In an earlier NICHD-supported study in Botswana, researchers showed that a single dose of nevirapine given during labor was effective at preventing mother-to-child transmission of HIV. Nevirapine is an inexpensive drug and is now commonly used in resource-poor countries to reduce the number of children born with HIV. The drug is also one of several drugs used in combination antiretroviral therapies for adults with HIV in resource-poor settings. Health professionals have questioned whether administration of the single dose of nevirapine during labor reduced the efficacy of antiretroviral therapy for the mother at a later time. To address this concern, researchers conducted a followup study and recruited 218 women who required antiretroviral therapy for their own health. After receiving antiretroviral therapy for at least 6 months, the level of HIV in the women's blood was assessed. Researchers found that the women who had received nevirapine during labor and who required antiretroviral therapy within 6 months after delivery still had detectable HIV levels. Conversely, the women who received a placebo during labor and who

required antiretroviral therapy 6 months after delivery did not have detectable HIV levels. Plus, the researchers found that regardless of whether women received nevirapine or placebo, if the women received antiretroviral therapy 6 months or more after delivery, they did not have detectable levels of HIV. The findings indicate that nevirapine-based antiretroviral therapy is a viable option for women who require treatment 6 months or more after receiving single-dose nevirapine during labor. However, women given single-dose nevirapine who require antiretroviral therapy treatment before 6 months should receive antiretroviral therapy that does not include nevirapine. NIH support for the study was provided by the NICHD and the John E. Fogarty International Center for Advanced Study in the Health Sciences (http://www.nichd.nih.gov/news/releases/nevirapine_therapy.cfm).

Women With HIV on Antiretroviral Therapy May Use DMPA Safely

Despite significant advances in antiretroviral treatments for HIV/AIDS, very little information was known about how hormonal contraceptives and antiretroviral drugs interact in women with HIV. NICHD-supported researchers investigated the interactions between Depo-medroxyprogesterone (DMPA), a popular progesterone-based injectable contraceptive given every 3 months, and selected antiretroviral agents, tracking any changes in the metabolism of both the DMPA and antiretroviral drugs, and assessed the safety of the DMPA in women with HIV. In the groups of women on antiretroviral therapy, researchers also assessed the antiretroviral levels over a 12-hour period before DMPA injection and then again 4 weeks later. The study results showed that DMPA remained at effective levels across groups for the 12 weeks after the injection without significant changes in HIV RNA levels or CD4+ cell counts. Side effects were similar to those in women without HIV and no pregnancies resulted after DMPA injection. These findings can reassure women with HIV, worldwide, who are of reproductive age and who are on antiretroviral therapy that there are effective hormonal contraceptive options for pregnancy prevention (Cohn, S.E., et al. *Clinical Pharmacology and Therapeutics* 81(2):222-227, 2007; Watts, D.H., et al. *Contraception* 77(2):84-90).

Hormonal Contraception Does Not Appear To Increase HIV Risk

More than 100 million women worldwide use hormonal contraceptives and over 18 million women are infected with HIV (transmission occurs mostly during heterosexual intercourse). Studies to date had been inconclusive about the impact of hormonal contraceptives on HIV risk. The NICHD commissioned a large study recruiting women without HIV seeking family planning services in Uganda, Zimbabwe, and Thailand to investigate the risk of HIV infection for women using the most commonly prescribed forms of hormonal contraception. The women were examined and treated for sexually transmitted infections and were offered their choice of contraceptive methods, either oral contraceptives or DMPA, as well as condoms. In all, 6,109 women participated in the study: 2,235 in Uganda; 2,296 in Zimbabwe; and 1,578 in Thailand. The women were tested for HIV four to five times a year, for 15 to 24 months. At the end of the study, 213 African women and only 4 Thai women had tested positive for HIV. The Thai cases were excluded from final analysis because of too few numbers for valid statistical interpretation. Researchers found no evidence that the use of hormonal contraceptives increased a woman's chances of becoming infected with HIV. The study could not rule out an increased risk for HIV infection among "highly exposed" hormonal contraceptive users such as sex workers. Researchers, however, did find that in this study, women using hormonal contraceptives with genital herpes had a lower risk of acquiring HIV when compared to women without genital herpes. The researchers agree that additional research is needed to confirm and explain why this was the case because previous studies have found genital herpes to be a risk factor for acquiring HIV (http://www.nichd.nih.gov/news/releases/hormonal_contraception.cfm).

International Women's Health

Intensive Training for Medical Staff in Latin American Hospitals Reduces Serious Complications of Pregnancy

The Global Network for Women's and Children's Health Research, a public–private partnership between the NICHD and the Bill and Melinda Gates Foundation, funded a clinical intervention study at 19 hospitals in Argentina and Uruguay. Additional funding for the study was also provided by the National Institute of Diabetes and Digestive and Kidney Diseases. The study showed that by training professionals to administer oxytocin to all women after vaginal delivery, to contract the uterus and stop uterine bleeding, and to reduce the incidence of episiotomies, a dramatic reduction in the rate of postpartum hemorrhage could be achieved. Leaders from 10 hospitals (physicians, midwives, and residents) were identified and invited to attend a 5-day workshop on how to develop and carry out guidelines for physicians and midwives based on the best scientific evidence. The leaders also developed evidence-based guidelines recommending against the routine use of episiotomy, considering risks such as blood loss, infection, and subsequent impairment of sexual functioning. The remaining nine hospitals in the study served as controls and did not receive any instruction in labor management techniques or for communicating with their peers. At the end of 18 months, the study data showed that oxytocin use increased from 2.1 percent of births before the trial began to 83.6 percent at the 10 intervention hospitals and by comparison, oxytocin use increased from 2.6 percent to 12.3 percent at the control hospitals. Episiotomies decreased from 41.1 percent of births to 29.9 percent at hospitals receiving the staff instruction and increased slightly at control hospitals, from 43.5 percent to 44.5 percent. The hospitals where the staff received the instruction had a 45 percent reduction in postpartum hemorrhages. The change in oxytocin use was much larger than the change in episiotomy use, suggesting that getting health professionals to adopt a new practice may be easier than getting them to eliminate an established practice (http://www.nichd.nih.gov/news/releases/may072008-latinAmStaffTraining.cfm).

Tobacco Use and Secondhand Smoke Exposure During Pregnancy May Threaten Health of Women and Children in Developing Nations

Pregnant women are a priority population for tobacco prevention efforts because tobacco use poses serious risks to fetal and maternal health. Findings from a study conducted by the NICHD and the National Cancer Institute indicate that rates of tobacco use during pregnancy, as well as exposure of pregnant women and their young children to secondhand smoke, are significant threats to health in several low- and middle-income countries. Researchers conducted the study at 10 sites in the NICHD Global Network for Women's and Children's Health Research, which focuses on improving maternal and child health in the developing world. Approximately 8,000 pregnant women were surveyed at five sites in Latin America (Argentina, Uruguay, Ecuador, Brazil, and Guatemala), two sites in Africa (Zambia and the Democratic Republic of the Congo), and three sites in Asia (two in India and one in Pakistan). The researchers found as many as 18 percent of pregnant women currently smoked cigarettes, up to one-third used smokeless tobacco, and as many as half were regularly exposed to secondhand smoke in the nations studied. Uruguay and Argentina had the highest levels of smoking during pregnancy across all 10 study sites (18 percent and 10 percent, respectively). At the Indian sites, one-third of all pregnant women used smokeless tobacco in Orissa and about 20 percent of pregnant women in Karnataka were often exposed to secondhand smoke. The highest levels of secondhand smoke exposure were found in Pakistan, where about half of all pregnant women and their young children were frequently or always exposed to secondhand smoke. Where tobacco use rates are still low, there is the opportunity to avert an increase in tobacco use among women, especially pregnant women, in the developing world. The data highlight the urgent need to adopt proven measures to prevent and control tobacco use and secondhand smoke exposure of women and girls worldwide (http://www.nichd.nih.gov/news/releases/tobacco_022808.cfm).

Activities in Selected Areas of Women's Health

Uterine Fibroids

- **Leiomyomata Uteri: Basic Science, Translational, and Clinical Research (PAR-08-102)**
  The NICHD, with support from the National Institute of Environmental Health Sciences and the ORWH, are encouraging research with the goal of transforming advances in our understanding of the molecular basis of leiomyomata uteri (uterine fibroids) into new therapeutic options for prevention and treatment of this common gynecologic disorder (http://grants.nih.gov/grants/guide/pa-files/PAR-08-102.html).

- **Cooperative Reproductive Science Research Centers at Minority Institutions Program**
  The Institute, in collaboration with the ORWH and the National Center for Research Resources, is supporting a clinical research study on uterine fibroids at Meharry Medical College, which may help researchers find answers for the condition's increased prevalence rates in minority women (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-06-017.html).

- **Women's Reproductive Health Research (WRHR) Career Development Program**
  In collaboration with ORWH, the NICHD is supporting an ongoing training and career development program for junior physician scientists. One of the WRHR scholars is currently conducting a research project with an emphasis on uterine fibroids (http://www.wrhrscholars.org/index.html).

- **Reproductive Medicine Clinical Trials Network**
  The NICHD continues to support this Network, which is poised to conduct randomized clinical trials on novel therapeutic interventions to treat fibroids, and through its intramural program, has already begun a fibroid tissue bank that will promote research on fibroid disease by providing access to tissue samples for NIH-funded investigators throughout the world. The ORWH is also collaborating in this effort (http://www.nichd.nih.gov/research/supported/rmn.cfm).

- **NICHD Uterine Fibroid Research Update Workshop (September 2007)**
  NICHD scientists have continued to examine the mechanisms responsible for uterine fibroid development and growth through basic, translational, and clinical research studies. The Institute, in collaboration with the ORWH, sponsored a workshop to provide a forum for NICHD intramural and extramural investigators to share current knowledge and recent findings, and to explore future directions in uterine fibroid research. The major objective of the workshop was to foster ongoing communication and stimulate future collaborations.

- **Defining a Classification System for Uterine Leiomyoma (September 2007)**
  Uterine leiomyoma (uterine fibroids) are a common gynecologic disorder that can cause infertility, irregular bleeding, and chronic pain. The NICHD assembled a panel of expert investigators to begin developing a standardized classification system for uterine fibroids to ensure standard research protocols for future research.

Vulvodynia

- **Vulvodynia Awareness Campaign and Hope Packet**
  The ORWH, with cosponsorship from the NICHD and other organizations, launched the Vulvodynia Awareness Campaign on October 24, 2007. A press conference was held at the National Press Club to combine efforts with partners, including advocacy groups, healthcare practitioners, research organizations, and Federal and non-Federal entities to increase awareness and understanding of vulvodynia. The ORWH and cosponsors created the Vulvodynia: Research, Resources, Treatment, Hope packet as a resource for women suffering from vulvodynia. The packet includes fact sheets and overview information about vulvodynia, resources for women who have been diagnosed with or who believe they have vulvodynia, and scientific journal articles about the latest research on the disorder. In addition, the NICHD

participated in an ORWH Podcast focused on vulvodynia awareness (http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5692).

- **Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (PA-07-182)**
  The NICHD, in partnership with the ORWH, is encouraging investigators to expand its research base in basic, translational, and clinical studies on vulvodynia to build a substantive scientific knowledge base of this debilitating condition (http://grants.nih.gov/grants/guide/pa-files/PA-07-182.html).

Endometriosis

- **The Art and Science of Endometriosis: Standardizing the Measurement of Pain and Diagnostic Criteria (October 2006)**
  Endometriosis is an enigmatic condition affecting millions of women worldwide. It is defined as the presence of functioning, endometrial-like tissue outside the uterus, which often induces a chronic, inflammatory reaction and is predominantly found in women of reproductive age, from all ethnic and social groups. The NICHD convened a conference in New Orleans to develop a consensus regarding the most appropriate entry criteria, outcomes, and management tools for clinical studies assessing treatments for endometriosis-associated pain (http://endometriosis-conference.nichd.nih.gov/).

Obstetric Pharmacology

- **Obstetric-Fetal Pharmacology Research Unit (OPRU) Network**
  The NICHD Obstetric-Fetal Pharmacology Research Unit Network was established, with support from the ORWH, to provide the expert infrastructure needed to test therapeutic drugs during pregnancy. The network allows researchers to conduct a whole new generation of safe, technically sophisticated, and complex studies that will help clinicians protect the health of women, while improving birth outcomes and reducing infant mortality.

- **Obstetrical Pharmacology Research Network—Data Coordination and Analyses Center (HD-07-019)**
  The NICHD is establishing a data coordinating and analyses center for the OPRU Network. The OPRU currently consists of four clinical research sites to carry out pharmacology research to enhance understanding of obstetrical pharmacokinetics and pharmacodynamics, and improve appropriate therapeutics during pregnancy (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-07-019.html).

- **Collaborative Meeting for the Obstetric Pharmacology Research Unit and the Pediatric Pharmacology Research Unit (PPRU) Networks (July 2007)**
  The OPRU and PPRU network scientists met during a 1½-day meeting to discuss common themes, review historical and current research activities in each network, and establish potential areas of cooperation between the two networks. The two networks identified several substantive areas that require increased emphasis, including but not limited to investigator-initiated research into therapeutics, an increased emphasis on obstetric pharmacology research, and training grants to develop new obstetric and pediatric pharmacologists.

- **Third 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 week-long course targeted at clinical and nonclinical scientists considering academic careers in studying therapeutics during pregnancy, the perinatal period, and lactation. Partners include the 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 fosters the development of a critical mass of

researchers and clinicians in the neglected area of maternal-fetal pharmacology (http://www.nichd.nih.gov/about/meetings/2007/080407.cfm).

Stillbirth

▶ **Stillbirth Collaborative Research Network (SCRN)**
This NICHD network is engaged in a study that will obtain a geographic, population-based determination of the incidence of stillbirth—defined as fetal death at 20 weeks gestation or greater—and determine the causes of stillbirth using a standard stillbirth postmortem protocol. The ORWH has also provided funding to support network studies. The SCRN provides an opportunity to diagnose and classify a large number of stillbirths with extensive information on each case to compare with live-born infants. In October 2007, the NICHD convened a workshop entitled "Stillbirth Classification System: Developing an International Consensus for Research," cosponsored by the Society for Maternal-Fetal Medicine, First Candle, and the NIH Office of Rare Diseases (https://scrn.rti.org/).

Violence

▶ **Research on Teen Dating Violence (December 2007)**
The HHS Office on Women's Health and NIH cosponsors, including the ORWH and NICHD, informed a meeting to build consensus on research and to develop a practical definition of teen dating violence. Experts discussed and reviewed current methods, measurements, and outcomes used for quantifying and defining teen dating violence, both in research and in practice, and examined the status of current research, both basic and applied on teen dating violence (http://www.ojp.usdoj.gov/nij/topics/crime/violence-against-women/workshops/teen-dating-violence-agenda.htm).

The NICHD also supports research concerning violence against women, especially in the area of women's reproductive health. Such studies include, among others, the following:

- Identifying the factors related to violence against wives, by both husbands and other family members, which lead to pregnancy complications and adverse postpartum maternal and infant health. The findings may be used to develop recommendations for family and clinic-based intervention programs.

- Examining patterns of abuse against women before, during, and after pregnancy, and the subsequent effects of domestic violence and prenatal stress on the risk of preterm birth and slowed fetal growth. The findings will help determine if the risk for domestic violence increases during certain periods related to pregnancy and if prenatal stress, in conjunction with domestic violence, results in poor pregnancy outcomes.

- Analyzing the impact of women's relative earnings on the prevalence of abuse against women. The study is designed to examine the impact of domestic violence on maternal and child health and the potential mitigating effects of economic resources. A better understanding of both the causes and consequences of abuse against women will help to inform domestic violence policies.

Training and Career Development

▶ **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 (http://www.asrm.org/Media/misc_announcements/CREST.html).

- **Women's Reproductive Health Research Career Development Program**
  This career development program was initiated by the NICHD in 1998 in response to concerns about the need for greater numbers of obstetrician-gynecologist physician scientists performing research on women's health. The ORWH and the National Cancer Institute collaborated with NICHD to support this program. This ongoing initiative addresses a continued need for bridging clinical training with an independent career in research addressing women's health concerns. Program sites provide departments of obstetrics and gynecology with an opportunity to build a talented pool of junior investigators in women's health research. The program also hosts research symposia to bring together junior faculty appointed to the program and established investigators to address the full spectrum of research in obstetrics and gynecology from basic science to clinical applications. Such meetings allow scholars to present their research, be exposed to the broad area of reproductive science, and seek opportunities for future collaborations (http://www.wrhrscholars.org/).

- **Extramural Loan Repayment Program for Contraception and Infertility Researchers (PA-07-438)**
  The NICHD established this program to invite qualified health professionals who agree to engage in contraception and/or infertility research for at least 2 years, and who agree to engage in such research for at least 50 percent of their work schedule. The objective of the program is to recruit and retain highly qualified health and/or allied health professionals as contraception and infertility research investigators with the long-range objective of evaluating, treating, or ameliorating conditions that pose challenges for couples to either conceive or give birth to children (http://grants.nih.gov/grants/guide/pa-files/PA-07-438.html).

- **Extramural Associates Summer Residency Workshop**
  Since 1978, the Extramural Associates Program has supported research infrastructure development for women and minority institutions. The workshop includes training international grantees on NIH policy and procedures, compliance and regulatory issues, and grantsmanship. The domestic grantees are joined by their international colleagues from India, Kenya, Uganda, and South Africa for a 10-week training program that takes place primarily on the NIH campus, with selected visits to other Federal and international agencies (http://www.nichd.nih.gov/about/org/dsp/ea/eap.cfm).

- **Americas Fellowship in Reproductive Sciences**
  The NICHD, with cosponsorship from the Fogarty International Center, developed the Americas Fellowship in Reproductive Sciences Program to provide a unique opportunity to qualified Latin American reproductive scientists, at junior or mid-career level, to receive up to 3 years of research training in the United States or Canada. The objective of the program is to prepare researchers for future leadership positions in research, academia, or public health institutions in their home country. The broader goal of the program is to strengthen the human resource capital of reproductive sciences research in Latin American institutions. It is hoped that the funding support will enhance the quality and quantity of international exchange in reproductive sciences research, while fostering long-lasting collaborations between Latin American and North American countries.

- **Third 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 week-long course targeted at clinical and nonclinical scientists considering academic careers in studying therapeutics during pregnancy, the perinatal period, and lactation. Partners include the 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 fosters the development of a critical mass of researchers and clinicians in the neglected area of maternal-fetal pharmacology (http://www.nichd.nih.gov/about/meetings/2007/080407.cfm).

- **Building Interdisciplinary Research Careers in Women's Health**
  The ORWH, in collaboration with the NICHD, other NIH Institutes and Offices, and the Agency for Healthcare Research and Quality, organized a research and training symposium to highlight research advances of the ORWH Building Interdisciplinary Research Careers in Women's Health (BIRCWH) and the Specialized Centers of Interdisciplinary Research on Sex and Gender Factors Affecting Women's Health (SCOR) programs. Institutional career development awards for the BIRCWH program support the mentored-research career development of junior faculty members, known as BIRCWH Scholars. These scholars, who recently completed clinical training or postdoctoral fellowships, are engaged in interdisciplinary basic, translational, behavioral, clinical, and/or health services research relevant to women's health or sex/gender factors. The goal of the BIRCWH program is to increase the number and skills of investigators through a mentored research and career development experience that will lead to an independent scientific career benefiting the health of women, and that may include research on sex/gender similarities or differences in biology, health, or disease (http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-004.html) (OD-06-004).

- **Fourth Annual Interdisciplinary Women's Health Symposium (November 2007)**
  The ORWH, in partnership with the NICHD, Food and Drug Administration, and Agency for Healthcare Research and Quality, sponsored a symposium to highlight research advances of the ORWH BIRCWH in Women's Health program and the SCOR program. The symposium provided an opportunity to share both the scientific and career development progress resulting from the two major ORWH interdisciplinary programs that aim to bridge basic and clinical research on sex/gender factors underlying women's health issues.

Health Disparities Among Special Populations of Women

- **NICHD and National Council of Negro Women (NCNW): Collaboration for Health**
  The NICHD is committed to reducing the incidence of maternal and childhood obesity. Minority women are disproportionately more likely to be obese and suffer from related chronic diseases like type 2 diabetes. To address this disparity, the NICHD is partnering with the NCNW to help women of color and children maintain a healthy weight, particularly within NCNW clusters around the United States. The NCNW is a council of 39 affiliated national African-American women's organizations and more than 240 clusters, which connect nearly 4 million women worldwide.

- **Jackson Medical Mall Launches Informative Health Series for Mississippi Residents**
  Mississippi residents are known to have some of the Nation's worst health outcomes, including sexually transmitted infections and infant mortality. The NICHD opened a new health information center at the Jackson Medical Mall in Jackson, MS, providing accurate, up-to-date health information. The center features health information materials from the NICHD and many other NIH Institutes and Centers and includes information on prenatal care, fibroids, cancer, heart disease, diabetes, Sudden Infant Death Syndrome, and many other health topics. The new center's opening was marked by the screening of a film on African-American midwives called "Bringing in Da Spirit" narrated by Phylicia Rashad. The film celebrates African-American women who committed themselves to the health and well-being of rural families, even in the face of misconceptions about the practice of midwifery.

- **NICHD Partnership with the National Council of La Raza (NCLR)**
  The NICHD and the National Human Genome Research Institute held a workshop at the NCLR Headquarters in Washington, DC, on April 21, 2008. NCLR is the largest national Hispanic civil rights and advocacy organization in the United States and works to improve opportunities for Hispanic Americans. The purpose of the workshop was to highlight public trust as a top priority of the National Institutes of Health and to promote opportunities for community engagement with the NICHD. The meeting provided a forum for the general public and the research advocacy community to discuss ways in which they could learn about and actively engage in NIH research and research planning.

- **Premature Ovarian Failure (POF) Booklet in Spanish—Tengo Falla Ovárica Prematura**
  The NICHD created a 28-page Spanish translation of its "Do I Have Premature Ovarian Failure?" booklet. The Spanish booklet explains the symptoms of POF, its possible causes, its associated conditions, and the latest NICHD research on the disorder. In addition, the booklet raises issues related to POF and infertility, lists possible options for women with POF who want to have children, and provides contacts for various POF support and information groups (http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5638).

Gender Analysis

- **Gender, Youth, and HIV Risk**
  Young women are disproportionately at higher risk of contracting HIV. To study the social, developmental, and environmental processes contributing to HIV risk in females and males under the age of 24, the NICHD and the National Institute of Mental Health plan to support research focusing on HIV risk in specific settings around the globe. Settings may include areas where HIV prevalence is high or increasing and relevant environmental contexts are changing rapidly (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-013.html) (HD-08-013).

- **Specialized Centers of Interdisciplinary Research**
  The NICHD cofunds this ORWH partnership, along with five other NIH Institutes and Centers and the Food and Drug Administration, to support 11 centers. The program centers provide new opportunities for interdisciplinary approaches to advance studies on how sex and gender factors affect women's health. Each SCOR center develops an interdisciplinary research agenda bridging basic and clinical research on sex and gender factors underlying a priority women's health issue (http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-003.html).

- **Advancing Novel Science in Women's Health Research (ANSWHR)**
  The ORWH and cosponsors, including NICHD, are partnering to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex and gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. The ORWH and cosponsors are particularly interested in encouraging researchers to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health (http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html) (PAS-07-381).

Initiatives

Requests for Applications

Research Networks

- **Specialized Cooperative Centers Program in Reproduction and Infertility Research (SCCPIR)**
  Since it began in 1998, the main objective of the SCCPIR was to establish a national network of centers aimed at improving human reproductive health through accelerated transfer of basic science findings into clinical practice. The SCCPIR is a research-

based centers program designed to promote multidisciplinary interactions between basic and clinical scientists. Center investigators work with the NICHD staff in facilitating research collaborations and interactions within and between centers, as well as with private foundations and industry (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-001.html) (HD-08-001).

- **Global Network for Women's and Children's Health Research**
  The NICHD supports an ongoing multicenter international research network designed to perform randomized clinical trials of interventions to reduce the major risks to maternal, infant, and early childhood health in resource-poor countries. The Institute is now supporting the addition of research units from Africa and India to complement the existing Global Network. The objective of this program is to help solve maternal and pediatric health problems by establishing a network of research units (paired U.S.-based and foreign centers) that will use common protocols to implement randomized clinical trials and thus contribute to the evidence base for clinical, programmatic, and policy decisions (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-07-016.html) (HD-07-016).

- **Obstetrical Pharmacology Research Network—Data Coordination and Analyses Center**
  The NICHD is establishing a data coordinating and analyses center for the OPRU Network. The OPRU currently consists of four clinical research sites, funded by the NICHD, to carry out pharmacology research to enhance understanding of obstetrical pharmacokinetics and pharmacodynamics, and improve appropriate therapeutics during pregnancy (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-07-019.html) (HD-07-019).

- **Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network**
  The National Institute of Diabetes and Digestive and Kidney Diseases, in collaboration with the NICHD, National Institute of Neurological Disorders and Stroke, and the ORWH, established the MAPP Network to conduct multidisciplinary, collaborative, multisite basic, translational, and clinical research addressing chronic pelvic pain. Study findings will increase our understanding of the pathophysiology, biological and behavioral risk factors, natural history, and genetics of chronic pelvic pain. The ultimate aim is to provide findings useful for development of future prevention or treatment strategies (http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-07-003.html) (DK-07-003).

- **New Interventions for Menopausal Symptoms**
  In collaboration with the National Institute on Aging, the NICHD, the National Center for Complementary and Alternative Medicine, and the ORWH established a Menopausal Symptoms Clinical Research Network to facilitate clinical intervention studies targeting bothersome vasomotor symptoms (issues related to the opening and closing of blood vessels) and related sleep disturbance, mood disorders, and vaginal dryness in a collaborative, multidisciplinary, multicenter setting (http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-08-004.html) (AG-08-004).

HIV/AIDS

- **Women's Interagency HIV Study (WIHS) IV**
  The WIHS is a multisite prospective epidemiology cohort study of women in the United States who are either infected with HIV or at increased risk for infection. The WIHS was established in 1994 and since that time, there have been followup visits with the study participants at 6-month intervals. The National Institute of Allergy and Infectious Diseases, in collaboration with the NICHD, National Cancer Institute, and National Institute on Drug Abuse, continues to support projects at seven WIHS sites (http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-07-004.html) (AI-07-004).

- **Addressing the Role of Pregnancy in HIV Prevention**
  In addition to supporting research on the prevention and treatment of HIV in women,

the NICHD is supporting a program to examine how the risk for HIV infection affects the desire to have children in the future, for women, men, and couples. Both basic and applied behavioral and social science studies are being supported (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-07-020.html) (HD-07-020).

Program Announcements

Fertility

- **Optimizing Technologies for the Preservation of Fertility**
  In response to a growing need for technologies for fertility preservation, the NICHD is encouraging research that optimizes technologies designed to increase the fertility preservation options for individuals who are or may become infertile as a result of chronic disease or disease treatment, exposure to environmental or occupational hazards, advanced reproductive age, or genetic predisposition (http://grants.nih.gov/grants/guide/pa-files/PA-08-104.html) (PA-08-104).

- **Role of Adipose Tissue as an Endocrine Organ in Reproduction and Infertility**
  The NICHD is encouraging research to better understand the role of adipose tissue in the normal physiological regulation of reproduction, to discern its possible role in the etiology of diseases and disorders that impact human fertility, and to probe its potential importance in different racial/ethnic groups (http://grants.nih.gov/grants/guide/pa-files/PA-08-059.html) (PA-08-059).

Reproductive Health

- **Female Health and Egg Quality**
  The NICHD, in collaboration with the National Institute on Alcohol Abuse and Alcoholism, is promoting basic and/or clinical research on the short- and long-term epigenetic and genetic impact of adverse female health situations on the quality of human eggs prior to and around the time of fertilization and of preimplantation embryos. Such adverse health conditions may include poor nutrition, diabetes, polycystic ovary syndrome, endometriosis, aging, and alcohol consumption, as well as assisted reproductive technologies (http://grants.nih.gov/grants/guide/pa-files/PAR-07-350.html) (PAR-07-350).

- **Fragile X Premutation and Ovarian Function**
  In 2005, the NICHD convened the "Workshop on Reproduction and the Fragile X Premutation." In response to panel recommendations, the Institute is encouraging basic, clinical, or translational research on the effects of the Fragile X premutation on ovarian function, with a focus on premature ovarian failure or early menopause (http://grants.nih.gov/grants/guide/pa-files/PA-07-219.html) (PA-07-219).

- **Adverse Outcomes of Assisted Reproductive Technologies**
  While most children born through the help of assisted reproductive technologies (ARTs) appear to be healthy and developing normally, there are some reports of adverse outcomes and some concerns owing to the variety and type of ART protocols in use. To begin addressing these concerns, the NICHD is encouraging research to study the ways in which ART may affect eggs, sperm, and preimplantation embryos that could, in turn, lead to adverse outcomes during fetal development, the perinatal period, childhood, adulthood, or even subsequent generations (http://grants.nih.gov/grants/guide/pa-files/PA-08-104.html) (PA-08-104).

- **Leiomyomata Uteri: Basic Science, Translational, and Clinical Research**
  The NICHD, with support from the National Institute of Environmental Health Sciences and the ORWH, encourage research with the goal of transforming advances in our understanding of the molecular basis of leiomyomata uteri (uterine fibroids) into new therapeutic options for prevention and treatment of this common gynecologic disorder (http://grants.nih.gov/grants/guide/pa-files/PAR-08-102.html) (PAR-08-102).

International Health

- **Indo-U.S. 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 United States, India, and globally, with specific emphasis on the need for more "translational" types of research intended to move beyond basic science and discovery to product development and delivery. High-priority areas include long-acting and hormonal contraceptives, identification and development of potential microbicides, and projects focused on biomedical and social behavioral factors that influence reproductive health; effective family planning, including strategies to address infertility in women and men; and disease prevention (http://grants.nih.gov/grants/guide/pa-files/PAR-07-217.html) (PAR-07-217).

- **Indo-U.S. Program on Maternal and Child Health and Human Development Research**
  Through a cooperative program, the Republic of India and the United States are supporting research projects involving U.S. and Indian investigators to enhance maternal and child health, disease prevention, product development, and/or technology transfer. The Maternal and Child Health and Human Development Research 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. Emphasis is placed on studies addressing social and behavioral factors affecting prevention, care, and treatment of disease/poor health in women, infants, and children (http://grants.nih.gov/grants/guide/pa-files/PAR-08-163.html) (PAR-08-163).

Training

- **Extramural Loan Repayment Program for Contraception and Infertility Researchers**
  The NICHD established this program to invite qualified health professionals who agree to engage in contraception and/or infertility research for at least 2 years, and who agree to engage in such research for at least 50 percent of their work schedule. The objective of the program is to recruit and retain highly qualified health and/or allied health professionals as contraception and infertility research investigators with the long-range objective of evaluating, treating, or ameliorating conditions that pose challenges for couples to either conceive or give birth to children (http://grants.nih.gov/grants/guide/pa-files/PA-07-438.html) (PA-07-438).

Conferences and Workshops

- **The Art and Science of Endometriosis: Standardizing the Measurement of Pain and Diagnostic Criteria (October 2006)**
  Endometriosis is an enigmatic condition affecting millions of women worldwide. It is defined as the presence of functioning, endometrial-like tissue outside the uterus, which often induces a chronic, inflammatory reaction and is predominantly found in women of reproductive age, from all ethnic and social groups. The NICHD convened a conference in New Orleans to develop a consensus regarding the most appropriate entry criteria, outcomes, and management tools for clinical studies assessing treatments for endometriosis-associated pain.

- **Collaborative Meeting for the Obstetric Pharmacology Research Unit and the Pediatric Pharmacology Research Unit Networks (July 2007)**
  The OPRU and PPRU network scientists met during a 1½-day meeting to discuss common themes, review historical and current research activities in each network, and establish potential areas of cooperation between the two networks. The two networks identified several substantive areas that require increased emphasis, including but not limited to investigator-initiated research into therapeutics, an increased emphasis on obstetric pharmacology research, and training grants to develop new obstetric and pediatric pharmacologists.

- **Galactosemia and Primary Ovarian Insufficiency (September 2007)**
  In collaboration with the NICHD Parents of Galactosemic Children, International Premature Ovarian Support Group, American Society for Reproductive Medicine, National Institute of Mental Health, National Center for Complementary and Alterna-

tive Medicine, and the ORWH, the NICHD led a meeting to better understand mechanisms of ovarian toxicity related to galactosemia (a rare metabolic disorder that is associated with the development of primary ovarian insufficiency). Topics of interest included hormone replacement in women with galactosemia who have primary ovarian insufficiency, mental health aspects of primary ovarian insufficiency as it relates to galactosemia, and pregnancy in women with galactosemia.

- **Defining a Classification System for Uterine Leiomyoma (September 2007)**
  Uterine leiomyoma, commonly referred to as fibroids, are a common gynecologic disorder that can cause infertility, irregular bleeding, and chronic pain. The NICHD assembled a panel of expert investigators to begin developing a standardized classification system for uterine fibroids to ensure standard research protocols for future research.

- **NICHD Uterine Fibroid Research Update Workshop (September 2007)**
  NICHD scientists have continued to examine the mechanisms responsible for uterine fibroid development and growth through basic, translational, and clinical research studies. The Institute sponsored a workshop to provide a forum for NICHD intramural and extramural investigators to share current knowledge, recent findings, and explore future directions in uterine fibroid research. The major objective of the workshop was to foster ongoing communication and stimulate future collaborations among investigators within NICHD's immediate research community.

- **Fourth Annual Interdisciplinary Women's Health Symposium (November 2007)**
  The ORWH, in partnership with the NICHD, Food and Drug Administration, and Agency for Healthcare Research and Quality, sponsored a symposium to highlight research advances of the ORWH BIRCWH program and the SCOR program. The symposium provided an opportunity to share both the scientific and career development progress resulting from the two major ORWH interdisciplinary programs that aim to bridge basic and clinical research on sex/gender factors underlying women's health issues.

- **Research on Teen Dating Violence (December 2007)**
  The Department of Health and Human Service's Office on Women's Health and NIH cosponsors, including the ORWH and NICHD, informed a meeting to build consensus on research and develop a practical definition of teen dating violence. Experts discussed and reviewed current methods, measurements, and outcomes used for quantifying and defining teen dating violence, both in research and in practice, and examined the status of current research, both basic and applied on teen dating violence (http://www.ojp.usdoj.gov/nij/topics/crime/violence-against-women/workshops/teen-dating-violence-agenda.htm).

- **Preconception Care Research: Improving Birth Outcomes and Reproductive Health Workshop (April 2008)**
  The NICHD, with cosponsorship from the ORWH, HHS, NIH Office of Rare Diseases, Centers for Disease Control and Prevention, and other organizations, including but not limited to March of Dimes, Society for Maternal-Fetal Medicine, and American College of Obstetricians and Gynecologists, held a 2-day workshop to bring together a broad spectrum of scientific experts to define a multidisciplinary framework for developing a research agenda in preconception care research. Participants addressed the current state of knowledge, identified emerging issues or continuing gaps in knowledge, and explored future opportunities for research (http://www.nichd.nih.gov/about/meetings/2008/pcr/agenda.cfm).

National Institute on Deafness and Other Communication Disorders

Executive Summary

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 to fully characterize 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.

NIDCD supports both basic and clinical studies to better understand the relationship between congenital CMV infection and hearing loss. NIDCD-supported investigators have developed an animal model (mouse) of congenital cytomegalovirus infection and are pursuing fundamental questions concerning disease pathogenesis. Human studies are aimed at the characterization of maternal CMV status in an effort to determine the relationship between the type of maternal infection (recurrent or primary) and congenital CMV infection. This research is critical for fully determining the features in the natural history of maternal CMV infection and mother-to-child transmission that contribute to SNHL and late-onset SNHL. Such studies are essential for the development of rational clinical approaches aimed at ameliorating CMV-induced congenital hearing loss.

In July 2005, the NIDCD awarded a contract entitled "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 (1) to correlate CMV status at birth with the presence of permanent/progressive sensorineural hearing loss; (2) to acquire data on the incidence, time course, and audiologic outcomes of CMV-related hearing loss; and (3) to determine the extent to which CMV screening can improve detection and prediction of either existing or progressive hearing loss if combined with the metrics already in use for newborn screening. The necessary milestones have been achieved in Phase II. The study is expected to transition to Phase III, in March 2009, which involves completion of newborn CMV screening and the followup of CMV-infected children.

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, which are important mediators of proper nutrition, cardiovascular disease, obesity, 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 demyelin-

ation 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 overall health status. NIDCD-funded research will define the nature of the olfactory dysfunction present in multiple sclerosis in women and will determine the relationship between the degree of olfactory deficit, cognitive function, and pathological alterations within specific central nervous system structures.

Gestational Diabetes and Altered Taste Sensitivity

Gestational diabetes is a common complication of pregnancy that requires special attention to diet to insure proper maternal and child health. NIDCD-funded research has shown that gestational diabetes can adversely affect nutrition by increasing the preference for and intake of sweet-tasting foods. Altered sweet sensitivity appears to be related to the blood levels of certain hormones and metabolites, and to a change in glucose tolerance that often accompanies pregnancy. The long-term goals of these studies are to better understand the various mechanisms underlying gestational diabetes, to isolate risk factors, and to develop better preventive and therapeutic dietary interventions.

Balance

Maintaining upright posture requires the body center of mass to avoid swaying too far from the feet as a base; it depends on sensory input and on biomechanical factors, including muscle strength. Elderly women are reported to have a higher incidence of falls than elderly men, a difference attributable mostly to differences in biomechanics. Balanced human posture is improved by the combination of sensory information from the eyes, ears, and joints. Imbalance in those with pathological vestibular loss may result partly from insufficient adaptation of the brain to changes in the relative contributions from these various sensory systems. NIDCD-funded research tested whether sound signals to both ears could provide a useful additional feedback cue. The loudness and pitch of the sound was linked to the amount and direction of body sway, which was measured while standing on a force plate. The auditory feedback was found to reduce the amount of postural sway, under conditions of varying sensory loss, so the auditory feedback apparently can provide a sensory substitution for some loss of normal sensory input. This study suggests that added auditory information may help subjects compensate for sensory decline or loss by facilitating the brain's integration of sensory information for postural control. Use of such auditory feedback may provide useful strategies for postural adaptation to help prevent falling and consequent injury during aging or rehabilitation.

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. NIDCD awarded a number of applications responsive to the funding opportunity announcements released soliciting research in stuttering.

Assessment and Treatment of Voice Disorders

Voice disorders affect millions of Americans, influencing their quality of life and impairing their ability to communicate effectively and to function in our society. A number of voice disorders appear to affect women more frequently than men. NIDCD currently supports a number of projects focused on normal and disordered voice processes. Of note are studies examining behavioral vocal hyperfunction. Vocal hyperfunction is not organic in origin, but rather a result of a habitual pattern of overuse, misuse, or possibly abuse of the vocal mechanism. A currently funded project is examining the vocal performance of teachers, a profession predominantly composed of women.

Spasmodic Dysphonia (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 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. Future voice research with women volunteers should enhance our knowledge of this human ability and maximize laryngeal health and prevention of injury. Efforts to study voice restoration would minimize disabling effects and function and enhance quality of life.

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 of Dental and Craniofacial Research

Executive Summary

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. This includes funding clinical and basic research to understand, prevent, and treat oral and craniofacial diseases that disproportionately or solely affect women. These diseases include oro-facial pain, diseases of the temporomandibular joint (TMJ), osteoporosis of the craniofacial complex, salivary gland diseases, autoimmune diseases, and oral diseases of pregnant women.

NIDCR women's health clinical initiatives in FY 2007 and FY 2008 included large cohort studies designed to identify risk factors and to characterize diseases impacting women. One study is following a large group of young women to identify those who develop temporomandibular joint and muscle disorders (TMJMDs). Two groups supported by the NIDCR continue to characterize individuals with Sjögren's syndrome, an autoimmune disease that severely impacts oral health. Other researchers investigated the benefits of adjunctive therapies for treatment of periodontal disease in osteopenic women, treatments for severe TMJ diseases, and the effect that treatment of periodontal disease during pregnancy has on the incidence of preterm birth and associated growth restriction. Studies of poor inner-city women helped define factors that make them more susceptible to oral diseases.

The NIDCR also supports basic science studies examining growth and development of teeth, cartilage, and bone. These studies have led to advances in biomaterials research and to the emerging fields of tissue engineering and biomimetics, fields that use the body's own cellular and molecular processes to repair and regenerate tissues and organs. These include in-depth studies of the characteristics of the TMJ disc at the cellular level.

Recognizing the importance of gene-to-gene, gene–environment, and behavioral interactions, the NIDCR has long emphasized the importance of genetic, behavioral, social science, and epidemiological research. Researchers supported by the NIDCR during FY 2007 and FY 2008 have defined genes associated with primary Sjögren's syndrome, and cleft lip and palate, and they have characterized features of women more likely to develop chronic pain. Ongoing studies hope to define susceptibility genes for TMJMD and other genes associated with craniofacial diseases.

This report highlights accomplishments and initiatives in the areas of chronic pain and temporomandibular disorders, osteoporosis and basic bone biology, bisphosphonate-associated osteonecrosis of the jaw, the oral health of pregnant women, oral health disparities, Sjögren's syndrome, human immunodeficiency virus (HIV) infection, and craniofacial anomalies related to the health of women.

Accomplishments

Pain Research

For many years, NIDCR has supported research that examines pain conditions,

including those that primarily affect women. Findings from studies continue to demonstrate there are sex differences in responses to painful stimuli, and that women are more likely to develop chronic pain. Human and animal studies include research in the following areas.

Sex Differences in Pain

Approximately 20 percent of all chronic pain is associated with the head and neck, and this pain disproportionately affects women. A recent survey found that over 70 percent of individuals suffering chronic pain of the head and neck regions were female. The NIDCR supports several investigators examining sex differences in pain, including differences in sensitivity to pain stimuli and autonomic nervous system tone. Results published to date suggest that females are more sensitive to acute noxious stimuli than males. In addition, human females have a higher resting, tonic activation of the sympathetic nervous system, that is, more vasoconstriction. These findings suggest that women should be more sensitive to noxious cold than males. Results from recent animal studies confirm these findings and highlight the importance of studying sex differences in pain research.

NIDCR researchers have developed a new noninvasive way to measure TMJ pain in animals that is based on an analysis of meal pattern duration. Results of experiments using this model indicate that females experience reductions in TMJ pain more rapidly than males. The interpretation of these results is complex, but the results suggest that both estrogen and progesterone may play an important role in regulating pain responses to noxious inflammatory insults.

Temporomandibular Joint and Muscle Disorders

TMJMDs are important chronic pain conditions of particular interest to the NIDCR. Examples of NIDCR basic and clinical research on TMJMD include the following:

- A recent study estimated the prevalence of myofascial temporomandibular joint disorder (M-TMJD) in community dwelling women to be 10.5 percent. Twenty thousand women, selected at random, completed a telephone survey of facial pain. About 2,000 of these women were invited for an examination to determine if they have M-TMJD. A diagnosis was determined using current research diagnostic criteria for TMJD. The overall prevalence was estimated to be 10.5 percent, and the prevalence appeared to be higher in younger women, women of lower socioeconomic status, African-American women and non-Hispanic women.
- Psychological characteristics potentially may be a cause or consequence of temporomandibular disorder (TMD). This study determined if psychological characteristics associated with pain sensitivity would influence risk of first-onset TMD, while accounting for the effect that could be attributed to variation in the gene encoding catechol-O-methyltransferase (COMT). Particular variations in the gene encoding COMT are associated with different pain sensitivity. A prospective cohort study of healthy female volunteers aged 18–34 years were followed for up to 3 years, and 8.8 percent were diagnosed with first-onset TMD. Depression, perceived stress, and dysphoric mood were associated with pain sensitivity and were predictive of two- to threefold increases in risk of TMD ($p < 0.05$). However, the magnitude of increased TMD risk due to psychological factors remained unchanged after adjustment for the COMT haplotype. Psychological factors linked to pain sensitivity influenced TMD risk independently of the effects of the COMT haplotype on TMD risk.
- The NIDCR is funding a 7-year clinical study that will accelerate research on our understanding of the biological and psychological risks for developing chronic TMJMD and their treatments. The study, named Orofacial Pain: Prospective Evaluation and Risk Assessment or OPPERA, is the first large longitudinal, prospective clinical study to identify risk factors for the onset and persistence of TMJMD. Investigators are following 3,200 healthy volunteers from 3 to 5 years to see how many develop the disorder. The multicenter research program involves investigative units at University of Florida

at Gainesville, University of Buffalo-State University of New York, University of Maryland at Baltimore, and University of North Carolina at Chapel Hill. Enrollment in this study was just finished and initial baseline measurements from 3,400 subjects have been completed. Plans have been developed for the initial analysis and publication of baseline data from these subjects.

- A study to test and improve the reliability and validity of the widely used Research Diagnostic Criteria for TMJMD (RDC/TMD) was recently completed. These criteria are used to diagnose individuals for clinical studies and clinical trials of TMJMD. Several components of the RDC/TMD have been modified and validated, which is likely to provide clinicians with more reliable instruments in the treatment and study of these disorders. Investigators also found that more than one-fourth of clinically normal subjects, with no lifetime history of TMJMD symptoms, have TMJ changes by magnetic resonance imaging (MRI) 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. Future studies are needed to determine if MRI disc changes predict future TMJ pain.
- Two percent of TMJMD patients have jaw locking from a permanently displaced intra-articular disc or TMJ closed lock. This advanced disorder can cause significant pain and interfere with jaw movement and function. Current interventions for TMJ closed lock vary from minimal treatment to surgery. In a single-blind trial, individuals with TMJ closed lock were randomized to one of four conditions: medical management (education, optimistic counseling, a self-help program, and a 6-day regimen of oral methylprednisolone followed by nonsteroidal anti-inflammatory drugs for 3–6 weeks with muscle relaxants and over-the-counter analgesics); rehabilitation (medical management plus an intraoral splint, physical therapy, and cognitive-behavioral therapy); arthroscopy (superior joint space lavage, intracapsular adhesion lysis, and injection of intracapsular betamethasone); or arthroplasty (open-joint surgery with disc repositioning or disc removal procedure). All four treatment approaches represent current standard practice. Evaluations of jaw function and TMJ pain at baseline, 3, 6, 12, 18, 24, and 60 months found no between-treatment group differences, while all four groups had within-group improvement ($p < 0.0001$). This preliminary study suggests that individuals with TMJ closed lock should be treated with noninvasive techniques (medical management or rehabilitation) initially.
- Another clinical trial comparing Standard Treatment (STD), consisting of an intraoral splint plus anti-inflammatory agents, to Standard Treatment + Cognitive-Behavioral Treatment Program (STD+CBT) for the reduction of TMJMD pain and psychosocial distress is nearing completion. Blood markers for physiologic stress and inflammation will also be examined.
- The NIDCR recently funded a study to assess an instrument's ability to predict whether or not a patient with acute TMJMD is likely to progress to chronic TMJMD, and to determine the best therapy for those most likely to develop chronic TMJMD. TMJMD patients will be recruited from the community and screened to determine the likelihood that their condition will become chronic. Those at highest risk for developing chronic TMJMD will be randomly assigned to one of two possible treatments.

Reconstruction of the TMJ

Ongoing studies are characterizing the TMJ disc at cellular and tissue levels. This knowledge could be used to engineer in vitro TMJ disc prototypes that approximate native disc structure and function for use in future clinical trials testing treatments of individuals with advanced TMJ destruction. Other studies

are developing stem cell-based approaches for regeneration of the TMJ, and creating optimal scaffolds to use for TMJ bone regeneration. Research in the area includes the following studies:

- Detailed studies are underway to investigate the influences of engineered scaffold mechanical properties on bone regeneration. The central hypothesis to be tested is that the scaffolds with the highest interconnected porosity and minimum elastic modulus will promote the greatest degree of bone regeneration. Achieving the goals of this work will facilitate derivation of tissue engineering-based bone regeneration strategies for treatment of severe TMJ disorders with advanced disc and condylar destruction.
- The biochemical content, mechanical properties and ultrastructural tissue organization of the porcine TMJ disc is being investigated with the goal of determining TMJ disc-specific structure/function relationships. These findings will facilitate derivation of rational tissue engineering-based approaches for treatment of human TMJ disorders. The investigators have already obtained sufficient information to begin optimizing their tissue-engineered constructs.
- Advanced tissue engineering bioreactors are being developed to derive functional composite tissue-engineered osteochondrial TMJ constructs. These novel bioreactors support cultivation of complex tissues because they have a two-compartment design. One compartment enhances cartilage development, while another compartment is designed to optimize bone regeneration. The investigators expect that their advanced bioreactors will generate an excellent experimental system for testing tissue engineering-based strategies for treatment of TMJ disorders. Other investigators are using human umbilical cord matrix (HUCM) stem cells as a novel cell source, and a gradient-driven scaffold design for manufacturing of their TMJ constructs. The combination of these new technologies should lead to engineered jaw condyles with superior quality tissues and continuous transition between the cartilage and the bone that mimics the natural joint. Achieving the goals of this work may lead to generation of new paradigms for a variety of tissue engineering applications, including the treatment of TMJ disorders.

Temporomandibular Joint Disorder (TMJD) Awareness Effort

NIDCR launched an initiative in spring 2008 to raise awareness about temporomandibular joint and muscle disorders and the availability of the Institute's patient education booklet on this topic, TMJ Disorders. The overall goal of this awareness effort is to help people with TMJ problems make prudent decisions about their care. The message "Less Is Often Best in Treating TMJ" targets women ages 25–44, the group most commonly affected by this condition, and cautions against unnecessary and potentially harmful treatments. Media kits and e-mail blasts sent to editors of national women's and health magazines highlight the issues addressed in the TMJ Disorders booklet and include "Less Is Often Best" ready-for-print ads featuring women in the TMJD demographic.

Channeling this outreach effort to the local community, NIDCR arranged with the Washington, DC, area transit system to display "Less Is Often Best" ads on Metro buses throughout the city and at Metro subway stations in areas where large numbers of women in the target population work and live. Links to the TMJ Disorders booklet, article for consumers, and advertisements suitable for use in newsletters, magazines, and other publications are available on the TMJD page of the NIDCR website: http://www.nidcr.nih.gov/OralHealth/Topics/TMJ/.

Mineralized Tissue Studies in Health and Disease

The study of teeth, bone, and other mineralized tissues has been a mainstay of NIDCR-supported research since the Institute's inception, not only because of its importance as it relates to teeth and jaws, but also as it relates to the growth and development of the entire craniofacial complex.

Bone is an active and dynamic tissue that continuously remodels throughout life. The process of bone remodeling consists of the

cycle of bone formation and resorption. An imbalance between bone formation and resorption will lead to a change in bone mass. In young or developing (< 20 years old) bone, bone formation dominates resorption, resulting in bone growth and development. In healthy adult (20–40 years old) bone, the processes of bone formation and resorption are delicately equilibrated, and no increase or decrease in bone mass occurs. However, in aging bone, an imbalance of resorption over formation often induces loss of bone mass, and can lead to osteoporosis, a skeletal disease that affects bone architecture and increases the risk of fracture, and disproportionately affects women, who are four times more likely than men to develop the disease.

Several investigators have studied basic biological processes involved in the development and maintenance of bone, cartilage, and/or teeth:

- Dentin Sialophosphoprotein (Dspp) was first isolated and characterized in developing teeth and thought to be dentin specific. However, more comprehensive analysis revealed that Dspp is also expressed in bone. In order to study the function of Dspp during mineralization of bones and teeth, investigators generated Dspp-deficient mice. These animals exhibited defects in dentin formation similar to dentinogenesis imperfecta observed in human patients. These mice had modest but significant changes in their bone material properties at each of the three time points studied. The findings suggest that Dspp regulates bone mineralization as well as remodeling, and in particular, that Dspp deficiency may contribute to age-related bone fragility similar to osteoporotic conditions.
- Oxysterols are naturally occurring byproducts of cholesterol metabolism. Previous studies have demonstrated that oxysterols can promote the development of bone-forming cells called osteoblasts. In order to study the function of oxysterols in physiological conditions, investigators utilized a rat bone healing model. Bony defects were treated with scaffold implants either with or without oxysterols. In oxysterols-treated animals, the defect healed faster and more completely. The results suggest that oxysterols can enhance bone formation through local delivery, and may present an additional opportunity for developing oxysterols as agents to augment bone growth at the systemic level.
- In studies of the genetic regulation of bone formation, investigators supported by the NIDCR showed that mice with targeted disruption of the ATF4 gene exhibit low bone mass due to delayed bone formation and mineralization. Strikingly, since the mechanism of action of ATF4 is the regulation of amino acid transport, the skeletal abnormalities in ATF4-deficient animals were corrected by feeding the animals a high-protein diet. This study uncovers the important molecular connection between nutritional status and the manifestation of skeletal disorders.
- Other work is seeking to increase the differentiation of mesenchymal stem cells (MSCs) into functional bone tissue using treatment with estrogen. In particular, the investigators are assessing the effects of different concentrations of estrogen. The results of this investigation will provide initial data for designing optimal strategies for hormonal control of functional bone generation for a wide range of tissue engineering applications.
- Other studies are examining the potential of muscle derived stem cells (MDSCs) to improve bone healing. In particular, the researchers are analyzing the effect of the sex and age of donor mice on the number and the bone-forming potential of MDSCs. They also are determining if variables such as the size or source of muscle biopsy, time of culturing, or hormonal stimulation affect the number of MDSCs and their osteogenic potential. The results generated from these experiments will advance the development of bone through tissue engineering.

Diseases that affect mineralized tissues of the craniofacial complex include periodontal disease, osteoporosis, and bisphosphonate-associated osteonecrosis. Advances in this area include publication of a clinical trial testing treatments for periodontitis in osteopenic

women, and clinical studies defining risk factors for osteonecrosis of the jaw.

- Tetracyclines and related drugs (including minocycline and doxycycline) can inhibit processes that help mediate bone resorption. For example, minocycline can increase bone formation and decrease bone resorption, resulting in increased systemic bone density in ovariectomized rats. Estrogen deficiency in postmenopausal women is a factor in the pathogenesis of osteoporosis. It involves accelerated bone resorption and has, in recent years, been associated with increased tooth loss and oral bone loss. These findings provided the basis for a clinical trial to determine the efficacy of 2-year continuous low-dose doxycycline on alveolar bone in postmenopausal osteopenic, estrogen-deficient women undergoing periodontal maintenance therapy. All received periodontal maintenance therapy. Outcome: There was no statistically significant effect of doxycycline on the bone loss associated with periodontal disease of the entire group, though subgroup analyses suggest some benefits. A significant clinical finding from the study was that conventional periodontal therapy controlled periodontal disease of most tooth sites (81–95 percent) of postmenopausal osteopenic women at risk for tooth loss.

Bisphosphonates (BPs) are drugs that inhibit the activities and functions of osteoclasts (bone-resorbing cells) and perturb the differentiation of osteoblasts (bone-forming cells). Intravenous bisphosphonates are primarily used to treat bone erosion and hypercalcemia associated with bone metastasis, Paget's disease, and multiple myeloma. Oral bisphosphonates are used to prevent bone loss and are prescribed for patients with osteoporosis or osteopenia. In 2003, reports appeared in the literature that suggested use of BPs could lead to development of nonhealing, exposed necrotic bone in the maxillofacial region. The clinical condition was named osteonecrosis of the jaw (ONJ). Most cases of ONJ are related to intravenous (IV) bisphosphonate use in cancer patients, but several cases are associated with oral bisphosphonates. Patients with ONJ present with painful, exposed, and necrotic bone, which may develop after invasive dental procedures or spontaneously. These lesions are nonhealing or slow to heal, and can be complicated by secondary infection. The NIDCR recognized the significance of the clinical problem and has funded studies examining the etiology and epidemiology of the problem.

- One study used medical claims data from 714,217 people with osteoporosis or cancer to identify diagnostic codes or procedure codes for three outcomes: inflammatory conditions of the jaws, including osteonecrosis; major jaw surgery necessitated by necrotic or inflammatory indications; and jaw surgeries necessitated by a malignant process. Their results indicate that oral administration of BPs decreases the risk of adverse bone outcomes, but IV administration strongly and significantly increases the risk ($p < .05$) of adverse jaw outcomes or surgery. Across both osteoporosis and cancer, patients receiving IV BPs had a fourfold increased risk of having inflammatory jaw conditions and a greater than sixfold increased risk of having undergone major surgical resection in the jaw. More clinical studies are needed to replicate and clarify these observed associations.
- The three NIDCR-funded Dental Practice-based Research Networks are completing a study to define risk factors for ONJ in patients (primarily women) treated with bisphosphonates. Preliminary data suggest that the risk of developing ONJ is low, but may be associated with particular dental procedures and aggravated by other systemic medical conditions.

Oral Health Disparities Research

The NIDCR's strategic plan includes as a goal the elimination of disparities in oral health status of vulnerable populations, including women of racial and ethnic minority backgrounds, the poor, and those with developmental or acquired disabilities. Several studies of the Centers for Research to Reduce Oral Health Disparities 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. In FY 2008, NIDCR made five new awards to continue the work of Centers for Research to Reduce Oral Health Disparities. These new funds will be used to conduct interventional studies to reduce oral diseases in vulnerable populations. Four planned studies seek to reduce ECC with behavioral interventions directed at pregnant women or mothers of very young children. Another study is testing an intervention to reduce untreated dental decay in pregnant women who are eligible for Medicaid.

- One randomized clinical trial that was just completed is testing approaches to disrupt the transmission of caries-causing microbes from mother to child through the use of chlorhexidine rinse by the mother, prenatally, in combination with fluoride varnish use with the infants. Results should be published within the year.
- Another study examined the relationship between dietary patterns and caries experience in a representative group of low-income African-American adults. Participants were residents of Detroit with household incomes below 250 percent of the federally established poverty level (n = 1,021). Over 80 percent were female. Dietary histories were obtained by trained interviewers in face-to-face interviews with the adult participants. Caries was extensive, with 82.3 percent of the 1,021 participants (n = 839) having at least one decayed tooth. Nearly three-quarters of the adult participants were overweight or obese. This population had severe caries, poor oral hygiene, and diets that are high in sugars and fats and low in fruits and vegetables. Apart from tap water, the most frequently consumed food item by adults of all ages was soft drinks; 19 percent of all energy from sugar came from soft drinks alone. Frequency of soft drink consumption and the presence of gingival plaque deposits were significantly associated with caries. Interventions to promote oral health are unlikely to be successful without improvements in the social and physical environment.

Oral Health of Pregnant Women

Previous studies suggest that the infectious organisms causing periodontal disease and the inflammation associated with untreated periodontitis could have serious deleterious effects during pregnancy.

- NIDCR sponsored two large randomized trials to determine if nonsurgical treatment of periodontal disease during pregnancy reduced the incidence of preterm birth and associated growth restriction. Both the Obstetrics and Periodontal Therapy Trial (OPT Trial) and the Maternal Oral Therapy to Reduce Obstetric Risk Trial (MOTOR Trial) were designed to determine whether pregnant women having nonsurgical periodontal therapy during the second trimester of pregnancy had fewer premature and/or low-birthweight infants as compared to women having periodontal therapy delayed until after delivery. Findings indicated that pregnant women who received nonsurgical treatment for their periodontal disease did not significantly lower their risk of delivering a premature or low-birthweight baby. This study also evaluated the safety of general dental care during pregnancy. It found that dental treatment through the second trimester—both general dental and periodontal care—did not increase the number of adverse events for women. The MOTOR study was completed in FY 2008 and results should be available in the near future.
- In previous cross-sectional or case-control studies, clinical periodontal disease has been associated with gestational diabetes mellitus. To test the hypothesis that, in comparison with women who do not develop gestational diabetes mellitus, those who do develop it will have had a greater exposure to clinical and other periodontal parameters, investigators measured clinical, bacteriological (in plaque and cervicovaginal samples), immunological, and inflammatory mediator parameters 7 weeks before the diagnosis of gestational diabetes mellitus in 265 predominantly Hispanic (83 percent) women in New York. Twenty-two cases of gestational diabetes mellitus emerged from the cohort (8.3

percent). When the cases were compared with healthy control individuals, higher prepregnancy body mass index ($p = 0.004$), vaginal levels of the periodontal pathogen Tannerella forsythia ($p = 0.01$), serum C-reactive protein ($p = 0.01$), and prior gestational diabetes mellitus ($p = 0.006$) emerged as risk factors, though clinical periodontal disease did not.

- The NIDCR has funded several studies that are seeking new ways to diagnose dental caries without the use of x-rays and the associated exposure to ionizing radiation. These techniques harness the natural bioluminescent properties of the tooth to provide images that clinicians may be able to use to more accurately detect and assess caries activity.

Salivary Hypofunction (Dry Mouth)

The exocrine salivary glands produce saliva, a complex fluid that is central to maintenance of oral health. If insufficient quantities of saliva are made, severe impairments in oral health can develop. These include sometimes dramatic increases in dental caries; difficulty in swallowing, chewing, and speaking; loss of enjoyment of food; mucosal infection with the Candida species; and reduced quality of life. Many diseases and conditions can induce salivary gland hypofunction. The autoimmune diseases Sjögren's syndrome (SS) and rheumatoid arthritis, which disproportionately affect women, often have associated salivary dysfunction that is thought to be caused by a plasmolymphocytic infiltration of the salivary glands.

- Intramural scientists continue to examine the physiology, growth, and development of salivary glands. These investigations help identify pathways that could be targeted by therapeutic medications, or define how salivary glands could be reengineered to regain their function.
- Several studies in animals suggest that salivary glands can be used to make new proteins through gene therapy—findings with potential for disease treatment. However, it is important to determine if this approach is equally successful in males and females. In one study, scientists compared male and female mice that received a protein expression vector directly into the right submandibular salivary gland. A significant sex-related difference in vector biodistribution was found. Male mice had more than twice the amount of vector expression in the salivary glands than did females, and vector expression lasted longer in males. These experiments demonstrate that sex may be a significant factor that influences the clinical application of gene therapy in salivary glands.

Autoimmune Diseases and Sjögren's Syndrome

Autoimmune disorders disproportionately affect women and cause an unintended destruction of the body's own tissues. The autoimmune condition that most severely impacts the oral cavity is SS, a disease characterized by reduced secretions from salivary and lacrimal glands. It is the second most common autoimmune disease in the United States, estimated to affect 1–2 million people with a female-to-male ratio of nine to one. Typically, patients with SS have increased numbers of lymphocytes and other immune cells residing in their salivary and lacrimal glands, a process thought to ultimately reduce saliva and tear production. The most serious complication of SS is the greatly increased risk for developing malignant lymphoma, which is estimated to occur 40 times more frequently in these patients.

- Intramural NIDCR researchers continue to study the natural history and immunopathogenesis of SS. Recent findings from investigators include a genetic study that demonstrated that the STAT4 polymorphisms associated with rheumatoid arthritis and systemic lupus erythematosus are also associated with the primary form of SS. These intramural investigators also recently completed a clinical trial that tested the drug Raptiva (efalizumab) for treatment of primary SS and are conducting an ongoing clinical study characterizing autonomic function in SS.
- The NIDCR continued to fund the International Research Registry Network for SS with the purpose of (1) examining the sensitivity and specificity of current

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. Over 600 subjects have been enrolled. Many of these will be re-examined after 2 years to determine how quickly the disease progresses. In addition, specimens of tissues, blood, saliva, and tears are collected for future studies, including studies examining the genetics of primary SS.

- SS is a complex disease that presents symptoms shared by many other conditions and therefore can go undiagnosed for several months to years. Early detection and diagnosis of SS present greater opportunity for intervention to slow, inhibit, or even reverse disease progression. Investigators conducted comprehensive analysis of the composition of whole saliva from 10 primary Sjögren's patients and 10 matched control subjects. Out of hundreds of proteins and thousands of messenger RNA transcripts profiled, 16 peptides and 27 transcripts were found to be differentially expressed between Sjögren's patients and controls. Some markers were representative of damaged salivary gland cells, or the autoimmune response, while others were not previously associated with the condition. Taken together, this study is a significant first step toward defining a molecular profile for SS that could be garnered from a simple saliva sample. Significant effort is now required for the validation of this panel of potential biomarkers.

Studies With Animal Models of Sjögren's Syndrome

- Transforming Growth Factor beta (TGFbeta) plays a key role in the onset and resolution of autoimmune diseases and chronic inflammation. In this study, TGFbeta signaling in mouse salivary glands was impaired by conditionally inactivating expression of TGFbeta receptor type I (TGFbetaRI). TGFbetaRI-conditional knockout (TGFbetaRI-coko) mice were born normal; however, female TGFbetaRI-coko mice developed severe multifocal inflammation in salivary and mammary glands and in the heart. The inflammatory disorder affected normal growth and resulted in the death of the mice at ages 4–5 weeks. Interestingly, male TGFbetaRI-coko mice did not exhibit any signs of inflammation. The female TGFbetaRI-coko mice also showed an increase in Th1 proinflammatory cytokines in salivary glands and exhibited an up-regulation of peripheral T cells. In addition, these mice showed an atypical distribution of aquaporin 5 in their salivary glands, suggesting likely impairment of salivary function; following targeted disruption of TGFbetaR1 localized to the salivary glands, only the female mice showed inflammatory foci in their salivary glands These results suggest that female mice are uniquely more susceptible to developing inflammatory disorders due to impaired TGFbeta signaling in their salivary gland.
- Another study examined the nonobese diabetic (NOD) mouse, a widely used model for SS and diabetes mellitus. Findings from a 2-year period indicated a changing SS phenotype in these mice, and this phenomenon was investigated. Data from six different experimental studies over 2 years were analyzed and compared. Salivary flow rate, focus score, and submandibular gland (SMG) cytokines interleukin (IL)-2, IL-4, IL-6, IL-10, IL-12(p70), tumor necrosis factor-alpha and interferon (IFN) gamma showed changes over time. There were no differences for body weight, diabetes mellitus prevalence, or blood glucose level of nondiabetic mice. This report suggests additional animal models for the study of SS are needed.
- A number of proinflammatory cytokines have been detected at elevated levels in salivary glands of Sjögren's patients. However, whether these cytokines are mere consequences of local inflammation, or may perpetuate glandular destruction, remains to be determined. Investigators characterized the effects of tumor necrosis factor (TNF) alpha and IFN gamma on the physiological performance of salivary

epithelial cells using polarized rat parotid epithelial cells. Results demonstrated that these cytokines caused a breach in the epithelial tight junction integrity that was necessary for establishing transepithelial ion gradients to drive saliva secretion. Therefore, anti-inflammatory strategies that block these cytokines may restore salivary gland function in Sjögren's patients.

- Recently, a subset of T cells was described to be able to secrete the IL-17 family of cytokines and possibly linked to autoimmunity. In an attempt to study whether these molecules are present in the autoimmune disorder Sjögren's syndrome, investigators utilized a series of immunoassays to detect the presence of IL-17 and IL-23 in salivary tissues, saliva, and serum in Sjögren's patients and a corresponding mouse model. Histological findings showed elevated expression of IL-17 and IL-23 in human and mouse salivary tissue samples. IL-17 could not be detected in mouse saliva although it was positive in mouse serum. In contrast, IL-17 was present in the biofluids of Sjögren's patients, albeit at varying levels. These results indicate that IL-17 may be a viable pursuit as a biomarker of Sjögren's syndrome, as well as a candidate gene to explain the pathologies of the condition.

Other autoimmune diseases significantly impact oral health. Persons with systemic sclerosis may have severe destruction of the mandibular condyles that form part of the TMJ. A study just funded by the NIDCR will examine oral health of this population.

Human Immunodeficiency Virus (HIV)

The study of the oral manifestations of HIV infection has been of great interest to the NIDCR because oral changes in HIV-infected individuals are frequent and varied, and are among the first symptoms of infection. The impact of HIV/AIDS on women has grown substantially since the beginning of the epidemic.

- Persons with HIV infection may develop enlarged salivary glands and/or decreased salivary gland function. In a recently published study, the impact of highly active antiretroviral therapy (HAART) on salivary gland function in HIV-positive women from the Women's Interagency HIV Study (WIHS) was reported. Oral study visits with a total of 668 HIV-positive women from the WIHS cohort assessed salivary gland function. Protease inhibitor- (PI-) based HAART was found to be a significant risk factor for developing decreased salivary flow rates ($p = 0.0004$) as well as for developing salivary gland enlargement ($p = 0.006$) as compared with non-PI-based HAART.

Craniofacial Anomalies

Clefts of the lip and palate are common human birth defects of multifactorial etiology. The NIDCR supports genetic and clinical studies to define the genetic pathways resulting in cleft lip/palate and to find treatments to prevent oral clefting.

- The Oral Cleft Prevention Program, supported by the NIDCR, is testing two concentrations of folic acid supplementation to determine if either dose can reduce the number of nonsyndromic cleft lip and/or palate babies born to women in a high-risk group for having a baby with an oral cleft. These are women who either have an oral cleft themselves or women who have already borne a child with a cleft. Women take the folic acid preconception and through the first 3 months of pregnancy. The design is a randomized clinical trial that is being conducted in Brazil.

Initiatives

Funding Opportunity Announcements (FOAs)

- **Advancing Novel Science in Women's Health Research (ANSWHR)**
  The purpose of this FOA, issued by the Office of Research on Women's Health (ORWH) and cosponsoring National Institutes of Health (NIH) Institutes and Centers (ICs), is to promote innovative, interdisciplinary research that will advance

new concepts in women's health research and the study of sex/gender differences, especially relating to studies on how sex and gender factors affect women's health PAS-07-381, PAS-07-382.

- **Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Comorbid Conditions (R01)**
  The purpose of this FOA is to stimulate research on discovering etiological and pathophysiological mechanisms underlying a set of chronic, comorbid conditions associated with TMJMDs. TMJMDs are a complex collection of diseases involving one or more tissues of the TMJ and facial musculature. Primary symptoms include chronic pain in facial muscles and limited and painful movement of the jaw. In addition, these and other symptoms of TMJMD can occur together with other chronic illnesses such as fibromyalgia, atypical face pain, trigeminal neuralgia, chronic fatigue syndrome, multiple chemical sensitivity, irritable bowel syndrome, complex regional pain syndrome, migraine headache, speech, hearing, swallowing, balance, smell, and taste disorders, and certain cardiovascular diseases. This program announcement seeks research applications that use state-of-the-art, multidisciplinary, and interdisciplinary approaches to discover molecular, physiological, and behavioral mechanisms responsible for the overlapping symptoms manifested in the set of disorders that may coexist with TMJMD (PA-07-150).

- **Mechanisms, Models, Measurement, & Management in Pain Research (R01); Mechanisms, Models, Measurement, & Management in Pain Research (R21); Mechanisms, Models, Measurement, & Management in Pain Research (R03)**
  The purpose of this FOA, is to inform the scientific community of the pain research interests of the various ICs at the NIH and to stimulate and foster a wide range of basic, clinical, and translational studies on pain as they relate to the missions of these ICs. New advances are needed in every area of pain research, from the micro perspective of molecular sciences to the macro perspective of behavioral and social sciences. Although great strides have been made in some areas, such as the identification of neural pathways of pain, the experience of pain and the challenge of treatment have remained uniquely individual and unsolved, especially in chronic pain experiences such as those suffered by TMJD patients (PA-07-282, PA-06-542, PA-06-543).

- **Pathophysiology of Bisphosphonates-Associated Osteonecrosis of the Jaw (R01); Pathophysiology of Bisphosphonates-Associated Osteonecrosis of the Jaw (R21); Pathophysiology of Bisphosphonates-Associated Osteonecrosis of the Jaw (R03)**
  The purpose of this FOA is to stimulate research to determine the pathophysiology of ONJ, a morbid bone disorder that is associated with bisphosphonate use. Bisphosphonates are prescribed to alleviate bone pain in certain cancer patients, or to reduce bone loss in osteoporotic or osteopenic individuals. Recent reports suggest there is an association between the use of bisphosphonates and ONJ in a subset of these patients. Whether bisphosphonates are causal to the development of ONJ remains to be determined, and the physiological mechanisms by which ONJ manifests in bisphosphonate users are unknown. Although there is a knowledge base on the effects of bisphosphonates on bone quality and strength, there is a gap in our understanding of how bisphosphonates may interfere with bone healing and repair at the genetic, molecular, cellular, and tissue levels. Therefore, we seek to support basic and translational studies that will address the knowledge gap and enhance our understanding of this clinical entity related to bisphosphonate therapy. This knowledge could also serve as the basis for the prediction, prevention, diagnosis, and treatment of this condition (PA-07-132, PA-06-501, PA-06-502).

- **Clinical Studies of Bisphosphonate Therapy and Osteonecrosis of the Jaws (R21)**
  The purpose of this FOA is to encourage well-designed observational studies in humans that investigate the association between ONJ and the use of bisphos-

phonate therapy (oral and intravenous). Research proposed in response to this FOA would help in determining the incidence of ONJ in patients using oral and intravenous bisphosphonate therapy as well as risk factors and management of this condition (PAR-06-556).

- **Interdisciplinary Research on Oral Manifestations of HIV/AIDS in Vulnerable Populations (P01)**
  The primary goal of this funding opportunity announcement is to drive interdisciplinary research to study the oral manifestations and complications associated with HIV/AIDS-related immunosuppression in vulnerable populations, including children and adolescents. Applicants are encouraged to include pediatric/adolescent populations in their research (PAR-08-117).

Conferences and Workshops

- **Rochester Oral Biology Research Conference on Saliva and Salivary Gland Function June, 26–28, 2008**
  This conference brought together investigators who presented the state-of-the-knowledge in salivary glands and salivary gland function.

- **Gordon Research Conference on Salivary Glands and Exocrine Secretion**
  The conference brought together investigators to present and discuss the most recent progress in understanding the molecular basis of development, function, and dysfunction of salivary and related exocrine glands.

- **NIDCR Seminar Series**
  In 2008, the NIDCR initiated a new seminar series highlighting advances in science. Three of the seminars—"From Basic Research to Therapy—The Latest Frontier: Self-Assembling Bioactive Biomaterials for Regenerative Medicine," "Pain-Specific Blockade—Targeting Analgesics Only to Where it Hurts," and "How Stress Kills: New Perspectives on Stress and Inflammation"—related directly to women's health.

- **2008 Biointerface Science Gordon Research Conference**
  The broad and long-term goal of this conference was to enhance the understanding of interactions between biomolecules and surfaces, and the behavior of complex macromolecular systems at materials interfaces, driven by the important role these interactions play in the fields of biology, biotechnology, diagnostics, and medicine.

- **9th International Conference on the Chemistry and Biology of Mineralized Tissues**
  This conference brought together investigators who presented the state-of-the-knowledge in mineralized tissue research.

- **National Institutes of Health 3rd Annual Research Symposium for Advances in Pain Research**
  This symposium, sponsored by several NIH institutes, included presentations about new discoveries in basic science research related to pain and translation of basic science findings into possible clinical therapies.

- **Fifth Temporomandibular Joint Association Scientific Meeting Entitled "Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?"**
  The meeting aimed to develop strategies for an integrated approach to research on temporomandibular joint diseases and disorders.

National Institute of Diabetes and Digestive and Kidney Diseases

Executive Summary

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 (ESRD)

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 erythrematosus). Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other Institutes and Centers (ICs), such as the importance of hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease. The NIDDK supports research that directly addresses the important women's health questions cited above, both through basic research directed to understanding underlying disease processes, and through clinical research that translates this understanding into therapies and preventive interventions. In FY 2007 and 2008, 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; estrogen and breast cancer; IBS and other functional gastrointestinal disorders; liver disease research; obesity and nutrition; kidney disease; PBS/IC; UTIs; and urinary incontinence. The Office of Research on Women's Health (ORWH) has worked with the NIDDK to foster research in many of these areas.

Accomplishments

Diabetes

An estimated 23.5 million Americans, including at least 11.5 million adult women, have diabetes. It is the leading cause of new-onset adult blindness, kidney failure, and nontraumatic lower extremity amputations. It also increases the risk of stroke, 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 minority women are affected disproportionately by ESRD 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 United States are at significantly increased risk of developing type 2 diabetes. The NIDDK supports many 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 Centers for Disease Control and Prevention (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 accumulating evidence is defining the role of estrogen in modulating insulin resistance at various stages in the lifecycle. NIDDK-supported research studies are examining the role of estrogen and other sex steroids in metabolic dysfunction and diabetes, including a study that is capitalizing on two large cohort studies (the Women's Health Study (WHS) and the Physicians' Health Study II (PHS II)) to examine the roles of endogenous steroid hormones and adipokines (fat cell cytokines) in the development of type 2 diabetes in women and men. Puberty confers insulin resistance and may precipitate type 2 diabetes in obese adolescents. NIDDK is supporting a multisite trial of treatment strategies for girls and boys already affected by type 2 diabetes in youth.

Continued Study of the Benefits of Preventing or Delaying Type 2 Diabetes

According to recent estimates, at least 57 million Americans have "prediabetes," a condition of impaired glucose metabolism that identifies them as high risk for developing type 2 diabetes. With cosupport from the ORWH, NIDDK undertook the landmark Diabetes Prevention Program (DPP) clinical trial. The DPP trial compared the effect of intensive lifestyle modification, treatment with the drug metformin, and standard medical advice on preventing the development of type 2 diabetes in adults at high risk. 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; ORWH support for the DPP 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. Now with continued support from the ORWH and other cosponsors, the NIDDK has completed "phase I" of the Diabetes Prevention Program Outcomes Study (DPPOS), a comprehensive followup study of participants in the DPP. The DPPOS is examining longer term effects of the trial interventions on prevention of type 2 diabetes and its cardiovascular complications in DPP participants. The DPPOS will compare outcomes for women and men, and by age and ethnicity. The DPPOS will enable researchers to better determine the lasting benefits to diabetes prevention and/or the delay of onset. The DPP itself also continues to yield new insights in diabetes risk and prevention. A recent study of DPP data revealed that participants in the lifestyle modification and standard medical advice arms who were also taking antidepressant medications at entry had a heightened risk of developing diabetes during the study. Depression is an established risk factor for diabetes. Future research should be pursued to determine whether antidepressant use independently influences diabetes risk, and, if so, what are the underlying mechanisms involved.

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 5 to 10 years following pregnancy. GDM occurs more frequently among obese women and women with a family history of diabetes, and 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 to 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—a result highlighted in the "Small Steps. Big Rewards. Prevent Type 2 Diabetes" campaign (see Information and Education Efforts To Reduce Health Disparities for more details). A newly funded study is building on these results by examining whether an exercise intervention in an ethnically diverse cohort of pregnant women with a history of GDM will help prevent its recurrence in subsequent pregnancy and thereby possibly help reduce adverse perinatal outcomes associated with GDM as well as the future risk for future type 2 diabetes.

New insights into how GDM develops have also been achieved. For example, during pregnancy, the body normally becomes less sensitive to the hormone insulin, and more insulin is needed to compensate. Studies suggest that, to meet this demand, the body's insulin-producing pancreatic beta cells proliferate, but whether impaired beta cell proliferation is key to GDM is still unclear. Working in a mouse model, researchers have discovered that changes in levels of a protein called menin (a protein previously known as an endocrine tumor suppressor) correlate with changes in

beta cell mass during pregnancy. Alteration of menin in pancreatic islets can lead to dysregulated glucose metabolism in pregnancy—suggesting that menin is also a key regulator of adaptive beta call proliferation during pregnancy. These results potentially point the way to a new therapeutic target for preventing or treating GDM in humans.

The NIDDK supports additional studies of glucose metabolism in pregnancy, including a study cofunded by the ORWH examining impaired glucose tolerance (one form of prediabetes) in pregnancy and subsequent maternal–fetal outcomes in young, low-income minority women, and a new pharmacogenetics study combining clinical data with genetic tools to see if variants in specific genes affect response to an insulin-sensitizing drug (pioglitazone) in women who have previously had GDM, in the hopes of being better able to identify individuals for whom this drug is an effective intervention.

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. Now, results from the SEARCH for Diabetes in Youth study, a large, population-based study of diabetes in racially and ethnically diverse youth, have shown that type 2 diabetes is diagnosed at a younger age in children exposed to maternal type 2 diabetes in utero. SEARCH is supported by NIDDK and the CDC. Ongoing initiatives that are directly addressing the rise of type 2 diabetes among children and adolescents should help to break this vicious cycle. These include the HEALTHY study, which 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. Researchers capitalizing on the SEARCH study have also found evidence that breastfeeding is protective against development of type 2 diabetes in African-American, Hispanic, and non-Hispanic White youth.

Understanding Sex Differences in Cardiovascular Complications of Diabetes

Cardiovascular disease (CVD) is the leading cause of death in patients with diabetes. The risk of death due to heart disease is increased two- to fourfold in all patients with diabetes as compared to their age-matched, nondiabetic counterparts. In women, the risk elevation is even greater—four- to sixfold. Moreover, while CVD mortality in men with diabetes has decreased, it has not decreased in diabetic women; the reasons for this sex difference may be due to biological, behavioral, or healthcare differences, or a combination of these factors. Researchers in the Translating Research Into Action for Diabetes (TRIAD) study supported by the CDC and NIDDK investigated sex disparities regarding the levels of control and the degree of medication treatment of CVD risk factors, such as levels of systolic blood pressure (SBP), LDL ("bad") cholesterol, and A1c (a measure of glycemic control), in a population-based cohort of managed care patients with diabetes. They found that in diabetic patients with a history of CVD, women had poorer control of SBP and LDL cholesterol than men, which may contribute to the sex disparity in CVD mortality trends. The study results suggest that diabetic women would benefit from more intensive treatment of these CVD risk factors. An ongoing clinical trial addressing cardiovascular disease and diabetes that may prove especially beneficial for women is the Look AHEAD (Action for Health in Diabetes) clinical trial. This long-term multicenter trial in over 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. Encouragingly, first-year results of the trial have shown that while A1C, blood pressure, and LDL cholesterol improved in both the lifestyle intervention and control groups, participants in the lifestyle intervention group saw greater improvement. Cosponsors include the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Nursing Research (NINR); the ORWH; the National

Center on Minority Health and Health Disparities (NCMHD); and the CDC.

Diabetic Women at Risk with Insulin Restriction

Type 1 diabetes is treated with insulin, usually administered via injections or a pump, to enable the body's cells to absorb glucose and to prevent life-threatening hyperglycemia. Intensive insulin therapy targeted at maintaining A1C close to nondiabetic levels has been proven to reduce risk of serious long-term health complications, including CVD. A number of psychosocial variables have been implicated as to why patients do not always adopt intensive diabetes management strategies despite these health benefits. They include general psychological distress (such as depression and anxiety), diabetes-specific distress, fear of hypoglycemia (a risk associated with intensive insulin therapy), concern about weight gain that accompanies insulin use, and related eating disorder behaviors. As a result of their concerns, some patients choose to restrict insulin use—that is, to take less than prescribed. Researchers examining the long-term impact of insulin restriction in a well-characterized cohort of women with type 1 diabetes found that insulin restriction reported at baseline was associated with not just a greater risk of complications, but also higher death rates over a decade later. Mortality appeared to be associated with insulin restriction in the context of eating disorders, rather than other issues. These results can inform future strategies for detecting women at risk for insulin restriction and its sequelae.

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. 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. For example, recent discoveries by these consortia have raised to 16 the known total of genes associated with development of type 2 diabetes. In many cases, the genetic variants were not previously known to be associated with type 2 diabetes. 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, AZ.

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 NIDDK, as well as the National Cancer Institute (NCI) and the National Institute on Aging (NIA) (through mid-2007), and NHLBI and the National Institute of Environmental Health Sciences (NIEHS) (beginning in mid-2007). Understanding the roles played by the nuclear receptor superfamily, a focused group of hormone-dependent and hormone-independent receptors important for development, metabolism, reproduction, and diseases is the central focus for NURSA. Using high throughput methods of genomic and proteomic analysis, coupled with computational approaches, NURSA has begun to understand how the receptors intersect with large complexes of coregulators at target genes to regulate expression.

Gene Regulation in Breast Cancer—Insights from NURSA and Other Studies

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 both the target genes and the driver of gene expression in hormone-sensitive breast cancers—DNA binding by the estrogen receptor—in an effort to better understand these cancers.

By applying computational models, NURSA investigators have been able to scan across multiple published gene arrays in breast cancer cells to identify important estrogen-dependent target genes. This method, a freely accessible Web resource called Gene Expression MetaSignatures (GEMS), provides the user a consensus for each gene in the system and overcomes lab-to-lab variability in microarray experiments to help identify important targets for further study to help understand the expression signature of breast cancer. One of the important advances of recent years has been the realization that hormones, such as estrogen, require coregulatory proteins to carry out their signaling program. One such coregulator, Steroid Receptor Coactivator-3, also called Amplified in Breast Cancer-1 (SRC-3/AIB-1) has been found to act as an important stimulus to estrogen-dependent growth, and when present in inappropriate amounts or times acts as a tumor promoter. Earlier studies had shown that SRC-3 is regulated by the addition of phosphate groups, as part of its activation. Now, researchers have identified an enzyme that removes the phosphate groups, down-regulating SRC-3. Other studies revealed additional sites where phosphate may be added, further demonstrating that a number of signaling pathways can intersect to stimulate the tumor-promoting effects of SRC-3. Understanding how estrogen and other hormones alter SRC-3 activity represents an important question in furthering our understanding of breast cancer.

In other studies, it has become clear that estrogen action at target genes includes recruitment of the basic cellular machinery necessary for the actual expression of a gene—most critically, the enzyme RNA polymerase II. However, it now appears that one major genomic outcome of estrogen signaling is the post-recruitment regulation of RNA polymerase II activity "preloaded" at target gene promoters—likely through specific chemical modifications to the enzyme—rather than recruitment of RNA polymerase II to the promoters. This advance helps to further our understanding of the complex interplay between hormone-receptor-coregulator and the target gene. Perturbations of individual parts of this signaling cascade can turn a normal signaling process into a deranged progression, leading to development of breast cancer. Finally, many studies have suggested that estrogen receptors may be activated by metabolites and drug-like compounds. Several of the latter have entered the clinic as Selective Estrogen Receptor Modulators (SERMs), with the ability to block estrogen action in estrogen-dependent tumors. Often, however, the tumor cells become resistant to the SERMs. Studies now show that some natural metabolites based on cholesterol, a natural element of the diet and product of the liver, can activate the estrogen receptor. One of these compounds, a naturally occurring oxysterol, appears to be present at high levels in some individuals and acts as a partial SERM on the estrogen receptor. In this case it may act to increase estrogen activity, an undesired effect when considering how best to treat estrogen-dependent tumors.

Osteoporosis

Osteoporosis occurs in people of all ethnic backgrounds. 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 this condition. Osteoporosis is characterized by low bone mass and deterioration of the bone architecture. The NIDDK supports extensive research on anabolic (growth-promoting) factors in bone, including calcium and vitamin D, parathyroid hormone (PTH), PTH-related protein (PTHrP), the Wnt family of nuclear receptors, sex steroids, and

bone-specific anabolic factors, such as the bone morphogenetic proteins. These are just some of the molecules that play a role in bone remodeling, the active breakdown and regeneration of bone that occurs throughout life. When these processes are perturbed, osteoporosis and other bone diseases can result. An exciting new study in mouse models has expanded our knowledge of the molecules that affect bone remodeling, which may in turn be critical to furthering our understanding of human bone diseases. The study focused on serotonin. Primarily thought of as brain neurotransmitter, most of the body's serotonin is actually produced and secreted into the circulation by the gut. To their surprise, the study investigators found that the crucial pathway affected in the bone diseases under study was the synthesis of serotonin in the gut; they subsequently found that serotonin inhibits proliferation of osteoblasts, explaining how serotonin can interfere with bone formation. Encouragingly, the study showed that reducing serotonin production in mice through genetic engineering could increase bone mass and prevent ovariectomy-induced bone loss, a condition that mimics postmenopausal osteoporosis. The discovery of a new role for gut-derived serotonin as a hormone inhibiting bone formation suggests potential new strategies to bolster bone mass. In another study, researchers investigated factors affecting bone density in HIV-infected women. They found evidence that bone mineral density is significantly reduced among low-weight versus normal-weight women, and that factors that may contribute to bone loss in HIV-infected women include reduced lean mass, reduced androgen levels, Caucasian race, and menstrual dysfunction. These results allow for developing strategies to screen, prevent, and treat bone loss in women with HIV.

Digestive Diseases

The NIDDK supports a substantial portfolio of basic and clinical research on digestive diseases, a number of which disproportionately affect women, including functional gastrointestinal disorders such as 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

In order to identify promising future research directions for digestive diseases, in 2005 the National Institutes of Health (NIH) established a National Commission on Digestive Diseases (NCDD) that was charged with developing a Long-Range Research Plan for the field. The NIDDK led NIH support for this effort, completed in 2008. The NCDD conducted an overview of the state-of-the-science in digestive diseases research and developed specific recommendations to improve approaches to diagnosis, treatment, and prevention; these are contained within the Commission's Plan. The ORWH joined the NCDD as an ex officio member, and will help coordinate NIH efforts to implement the research recommendations in the Plan for IBS and other digestive diseases that disproportionately affect women. In another effort, in December 2007, the NIDDK, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the NIH Office of Medical Applications of Research (OMAR), sponsored an NIH State-of-the-Science Consensus Conference on the Prevention of Fecal and Urinary Incontinence in Adults. Both these conditions are more common in women than in men. Cosponsors of the conference included ORWH, NINR, NCI, and NIA. NIDDK is working to implement recommendations from the Conference; for example, the Institute is laying the groundwork for a new campaign to increase awareness of fecal incontinence.

Irritable Bowel Syndrome

The functional gastrointestinal disorder IBS causes pain and constipation or diarrhea and 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 to design effective treatments. Researchers have also been examining sex and gender differences in this interplay. For example, investigators studying women with IBS have found that they perceive visceral pain associated with IBS differently than do healthy volunteers, and exhibit altered brain activity responses to both pain and the anticipation of pain. Pain responses are also heightened in women with IBS who have experienced physical abuse. Moreover, sex/gender-specific differences in brain activity in female and male IBS patients have been identified. These findings may lead to improved treatment strategies and outcomes for IBS-related pain. These studies were conducted by researchers at a Specialized Center of Research for Women's Health at the University of California, Los Angeles (UCLA), cofunded by NIDDK and ORWH, that is devoted to identifying sex-related differences in the visceral pain syndromes IBS and interstitial cystitis (a bladder disorder), which often occur in the same individual.

Liver and Biliary Disease Research

Liver and biliary disease is an important cause of morbidity and mortality in the United States. It disproportionately affects minority individuals and the economically disadvantaged. Women are disproportionately affected by certain liver diseases, such as primary biliary cirrhosis, drug-induced liver injury, and gallstones. A newly funded study will investigate genetic and environmental contributors to primary biliary cirrhosis using a biospecimen repository and registry of primary biliary cirrhosis patients and controls. An ongoing study cofunded by the ORWH is investigating how alpha-tocopherol (vitamin E) may adversely affect metabolism of therapeutic drugs and other xenobiotics by the liver, potentially providing new information about this commonly used dietary supplement.

To further research on liver and biliary diseases, the NIDDK is playing a leading role in promoting the implementation of the trans-NIH Action Plan for Liver Disease Research. This Plan, developed in 2004 under the auspices of the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee, 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; healthcare providers; and concerned lay persons. Implementation efforts include a recent review of progress for the first 3 years of the Action Plan, and planned meetings at the 5- 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 over half of non-Hispanic African-American women and over 40 percent of Mexican-American women are obese. Obesity increases risk for numerous life-threatening complications, including coronary heart disease, type 2 diabetes and its complications, stroke, and breast and colon cancer; it also causes morbidity by increasing the risks for osteoarthritis, gallstones, and urinary incontinence. The NIDDK supports basic and clinical research on multiple fronts—including nutrition, physical activity, epidemiology, behavioral intervention, surgery, neuroendocrinology, and fat cell biology—to help understand the underpinnings of obesity, including basic biological differences that predispose to sex/gender differences in fat accumulation and deposition; the role of the intrauterine environment on the development of obesity and other metabolic dysfunction in offspring; and how best to prevent overweight and effectively maintain a healthy weight. Ongoing special programs include the university-based core centers, the Clinical Nutrition Research Units (CNRUs) and the Obesity/Nutrition Research Centers (ONRCs). In 2007, in collaboration with the NIH Clinical Center, NIDDK opened a new NIH Metabolic Clinical Research Unit. This unit, located in the NIH Clinical Center,

houses facilities that are permitting investigators to conduct cutting-edge research on the physiology, prevention, and treatment of obesity. The NIDDK also supports the Weight-control Information Network (WIN). WIN provides health professionals and consumers with science-based information on obesity, weight control, and nutrition. (See Information and Education Efforts To Reduce 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 cochaired by the NIDDK and NHLBI Directors; multiple 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 is currently working toward an update of that plan. NIDDK efforts to meet the goals of the plan are being coordinated through its Office of Obesity Research. 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 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 United States) addressing these vulnerabilities; the ORWH is helping to foster this research. Several new and ongoing studies are testing strategies to prevent obesity in adolescent girls, including a randomized, controlled trial that will test the efficacy of an intervention that focuses on modifying diet, exercise, and other behaviors in college-age girls with body image concerns; a high-school-based program to increase physical activity among high school girls who are overweight or at risk of becoming overweight due to inactivity; and a study testing the effectiveness of a combined after-school dance program/reduced screen time intervention for preadolescent Latinas to reduce weight gain, improve metabolic and nutrition measures, and increase activity in these girls, who are at high risk for obesity. A new randomized clinical trial will test a community-based strategy to prevent transition to obesity among middle-aged, overweight African-American women by emphasizing current weight maintenance, rather than weight loss. Building on an ongoing study cohort of women recruited early in pregnancy (the Pregnancy, Infections, and Nutrition Study), a research team has uncovered a variety of risk factors for pregnancy weight gain in excess of Institute of Medicine recommendations, and retention postpartum. For example, women identified as having a pattern of unrestrained eating behavior prior to conception were more likely to have excessive gestational weight gain, suggesting that this is a group of women who would benefit from nutritional counseling during pregnancy. Another study is testing an intervention, "Active Mothers Postpartum," meant to help to induce greater weight loss and weight maintenance among women who were overweight or obese prior to pregnancy by leveraging naturally occurring weight changes and other aspects of the postpartum period that may help women to adopt behaviors that can help them attain a healthy weight.

Obesity Interventions

Researchers continue to identify and test successful strategies to induce and maintain weight loss. For example, the Program to Reduce Incontinence by Diet and Exercise (PRIDE) has found that weight loss resulting from an intensive, 6-month program of diet, exercise, and behavior modification reduces urinary incontinence in overweight and obese women (see section on Women's Urologic Health for more details); the added health benefit of reducing urinary incontinence may emerge as a significant motivator to help women achieve a healthier weight. The Look AHEAD clinical trial described previously is examining the health effects of an intervention to achieve and maintain long-term weight loss, through physical activity and decreased caloric intake, in obese adults with type 2 diabetes. Both Look AHEAD and PRIDE are cosupported by the ORWH. New research on obesity interventions includes a study, cofunded by the

ORWH, to understand factors associated with why primary care providers offer a no-cost weight reduction and management program to some women and not to others, as well as to understand factors associated with why women choose to enroll or not enroll in the program when it is prescribed; the ultimate goal is to understand factors that influence "reach" among minority and socioeconomically disadvantaged individuals and thereby uncover approaches to reducing health disparities. Surgical fat removal is employed both cosmetically and medically to reduce body fat, but the metabolic consequences of removing fat from different fat "compartments" in the body are still being investigated. A new study will focus on evaluating the effect of femoral lipectomy (liposuction) on subsequent regional adipose tissue reaccumulation and metabolic disease risk in pre- and postmenopausal women. Finally, a recent study has highlighted that bariatric surgery—a form of weight loss surgery—improves longevity for the severely obese. This retrospective study found significant reductions in death due to diabetes, CVD, and cancer among severely obese persons who had undergone surgery versus closely matched individuals who had not; deaths by all causes were reduced by 40 percent. At the same time, an observed increase in nondisease-related deaths (e.g., accidents and suicide) among the surgery patients warrants further research. The ongoing NIDDK-supported "Longitudinal Assessment of Bariatric Surgery (LABS)" consortium is conducting research on the effects of bariatric surgery on the health and well-being of patients with extreme obesity, in order 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. Sex/gender differences in the molecular mechanisms underpinning obesity development are also under study, such as gender-specific effects of genes involved in severe obesity. 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 are ongoing. NIDDK-supported researchers have made significant new discoveries in fat biology that may lead to new therapeutic approaches for obesity in both women and men. In particular, scientists have learned more about the origins and development of brown fat. Unlike white fat, which stores extra calories as fat for later use and is the tissue associated with obesity, brown fat (found in mammals) actually burns fat to generate heat, keeping an animal warm and slim. While it was thought for a long time that only human babies have brown fat, adults appear to retain some as well. Promising results from work in mouse models and tissue culture suggest approaches to increasing the proportion of brown fat as a possible intervention to counteract obesity. Capitalizing on knowledge of key metabolic pathways, scientists also recently found that they could boost muscle fibers and exercise endurance in mice with two different drugs—findings that, if extended to humans, could lead to better treatments for certain muscle disorders, frailty, obesity, and other conditions.

Kidney Disease and End-Stage Renal Disease

As of 2006, there were at least 506,000 persons receiving dialysis or living with a kidney transplant because of ESRD. Approximately 26 million people in the United States have earlier kidney disease. Diabetes and high blood pressure are the leading causes of kidney failure, and cardiovascular disease is a leading cause of death for ESRD patients. Prevalence of irreversible kidney failure is much higher in ethnic and racial minorities within the United States, and older American Indian and African-American women are affected disproportionately by kidney failure due to diabetes. Women are also differentially affected by certain kidney diseases, including kidney disease due to lupus and preeclampsia. A major 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 (see section on Information and Education

Efforts to Reduce 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; nearly half of those with kidney failure are African-American. 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. Newly funded studies include a genetics study cosupported by the ORWH that is identifying a new kidney disease susceptibility locus that has been identified in a lupus-prone mouse model, and two proteomic studies that, using large collections of urine samples derived from patients with lupus, aim to identify protein excretion patterns that are associated with flares of disease activity in patients with lupus nephritis.

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. New and ongoing studies are investigating the role of sex steroids in diabetic kidney disease and the possible mechanisms for the apparent protection of estrogen, including cross-talk between estrogen and the renin-angiotensin-system, and the effect of sex hormones on hemodynamics, vasoactive mediators, and fibrosis mediators in the diabetic kidney. These studies may help point the way to novel, gender-specific treatment strategies for diabetic nephropathy.

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. In 2007, the NIDDK completed the first full report of the "Urologic Diseases in America" (UDA) project. This important project has closed many of the former gaps in knowledge about the prevalence, incidence, treatment, and economic impact of urologic diseases in the United States; the Institute is working to promote the UDA findings. The Trans-NIH Women's Urology Research Planning Group (formerly the Women's Urologic Health Outreach Program), a partnership of the NIDDK and ORWH with input from Institutes across the NIH, is helping to identify and foster critical research and enhance outreach on urologic conditions that predominantly affect women. Already, the group has held a 2½-day scientific symposium on new research directions in urinary incontinence, and is planning a new symposium on urinary tract infections for 2009.

Advances in Treating Urinary Incontinence from the UITN

A conservative estimate is that approximately 13 million Americans, most of them women, suffer from urinary incontinence (UI). Urinary incontinence is a problem often associated with pregnancy, childbirth, and aging. Women can develop stress urinary incontinence (SUI), in which urine leaks under physical stress (e.g., coughing, laughing, sneezing, or lifting heavy objects); urge urinary incontinence, in which involuntary urine leakage occurs after a sudden urge to urinate; or a mixture of both. Research

is ongoing, but treatment options for urinary incontinence are currently limited to physical therapy to improve muscle tone and bladder control, medications, and surgical procedures. The NIDDK's Urinary Incontinence Treatment Network (UITN) is conducting clinical trials in order to improve these options. The UITN's Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) recently found that a procedure using a "sling" made from the patient's own tissue to support the bladder neck and prevent urine leakage under stress helps more women with SUI achieve dryness than the Burch colposuspension technique. This rigorous trial also provided insights into surgical therapy outcomes, such as differences in side effects from the two procedures, that will help women with SUI and their healthcare providers make better informed treatment decisions. An economic study of the SISTEr participants has also revealed the substantial personal economic costs of UI for these women prior to surgery. The UITN is currently conducting another trial for SUI, TOMUS (Trial Of Mid-Urethral Slings). TOMUS will compare the outcomes of two minimally invasive surgical sling procedures approved by the Food and Drug Administration (FDA) to treat this condition in women. These procedures use a synthetic mesh sling rather than patient tissue to support the bladder neck. Both procedures have been shown to be safe and successful in treating SUI, but it is unknown whether one is better than the other. UITN has also recently completed a treatment trial for women suffering primarily from urge urinary incontinence (UUI). Women with UUI are typically treated with either behavioral training to teach new habits or continence skills, or with drugs to reduce bladder activity; however, neither is completely effective for most women, and long-term medication adherence is difficult to achieve. The BE-DRI (Behavior Enhances Drug Reduction of Incontinence) trial tested whether women with UUI who received supervised behavioral training in addition to a course of drug therapy would have improved outcomes and possibly be able to discontinue drug therapy long term, versus women who received drug therapy alone. While the trial showed that adding a behavioral intervention was insufficient to help women stay off drug therapy and sustain treatment gains after short-term treatment (10 weeks), it also found that women in the combination behavioral intervention/drug therapy group reported more perceived improvement, satisfaction, and reduced symptom severity during active treatment—additional benefits of combination treatment that can now be explored. Finally, recruitment is beginning for a new trial to evaluate strategies for treating women with mixed incontinence. The UITN is cosponsored by NICHD and has also received support from the ORWH.

Weight Loss in Overweight and Obese Women Reduces Urinary Incontinence

Another key advance in UI treatment has emerged from the previously mentioned "Program to Reduce Incontinence by Diet and Exercise" clinical study. Obesity is an established risk factor for urinary incontinence in women. The PRIDE clinical trial, cosupported by the NIDDK and ORWH, recruited a total of 338 obese and overweight women who leaked urine at least 10 times per week and compared incontinence outcomes between women randomly assigned to a lifestyle intervention group—an intensive 6-month weight-loss program of diet, exercise, and behavior modification—or to a control group that received information about diet and exercise, but no training to help them change habits. Women in the intensive weight-loss group lost an average 8 percent of their body weight (about 17 pounds) and reduced weekly urinary incontinence episodes by nearly one-half (47 percent). In contrast, women in the information-only group lost an average of 1.6 percent of body weight (about 3 pounds) and had 28 percent fewer episodes. The PRIDE results demonstrate that weight loss significantly reduces episodes of urine leakage in overweight and obese women who experience incontinence. Identifying this additional health benefit of weight loss expands the options physicians and their patients can consider for treating incontinence in women. An economic study of the costs of the PRIDE weight-loss intervention is under way.

New Directions in Painful Bladder Syndrome/Interstitial Cystitis

Interstitial cystitis, 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 1 million, mostly women (90 percent). NIDDK-supported research is focused on elucidating the cause(s) of PBS/IC and on improving treatment and interventions. Recent studies suggest that clues to the etiology of PBS/IC may lie outside the bladder. NIDDK launched the multicenter Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network in 2008 to conduct innovative, collaborative studies of chronic urologic pelvic pain disorders in women and men—focusing on PBS/IC and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and the potential relationships between these conditions and other chronic pain disorders, such as fibromyalgia. The National Institute of Neurological Disorders and Stroke (NINDS), NICHD, and the ORWH will contribute scientific expertise to help shape the Network's research focus. Fundamental questions about potential causes, risk factors, and prevalence of PBS/IC are also being addressed through several large studies, including the RAND IC Epidemiology study, which is cosupported by the ORWH. Other PBS/IC studies include a study of the genetics of PBS/IC in human families, study of potentially altered gene expression in PBS/IC using an animal model, and a study to identify antibody biomarkers for this disease; the latter two are also cosupported by ORWH.

Mechanisms Underlying Recurrent Urinary Tract Infections

Urinary tract infections 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 7 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. Over the past several years, scientists at a Specialized Center of Research cosupported by the ORWH and NIDDK have been studying an *E. coli* lifecycle that may shed light on recurrent UTIs. Working in a mouse model, they have observed that UTI-causing *E. coli* can invade cells lining the bladder and form so-called intracellular bacterial communities (IBCs), which appear to help promote sustained infection. Following up on these intriguing findings in mice, the researchers recently uncovered evidence that IBCs play a role in human UTIs. Examining urine samples from women with either active infections or a history of UTIs, they found that urine from 14 of 80 women with UTIs (18 percent) contained IBCs, while samples from 20 asymptomatic women with a history of UTI showed no evidence of IBCs. Urine samples were also analyzed for the presence of filamentous bacteria—a form of the UTI-causing *E. coli* bacteria that can evade the host immune response. While nearly half of the urine samples from women with a UTI had filamentous bacteria, none were detected in the asymptomatic group. Filamentous bacteria were detected in all of the IBC-containing urines, compared to 29 percent of samples with no detectable IBCs. This study demonstrates, for the first time, that filamentous bacteria and IBCs do occur in some women with UTIs. Additional studies need to be done to determine whether IBCs contribute to recurrent infections in women as they do in mice. However, these results already suggest that new treatment strategies that address the host-evading nature of IBCs and filamentous bacteria may be beneficial for women who test positive for IBCs.

Vaccination May Help Prevent Recurrent Urinary Tract Infections in Women

In a recent clinical trial, researchers found that a vaccine approach may be effective at preventing recurrent *E. coli* UTIs in women. In the trial, adult women with a history of frequent UTIs were randomly assigned to one of three treatment groups. One group received placebos only, one group received primary vaccinations, and one group received primary vaccinations plus additional monthly vaccine "boosters." The vaccine was designed to build up the body's immune defenses in the urogen-

ital tract, where UTI pathogens take hold. The team found that vaccination was most effective against *E. coli* UTIs when vaccine boosters were provided. Almost 73 percent of vaccinated women who received boosters remained infection free 160 days after starting treatment, versus only 30 percent of those on placebos. The vaccine plus boosters regimen was especially effective at slowing the rate of *E. coli* UTI recurrence among sexually active women, and among women less than 52 years old. Currently, women are prescribed antibiotics to prevent UTI recurrences, but drug-resistant UTI bacteria are increasingly making this approach less effective. The encouraging results of this trial suggest that a vaccination strategy targeting the urogenital tract may prove a good alternative approach to prevent recurrent UTIs in women.

Understanding the Contribution of Diabetes to Urologic Conditions in Women

The NIDDK is supporting mechanistic studies of how diabetes—both type 1 and type 2—contributes to urinary incontinence and urinary tract infections in women; the ORWH is helping to foster these studies. New insights into prevalence and/or risk factors have emerged from studying urologic conditions in women with type 1 diabetes enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC), the followup study of the Diabetes Control and Complications Trial (DCCT) cohort. Investigators have found urinary incontinence is prevalent in these women, with the prevalence of urge incontinence far greater than that observed in women with normal glucose levels (using a subgroup of women who participated in the 2001 to 2002 National Health and Nutrition Examination Survey (NHANES) as the comparison group). Notably, the prevalence of urinary incontinence with monthly or greater frequency of incontinence episodes was greater than that of other, well-recognized diabetes complications—diabetic nerve, eye, and kidney disease. These results highlight the importance of screening for UI in women with type 1 diabetes. Similarly, women at year 10 of the EDIC study were surveyed to assess the prevalence of urinary tract infections (cystitis and pyelonephritis) in the preceding 12 months. Investigators found that, when compared to a subset of women participants in the NHANES III study (a different NHANES group), prevalence of cystitis was actually similar between women with type 1 diabetes and nondiabetic women. Sexual activity, rather than glycemic control or vascular complications, was associated with an increased risk of women with type 1 diabetes in this study. These results are particularly important in that there are few published studies that assess the prevalence of and risk factors for UTIs in women with type 1 diabetes (versus type 2 diabetes).

Initiatives

Program Announcements (PAs)

- **Collaborative Interdisciplinary Team Science in Diabetes, Endocrinology, and Metabolic Diseases (R24)**
  The purpose of the Collaborative Interdisciplinary Team Science Program described in this announcement is to provide support to enable strong investigative teams to do inter- and/or transdisciplinary research on a complex problem in biomedical science relevant to diabetes, endocrinology, and metabolic diseases (PAR-08-182).

- **Seeding Collaborative Interdisciplinary Team Science in Diabetes, Endocrinology, and Metabolic Diseases (R24)**
  This PA seeks to provide initial support to enable strong new investigative teams to form and to foster preliminary research activities in anticipation of applications to the parent PA (see PAR-08-182). PA sponsor: NIDDK (PAR-08-181).

- **Adverse Metabolic Side Effects of Second Generation Psychotropic Medications Leading to Obesity and Increased Diabetes Risk (R01)**
  This PA invites applications for studies examining the adverse metabolic effects of psychotropic medications in animal models and across the human lifespan (including pediatric, adult, and geriatric populations). Areas of interest include increasing the understanding of the nature, rates, and pathophysiology of adverse metabolic effects of psychotropic medications; elucidating biomedical and psychosocial risk

factors for the development of metabolic adverse effects of psychiatric therapeutics; and developing interventions to prevent and/or mitigate metabolic adverse effects across the lifespan. PA cosponsors: NIDDK and the National Institute of Mental Health (PAR-08-160).

- **The Role of Gastrointestinal Surgical Procedures in Amelioration of Obesity-Related Insulin Resistance and Diabetes Independent of Weight Loss (R01)**
  The objective of this PA is to encourage research that explains the underlying mechanism(s) by which various gastrointestinal surgical procedures ameliorate obesity-related insulin resistance and diabetes independent of the resultant weight loss. Studies of other technologies, procedures, or devices that may mimic the effect of gastrointestinal surgery will also be considered appropriate. PA sponsor: NIDDK (PA-08-014).

- **Identifying and Reducing Diabetes and Obesity-Related Health Disparities Within Healthcare Systems (R01)**
  This PA requests applications designed to identify or address factors or barriers that result in disparate outcomes within a healthcare system. Research is sought that examines at least one of the following factors in a healthcare system and/or the interaction among these factors: healthcare professionals, healthcare organizations, and the patients and communities they serve. PA sponsor: NIDDK (PA-07-388).

- **Diet Composition and Energy Balance (R01)**
  This PA invites applications investigating the role of diet composition in energy balance, including studies in both animals and humans, 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 cosponsors: NIDDK, NCI, National Center for Complementary and Alternative Medicine (NCCAM), NHLBI, NIA, National Institute on Alcohol Abuse and Alcoholism (NIAAA), NICHD, NINDS, and the Office of Dietary Supplements (ODS) (PA-07-218).

- **Development of Disease Biomarkers (R01)**
  The goal of this PA is to provide resources to validate candidate 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, for which there are no or very few biomarkers, or for which standard biomarkers are currently prohibitively invasive or expensive. PA cosponsors: NIDDK, National Institute of Biomedical Imaging and Bioengineering (NIBIB), NIAAA, ODS (PA-07-052).

- **Research on Improving Health Care for Obese Patients (R01)**
  This PA seeks applications from institutions/organizations that propose to conduct research to determine the barriers to optimal health care for obese patients, and to test innovations or modifications in care delivery to improve health outcomes for obese patients independent of weight loss. PA cosponsors: NIDDK, NCI, NHLBI, NIA, NICHD, and the National Institute of Nursing Research (NINR) (PA-07-013).

- **Basic Research in the Bladder and Lower Urinary Tract (R01)**
  This PA invites applications for research focusing on basic cellular, molecular, genetic, and developmental mechanisms of the normal and abnormal function of the bladder and lower urinary tract. Important goals of this PA include attracting 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, and encouraging basic science studies addressing sex/gender differences that may predispose women to bladder and lower urinary tract disorders. PA cosponsors: NIDDK, NCI, NIA, and ORWH (PA-07-023).

- **Noninvasive Methods for Diagnosis and Progression of Diabetes, Kidney, Urologi-**

cal, Hematological, and Digestive Diseases (R01)
This PA seeks to stimulate application of imaging and other non- or minimally invasive technologies to detect, characterize, diagnose, and identify persons with predisposition to, or monitor treatment of, diseases of interest to NIDDK, as well as to develop new, robust surrogate markers for clinical trial endpoints, and new ways to characterize normal and pathological tissues in vivo. PA sponsor: NIDDK (PA-07-025).

- **Health Disparities in NIDDK Diseases (R01)**
  This PA calls for research to understand and mitigate issues of health disparities in high-priority diseases within the NIDDK mission, 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 sponsor: NIDDK (PA-07-027).

- **Insulin Signaling And Receptor Cross-Talk (R01)**
  This PA seeks 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 our 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 cosponsors: NIDDK and NIA (PA-07-058).

NIDDK is also participating in the following:

- Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01) (PA-08-246)
- Research Supplements To Promote Diversity in Health-Related Research (PA-08-190)
- Research Supplements To Promote Reentry into Biomedical and Behavioral Research Careers (PA-08-191)
- The Effect of Racial and Ethnic Discrimination/Bias on Healthcare Delivery (R01) (PA-08-083)
- Research on the Economics of Diet, Activity, and Energy Balance (R01) (PA-08-078)
- Thyroid in Aging (R01) (PA-08-037)
- Improving Diet and Physical Activity Assessment (R01) (PAR-07-259)
- Health Disparities Among Minority and Underserved Women (R01))(PA-07-154)

Requests for Applications (RFAs)

(Note, this list includes select RFAs led by other ICs for which NIDDK is a cosponsor.)

- **Implementation Planning Grants for Educational, Behavioral, or Social Studies for Translation of Genetic Factors in Common Diseases (U34)**
  On behalf of the NIH Genes, Environment, and Health Initiative, NIDDK solicited Implementation Planning Grant (U34) applications from institutions/organizations that propose to plan for multicenter research on (1) educational and communication initiatives for healthcare providers and consumers regarding interpretation of and findings from genetic studies of common diseases and the results of their dissemination and (2) behavioral or psychosocial aspects of clinical application of genetic findings (RFA-DK-08-003).

- **Translation of Common Disease Genetics into Clinical Applications (R21)**
  On behalf of the NIH Genes, Environment, and Health Initiative, NIDDK solicited Exploratory/Developmental Clinical Research Grant (R21) applications from institutions/ organizations that propose (1) clinical studies using information from genome-wide association or other genetic studies in common diseases; (2) development and assessment of diagnostic, clinical trial, epidemiologic, and risk analytic tools for use in clinical research or practice; and (3) cost-effectiveness studies of clinical applications of genetic information (RFA-DK-08-004).

- **Limited Competition: Renewal of Diabetes Prevention Program Outcomes Study – Phase 2 (U01)**
  The purpose of this limited competition was to continue patient followup of the original Diabetes Prevention Program cohort through a Diabetes Prevention Program Outcomes Study Phase 2 cooperative agreement (RFA-DK-08-504).

- **Limited Competition: The Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D) (U01)**
  This RFA invited a Cooperative Agreement application for a limited competition from the Data Coordinating Center (DCC) for continuation of the STOPP-T2D studies, including TODAY and HEALTHY (RFA-DK-08-502).

- **Announcement of a Limited Competition for the Continuation of the Longitudinal Assessment of Bariatric Surgery (LABS) (U01)**
  This was a limited competition RFA soliciting cooperative agreement (U01) applications from investigators currently supported under RFA-DK-03-006 to continue the LABS Consortium to study bariatric surgery and its role in the understanding and treatment of obesity and its complications (RFA-DK-08-501).

- **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 NIDDK (RFA-DK-08-002).

- **Limited Competition: Continuation of the Chronic Renal Insufficiency Cohort (CRIC) Study (U01)**
  Recognizing the need to learn more about the relationship between chronic kidney disease (CKD) and CVD and the factors associated with rapid loss of kidney function leading to kidney failure, the NIDDK established the CRIC Study in 2001. This RFA was a limited competition for continuation of the CRIC Study and related research studies (RFA-DK-07-502).

- **Multidisciplinary K12 Urologic Research (KURe) Career Development Program**
  The purpose of this RFA was to solicit applications to support institutional career development programs in urological research that will assist M.D.s, Ph.D.s, and M.D./Ph.D.s interested in benign urological disease or urological research related to the mission of NIDDK to develop the skills necessary to initiate and sustain an independent research career (RFA-DK-07-006).

- **George M. O'Brien Urology Research Centers (P50)**
  The purpose of this program was to establish George M. O'Brien Urology Research Centers to create a research community for major urologic diseases and syndromes within the NIDDK mission interests (RFA-DK-07-004).

- **Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (U01)**
  This RFA invited applications from qualified investigators to participate in a multicenter cooperative research network to advance understanding of interstitial cystitis/painful bladder syndrome, and chronic prostatitis/chronic pelvic pain syndrome, CP/CPPS. Cosponsors included NICHD, NINDS, and the ORWH (RFA-DK-07-003).

- **Obesity Nutrition Research Centers (P30)**
  This RFA invited new and/or renewal applications for Obesity and Nutrition Research Centers. The ONRCs are core centers (P30) that are part of an integrated program of obesity and nutrition-research support provided by NIDDK (RFA-DK-07-001).

- **Silvio O. Conte Digestive Diseases Research Core Centers (P30)**
  This RFA invited applications for Silvio O. Conte DDRCCs, with the goal of supporting one new or renewal center. The DDRCCs are part of an integrated program of digestive and liver diseases research support provided by NIDDK (RFA-DK-06-017).

- **Silvio O. Conte Digestive Diseases Research Development Centers (R24)**
  This RFA invited new and renewal applications for Silvio O. Conte DDRDCs. The DDRDCs are part of an integrated

program of digestive and liver diseases research support provided by NIDDK (RFA-DK-06-018).

- **Minority Organ and Tissue Donation (R01)**
  This RFA invited investigators to apply for a grant to develop educational programs to increase the number of organs and tissue donated for transplantation in racial and ethnic minority communities, and other underserved populations (RFA-DK-06-016).

- **NIDDK Mentored Clinical Scientist Award to Promote Diversity in Health-Related Research (K08)**
  This RFA solicited applications for a 3-year career development award made to clinician scientists from diverse backgrounds, including individuals from underrepresented racial and ethnic groups and individuals from socially, culturally, economically, or educationally disadvantaged backgrounds. This award provides an opportunity career in laboratory or clinical research. Cosponsor: Office of Dietary Supplements (ODS) (RFA-DK-06-015).

- **Translating Basic Behavioral and Social Science Discoveries into Interventions to Reduce Obesity: Centers for Behavioral Intervention Development (U01)**
  This NHBLI-led RFA solicited cooperative agreement (U01) applications from institutions/organizations that propose to translate findings from basic research on human behavior into more effective clinical, community, and population interventions to reduce obesity and improve obesity-related behaviors. Cosponsors: NCI, NIDDK, Office of Behavioral and Social Sciences Research (OBSSR) (RFA-HL-08-013).

Conferences and Workshops

- **Mathematical Modeling of Human Metabolism and Body Weight Regulation (September 27–28, 2008)**
  An important new field is emerging that uses mathematical and computational methods to address key questions about human metabolism and body weight regulation. This workshop facilitated communication and collaboration between experts in obesity and metabolism research and leading investigators in the fields of mathematical and computational modeling researchers, and introduced new investigators to this exciting area of study.

- **2008 Diabetes and Obesity Disparities in Healthcare Systems Conference (June 30–July 1, 2008)**
  This conference focused on promoting healthcare-based research aimed at reducing or eliminating disparities in diabetes and obesity-related outcomes; it included a grants-writing workshop targeted to junior investigators or investigators new to the field.

- **NIDDK Defining the Urologic Chronic Pelvic Pain Syndromes (June 16–17, 2008)**
  This symposium convened a broad array of experts to discuss the multiplicity of factors involved in defining the urologic pelvic pain syndromes. The meeting explored the pros and cons of developing a unifying definition, as well as the need for phenotyping persons with these disorders.

- **Workshop on the Establishment, Maintenance, & Turnover of Fat Depots (May 21–22, 2008)**
  This workshop focused on the molecular players involved in the establishment, maintenance, and turnover of different fat depots. Speakers presented what is known about the molecular determinants of depot size and sites of deposition, cellular makeup (number and types of adipocytes, macrophages, and endothelial cells), and factors that control remodeling and turnover of different fat depots.

- **Diabetes Genes and Beta Cell Function (April 21–22, 2008)**
  This workshop focused on newly discovered risk loci for type 2 diabetes, specific beta-cell functions and pathways potentially influenced by these genes, and linkage of genes conferring risk to the clinical progression of diabetes, with the goal of identifying new strategies that enable an integrated correlation of at-risk loci with suboptimal beta-cell functioning.

- **Genes, Environment, and Health Initiative (GEI): Translating Whole-Genome Association Data into Clinical Practice (March 10–11, 2008)**
  This meeting explored the challenges in using GEI basic findings to have a positive impact on health. It featured presentations on important new genetic findings on certain diseases, approaches to using those findings for therapeutic or diagnostic purposes, and the ethical and social issues inherent in such research.

- **2008 Urologic Diseases in America (UDA) Symposium (February 25–26, 2008)**
  This meeting focused on both the current UDA and new ideas for a next phase of the UDA project.

- **NIH State-of-the-Science Conference: Prevention of Fecal and Urinary Incontinence in Adults (December 10–12, 2007)**
  Both fecal and urinary incontinence are more common in women than in men. This NIH conference was sponsored by NIDDK, in collaboration with NICHD and the NIH OMAR. Cosponsors of the conference included ORWH, NINR, NCI, and NIA.

- **Nuclear Receptors in Liver and Digestive Diseases: A Research Workshop (November 7–8, 2007)**
  This meeting brought together scientists focused on the mechanisms and basic science of nuclear receptor (NR) biology and translational and clinical investigators focused on digestive and liver diseases in which NR pathways have been implicated, to review the present state-of-the-art knowledge of nuclear receptors, to promote cross-fertilization among these investigators, and to integrate the current understanding of NR biology and the current clinical challenges for a variety of digestive and liver disease states.

- **Annual NMRI Southern Region Workshop (October 3–4, 2007)**
  This meeting of the Network of Minority Research Investigators (NMRI) focused on science, career development, and networking opportunities.

- **Clinical Proteomics in Diabetes and its Complications (July 20, 2007)**
  This workshop focused on the application of proteomic technologies to clinical studies relevant to diabetes and its complications.

- **Workshop on Advancing Urologic Science and Career Development (February 15–16, 2007)**
  This workshop convened a broad array of experts from NIH, academia, and health advocacy groups, and from within and outside of the urology field, to help identify gaps and opportunities for these entities to strengthen and foster urologic research and research training.

- **Frontiers in Painful Bladder Syndrome and Interstitial Cystitis Symposium (October 25–27, 2006)**
  This scientific meeting focused on the current state of research and clinical treatments for PBS/IC in the United States and abroad. Through oral presentations and poster sessions, the meeting provided a forum for discussion of the definition and etiology of interstitial cystitis and painful bladder syndrome, and the exchange of information and ideas on current and contemplated research on and treatments of the disease and its symptoms.

- **Predictors, Pathogenesis, and Prevention of Insulin Resistance and Type 2 Diabetes Meeting (October 4–5, 2006)**
  In collaboration with FDA, NIDDK convened this meeting for researchers to share the latest information about predictors for type 2 diabetes and discuss obstacles and solutions for widespread use of a predictor system; explore potential common etiology pathways for development of syndromes associated with insulin resistance, obesity, and type 2 diabetes; and reexamine the adequacy of the current data to support an indication to treat for prevention of diabetes.

Health Disparities

Research Efforts To Reduce Health Disparities in NIDDK Diseases

Several of the diseases that disproportionately affect racial and ethnic minority populations in the United States are high-priority

research areas for NIDDK. These include type 2 diabetes, obesity, nutrition-related disorders, hepatitis C, gallbladder disease, *H. pylori* infection, sickle cell disease, kidney diseases, and metabolic, gastrointestinal, hepatic, and renal complications from infection with HIV. Moreover, some of these diseases affect women and men differently within these disproportionately affected groups. The NIDDK Office of Minority Health Research Coordination (OMHRC) oversees Institute efforts to address these disparities. 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, Alaska Native, Native Hawaiian, and other Pacific Islanders. Through the NMRI, NIDDK elicits recommendations for strategies to enhance the opportunities and implement mechanisms for support of minority investigators in biomedical research. The NMRI is helping NIDDK to advance scientific knowledge and contribute to the reduction and eventual elimination of racial and ethnic health disparities. The OHMRC also promotes NIDDK and NIH research training programs that help promote diversity in the biomedical research community.

Web site: http://www2.niddk.nih.gov/Funding/FundingOpportunities/Minority_Health_Research_Coordination/.

Information and Education Efforts To Reduce Health Disparities

Several recent new or enhanced NIDDK-supported informational activities also address minority health disparities.

Trans-NIDDK

▶ **NIDDK Web site Features Health Information in Spanish**

The NIDDK has launched three new portals to feature Spanish-language materials and resources about diabetes, digestive diseases, and kidney and urologic diseases on its Web site. People looking for information about these diseases in Spanish can now go directly to the Spanish-language portal pages (see below), where they will find an A to Z list of topics and titles. Also, the online system for ordering NIDDK materials now includes descriptions in Spanish of available publications to help visitors choose the resources they want. Bilingual staff at the Clearinghouses can also assist with phone orders from Spanish-speaking requestors.

- Diabetes: http://www.diabetes-espanol.niddk.nih.gov
- Digestive Diseases: http://www.digestive-espanol.niddk.nih.gov
- Kidney and Urologic Diseases: http://www.kidney-espanol.niddk.nih.gov

▶ **NIDDK's Awareness and Prevention Series**

The NIDDK has developed a new health information series to raise awareness about diabetes, digestive diseases, and kidney and urologic diseases among people not yet diagnosed with these illnesses. The NIDDK developed the Awareness and Prevention Series for community health fairs, workplace health forums, family reunions, and other similar events. Publications in the series are each two-page fact sheets—one side in English, the other side in Spanish—on a wide range of health topics. Each sheet gives readers a snapshot of an illness, highlighting risk factors, symptoms, prevention tips, and where to go for more information. By raising awareness of these illnesses—many of which disproportionately affect racial and ethnic minorities—NIDDK is providing necessary information to the public to promote prevention and early diagnosis of many common conditions.

See: http://www2.niddk.nih.gov/HealthEducation/Awareness+and+Prevention+Series.htm

▶ **Diabetes**

Diabetes disproportionately affects racial and ethnic minorities in the United States. The National Diabetes Education Program, jointly sponsored by NIDDK and the CDC, works in partnership with public and private groups on efforts to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and,

ultimately, to prevent the onset of diabetes. The NDEP runs a national multicultural type 2 diabetes prevention campaign—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 ads. The "It's Never Too Early To Prevent Diabetes" component of this campaign is tailored to women with a history of gestational diabetes and their offspring—especially women from racial and ethnic minority groups in the United States, who are at particularly high risk for GDM. Another key NDEP campaign, "Control Your Diabetes. For Life," emphasizes the key elements of diabetes management to help prevent heart attack, stroke, and other diabetes complications. Materials for both campaigns are available in up to 15 different languages. Materials are also available to help children with diabetes, their families, and school personnel deal with diabetes. New consumer materials available from the NDEP include a CD/DVD called Movimiento for Hispanics and a CD/DVD called Step by Step for African-Americans; both were created to encourage active lifestyles, and include a music video and original songs. An educational toolkit targeting American Indian and Alaska Native youth called Move It! And Reduce Your Risk of Diabetes encourages more physical activity in schools. The kit contains posters, fact sheets, resource lists, success stories, and a CD–ROM. Finally, the NDEP has developed a version of its Web-based publications catalog in Spanish (see below).

- NDEP: http://www.ndep.nih.gov/
- NDEP catalog in Spanish: http://www.ndep.nih.gov/publications/Publicaciones.aspx
- NDEP youth materials: http://www.ndep.nih.gov/diabetes/youth/youth.htm

▶ **Obesity**

It is estimated that over 80 percent of adult non-Hispanic Black women in the United States are overweight or obese, using the body mass index measurement—placing them at risk for many serious health complications. The Weight-control Information Network 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 has also developed the "Sisters Together Program Guide." The Program Guide walks community leaders through the steps of program planning, implementation, and evaluation. WIN also offers six Spanish-language publications for adults and teens concerning healthy eating and physical activity such as "Hazte cargo de tu salud! Guia para jovenes (Take Charge of Your Health! A Guide for Teenagers!)" and its four-part series, "Como Alimentarse y Mantenerse Activo Durante Toda La Vida (Healthy Eating & Physical Activity Across Your Lifespan)." WIN has continued to pursue community outreach opportunities, including through an exhibition at the Women's Heart Day Health Fair in Washington, DC, in February 2007 and 2008.

http://www.win.niddk.nih.gov/index.htm.

▶ **Kidney Disease**

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 United States 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. This educational program seeks to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk—those with diabetes, high blood pressure,

cardiovascular disease, 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 created an educational brochure tailored specifically for African-Americans at risk for kidney disease. The brochure—Kidney Disease: What African-Americans Need to Know—explains the connections among diabetes, high blood pressure, and kidney disease, and encourages those at risk to talk to their healthcare providers about getting tested. 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. The NKDEP's Spanish-language initiative is meant to raise awareness about risk factors for chronic kidney disease among Hispanic Americans; it includes a Web site (http://www.nkdep.nih.gov/espanol/) and 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. To help primary care providers and other health professionals explain estimated GFR results to their Spanish-speaking patients, NKDEP has adapted its Explaining GFR: A Tear-Off Pad for Clinical Use into Spanish. In addition to including simple explanations of the kidneys, kidney function, and GFR results, as well as suggested actions for maintaining kidney health based on the GFR result, the tool presents key education concepts and talking points for providers in Spanish.

Sources of Statistics for NIDDK Report on Research on Women's Health FY 2007–2008

Diabetes

National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics, 2007 fact sheet. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 2008. NIH Publication No. 08–3892, June 2008. http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm.

Obesity

Statistics Related to Overweight and Obesity. http://win.niddk.nih.gov/statistics/index.htm. Updated May 2007.

Ogden et al., Prevalence of overweight and obesity in the United States, 1999–2004. *Journal of the American Medical Association* 295:1549–1555, 2006.

End-Stage Kidney Disease and Chronic Kidney Disease

U.S. Renal Data System, *USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD: 2008. (http://www.usrds.org/atlas.htm)

Coresh, J., et al., Prevalence of Chronic Kidney Disease in the U.S. during 1988-1994 and 1999-2004. *Journal of the American Medical Association* 298:2038-2047, 2007.

Urologic Diseases

The National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). Kidney and Urologic Diseases Statistics for the United States. NIH Publication No. 08–3895

February 2008. http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm#up

Litwin, M.S., Saigal, C.S., editors. *Urologic Diseases in America*. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2007; NIH Publication No. 07–5512 http://kidney.niddk.nih.gov/statistics/uda/

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National Institute on Drug Abuse

Executive Summary

As the foremost authority on drug abuse and addiction, sponsoring the vast majority of the world's research on the subject, National Institute on Drug Abuse (NIDA)-supported science addresses the most fundamental and essential questions about drug abuse. We do 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 effort is a major focus on investigating 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; has different consequences; and intervention outcomes may be enhanced by gender-specific considerations. In recognition of the important role that sex/gender plays in drug abuse, NIDA has strongly supported research to identify sex/gender differences and sex/gender–specific aspects of drug abuse and addiction and apply these findings to design, test, and implement more effective drug abuse prevention, treatment, and services for both males and females across the lifespan.

Our current knowledge base for understanding drug abuse in males and females is not equal. Historically excluded from drug 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 National Institutes of Health (NIH) published guidelines on including women and minorities as clinical research subjects, the number of reports being published on drug abuse treatment for women has increased steadily, but more research needs not only to 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.

Women's Health and Sex/Gender Research at NIDA

NIDA's Women and Sex/Gender Differences Research Coordinator and Deputy Coordinator, along with NIDA's Women & Gender Research Group (WGRG), lead the effort at NIDA to promote research on issues specific to women and sex/gender differences in drug abuse. The WGRG has representation from all of NIDA's divisions and offices, representing research topics that span from genetics and basic biology to risk factors, prevention, consequences, and treatment of drug abuse. The major goal of this effort, which has been ongoing for well over a decade, is to infuse the study of sex/gender differences and female-specific issues in all areas of drug abuse research and to disseminate resultant findings.

NIDA's Women and Sex/Gender Differences Research Program Coordinator and Deputy Coordinator serve in a coordinating role for NIDA's scientific research in this area and as liaisons with NIH Institutes and Centers (ICs), the U.S. Department of Health and Human Services (HHS) Office on Women's Health, and other HHS agencies, as well as scientific organizations. The Coordinator and Deputy Coordinator represent NIDA on the Office of Research on Women's Health's (ORWH's) Coordinating Committee on Research on Women's Health.

Accomplishments

The research findings summarized below and published over the past 2 years are representative of NIDA's research on women and sex/gender differences. These findings are presented under five major topics: Basic and Clinical Neuroscience; Epidemiology and Etiology Research; Prenatal Drug Exposure and Pregnant and Postpartum Women; Treatment and Health Services; and HIV/AIDS. Collectively, these findings provide evidence for the importance and fruitfulness of taking a sex/gender-based research approach and analyz-

ing data separately for males and females. Importantly, they strongly suggest that the identification and understanding of sex/gender differences can, in the long run, have implications for tailoring prevention and treatment interventions to optimize outcomes for both males and females.

Basic and Clinical Neuroscience Research

Our research in animals is providing proxy measures for humans and helping to identify biological and behavior factors underlying sex differences in response to drugs and their consequences. Our clinical studies similarly are exploring sex differences in the biological and behavioral mechanisms underlying drug effects, both with respect to etiology and consequences.

Basic Animal Model Research—from Prenatal to Comparisons of Adolescents and Adults

Sophistical animal models of addiction are helping us to better understand the nature of the addiction process and factors that affect it, as well as the behavioral and physiological consequences of drug addiction—across the lifespan, from the prenatal period to adolescence and adulthood. Adolescence is a particularly vulnerable time, as teens are more likely to suffer adverse drug abuse consequences, including addiction. Studying sex differences in rat models that reflect the adolescent years in humans can also signal differences by sex and has led to interesting and informative findings for various drugs of abuse, which may eventually inform responsive prevention and treatment approaches. Several basic NIDA-supported research findings are summarized below.

- **Consequences of Paternal Cocaine Exposure**
  A study in newborn rats shows reduction in biparietal head diameter in rat pups sired by males who inhaled cocaine prior to mating, suggesting a decreased cerebral volume. Deficits were also observed in tests of attention and working memory, with greater impairment of the latter exhibited by females than by males. These data raise the possibility that in humans, children may be negatively impacted by their father's preconception use of cocaine and perhaps other drugs as well.

- **Sex Differences in Adolescent-Onset vs. Adult-Onset Nicotine Self-Administration**
  Researchers at Duke University found that both male and female adolescent rats self-administered more nicotine on a per kilogram basis than adults. Additionally, two important sex differences also emerged: first, males were more vulnerable to this adolescent enhancement effect than females—threefold in males (compared to adults) versus twofold in females. Second, female rats persisted in higher rates of self-administration when they became adults, while male rats' self-administration normalized to adult-like levels. Thus, although male rats appear to be more vulnerable than females to the adolescent enhancement effect, only females exhibited a persistence of this enhancement into adulthood. This study supports previous studies showing potentially greater vulnerability to drug use consequences for females versus males.

- **Sex Differences in the Effects of Delta-9-Tetrahydrocannabinol (THC) on Spatial Learning in Adult and Adolescent Rats**
  Researchers at Duke University found that THC, the main psychoactive substance in marijuana, delivered acutely over five test sessions, disrupts spatial learning more potently in adolescent rats than in adults and more potently in adult females than adult males; male adults were unaffected. In a second experiment, designed to assess the effects of chronic THC on subsequent learning, separate groups of male and female adolescent and adult rats were treated with THC for 21 days and tested later for spatial learning. Chronic THC treatment did not produce learning deficits in any of the groups. The third experiment, with adolescent and adult females, was a THC dose-response acute study conducted to parallel a previously published experiment with males. Consistent with the earlier outcome in males, THC produced a dose-response impairment in spatial learning, with evidence of greater dose sensitivity in adolescents. The results of the present study

join a growing body of drug abuse research showing that outcomes observed in adult males do not always generalize to females and to adolescents, highlighting the potential limitations of research conducted with only adult male subjects.

- **Sex Differences and Hormonal Factors in the Acquisition and Maintenance of Cocaine Self-Administration in Adolescent Rats**
  Previous animal model research has found that females more rapidly acquire cocaine self-administration than males, that a greater percentage of females acquire self-administration, and that they exhibit greater motivation for cocaine. Additionally, cocaine self-administration in females is modulated by estrogen, whereas testosterone has not been found to play a role in cocaine self-administration in males. Replicating prior findings with adult rats, a study by researchers at the University of Virginia revealed that female adolescents acquired cocaine self-administration more rapidly than male adolescents, with the number of infusions varying with the estrus cycle; in males, serum testosterone was unrelated to the number of infusions. In a parallel control study, acquisition of lever-pressing for sucrose reinforcement and motivation for sucrose was compared in adolescent males and females, in order to assess potential sex differences in general learning and motivation. Findings revealed that males and females did not differ in the rate of acquisition or in motivation for sucrose. This research suggests that the observed sex differences in adult cocaine self-administration, and the modulation by the estrus cycle, are reflective of sex differences and underlying mechanisms present in adolescence. These results call for further research to explore the hormonal and nonhormonal basis of these sex differences.

- **Modulation of Drug Effects by the Dopamine System**
  In a study using nonhuman female primates, researchers found that in brain areas associated with drug abuse, dopamine D2 receptor availability was lower in the follicular phase than in the luteal phase of the menstrual cycle. This research highlights the need for models of the neurobiology of addiction to incorporate sex differences and the interactions of gonadal hormones and the neurotransmitter systems underlying addiction.

Clinical Studies—Sex Differences in Biological Mechanisms Underlying Drug Effects

- **Shared Genes for Attention Deficit Hyperactivity Disorder (ADHD) and Smoking?**
  Smoking rates are higher in adolescents and adults with ADHD than in the general population, and there is evidence that ADHD and smoking share similar candidate genes, which suggests common neurobiological mechanisms. In a sample of 1,900 adolescents and young adults, researchers studied the relationships of self-reported ADHD symptoms, smoking behavior, and genotype. An association was found between ADHD and smoking and the dopamine D2 receptor gene. Additionally, for girls, but not boys, there was an association with the MAOA gene, which is a metabolic regulator of dopamine D2 activity. This is the first study to show that ADHD symptoms interact with genotype to predict smoking or any other drug abuse behaviors.

- **Sex Differences in Brain Mechanisms of Nicotine Dependence**
  In a sample of 30 moderately dependent smokers, researchers at Duke University found relationships between brain responses to nicotine visual cues, as assessed by fMRI-BOLD, and several individual difference variables: degree of self-reported nicotine dependence, degree of prescan craving, self-reported negative affect produced by withdrawal and sex; negative relationships were observed for craving. Interestingly, both being male and self-reported negative affect were independently associated with similar patterns of brain activation, that is, increased activation in the orbital frontal cortex and the left hippocampus in response to the visual cues. However, these two variables were only modestly correlated with each other, and the level of negative affect was greater in women than men. In females, brain reactivity to the cues occurred in brain areas that did not overlap

with the other study variables, including the cuneus and the left superior temporal gyrus. Along with considerations of the functions these brain regions subserve, these data are consistent with prior research suggesting sex differences in the brain mechanisms of nicotine dependence, which could have implications for the need for the design of differential treatment approaches.

- **Brain Imaging Shows Sex Differences in Cocaine Users**
  Regional cerebral blood flow (rCBF) was examined in cocaine-dependent treatment-seeking individuals who had been abstinent at least 11 days. Decreased rCBF was observed in the right and left lateral orbitofrontal cortex (OFC), but only in males. Conversely, only females showed decreased rCBF in the medial OFC. Additionally, increases found in rCBF in diffuse regions in males did not show any significant increases in females—in other words, cerebral blood flow was disturbed to a greater extent in males and in different areas than in females. These findings could have differential implications for the clinical course and treatment of cocaine addiction in men and women.

- **Effects of D-Amphetamine on Risk-Taking Vary by Gender and Personality**
  In a laboratory study conducted at the University of Chicago, researchers examined whether gender and various personality factors moderated the relationship between experimentally administered d-amphetamine and performance on a risk-taking task. One personality dimension, Agentic Positive Emotionality (AgPEM), is thought to reflect functioning of the ascending ventral tegmentum area dopamine projections that modulate approach and incentive motivation. For males, this trait highly correlated with performance on the impulsivity task and experimentally administered d-amphetamine. Among males whose AgPEM scores were in the lower half of the distribution, d-amphetamine reduced risktaking, but among those whose scores were in the upper half, risktaking was increased. The drug did not affect risk taking in females. This line of research study not only points to the role of personality factors in determining vulnerability to the effects of drugs on behavior, it also underscores the importance of stratifying outcomes by gender.

- **Neurological Measures Linked to Marijuana Addiction Stronger in Females**
  A recent study sought to increase the scant knowledge of the neurological correlates of marijuana addiction in Native Americans, a population in which use and abuse rates are particularly high. The study examined participant responses to a facial recognition task in an adult sample of 317 Southwest California Indians with (1) no drug dependence diagnosis; (2) marijuana use, but no other drug dependence diagnosis; and (3) marijuana dependence, as well as other drug dependence diagnoses. After taking age, gender, and the presence of a lifetime diagnosis of alcohol dependence into consideration, longer latencies were found in the P450 component peaks in individuals addicted to marijuana, an outcome suggestive of delays in identifying and evaluating emotional stimuli. Additionally, latencies were longer in females than males, which may indicate greater toxicity associated with females' marijuana dependence. These findings highlight the need for more studies focused on this high-risk and understudied ethnic group and to determine whether these observed outcomes are related to predisposing or comorbid factors.

Research Translation—Moving Laboratory Results into Practice Potential

Basic laboratory studies with animals and humans are finding that the estrus and menstrual cycle play a role in drug effects. Other studies are seeking to understand the biological bases of these outcomes. These lines of research are beginning to show promise in clinical applications.

- **Menstrual Cycle Implications for Treatment Management**
  Laboratory studies have shown that the menstrual cycle modulates the subjective effects of stimulants in humans and the reinforcing effects in nonhuman primates, with effects greater in the follicular than luteal phase. Studies that initially find no

sex differences in drug outcome measures often find differences when data are further analyzed by menstrual cycle phase. These menstrual cycle studies are of particular importance because they raise the possibility that knowledge of a women's menstrual cycle phase may be an important consideration in treatment. Preliminary studies have indeed shown that smoking cessation outcomes are related to the phase in which cessation is initiated. The role of the menstrual cycle in treatment of illicit drugs has yet to be explored.

- **Gonadal Hormones May Have Pharmacotherapeutic Value**
  Recent research on the mechanisms by which the menstrual cycle modulates drug effects has focused on the role of the gonadal hormone progesterone in cocaine self-administration studies in rodent models and in cocaine studies with humans. In an escalation model of cocaine self-administration, which is a commonly used rodent model of the transition from moderate drug use to addiction, progesterone prevented escalation whereas estrogen facilitated escalation in ovariectomized female rats. In a reinstatement model of cocaine seeking, which is commonly used to model relapse to drug use, reinstatement of cocaine seeking was inversely related to plasma progesterone levels in freely cycling female rats across the estrous cycle, and was suppressed when progesterone was experimentally administered, an outcome mediated by progesterone's metabolite allopregnanolone. Results from these rodent studies complement findings in human studies that cocaine cue-induced craving is inversely related to circulating plasma progesterone levels in women and that experimentally administered progesterone decreases the positive subjective effects of cocaine in women, although not in men. Such evidence for progesterone's inhibitory effect on cocaine behavior has led NIDA investigators to begin to explore its use as a medication for cocaine abuse.

Epidemiology, Etiology, and Prevention Research

Growing numbers of NIDA-supported epidemiological and etiological field-based research focuses on identifying gender differences in the trajectories and risk and protective factors for drug use, yielding outcomes that can be targets for prevention programs, which themselves often find that outcomes vary by gender. Some of these research findings are highlighted below.

Identifying Trajectories of Drug Use by Gender

In examining population-based epidemiological data, which generally find that the population prevalence of drug use and dependence is greater in males than females, one must bear in mind that population prevalence alone does not tell the whole story when it comes to sex/gender differences in drug abuse vulnerabilities and consequences. For example, many animal model studies as well as epidemiological and clinical studies reveal that even with less or equal use than males, female users show a greater propensity to develop subsequent problems with dependence.

- **Comparing Research Results for Males and Females—The Case for Differentiation of Outcomes by Gender**
  A study using data from the National Comorbidity Survey found that risk for developing cannabis and cocaine dependence after first use differed between males and females: male risk for cannabis dependence peaked at 2 years after initial use—going from 1 percent to 4 percent per year before declining; whereas female cannabis users' risk of dependence stayed at 1 percent for 3 years, without the peak. For cocaine, both male and female users had an estimated risk of dependence of 5 to 6 percent within the first year after use. Conversely, in a study of smoking trajectories among African-American and Puerto Rican participants, from adolescence to young adulthood, females were more likely than males to start early and continue smoking, reaching higher smoking levels than males by age 14. This was true, even though slightly more females than males

were nonsmokers. In another longitudinal cohort of more than 2,800 intravenous drug users (IDUs) in Baltimore, MD, "street methadone" use (i.e., methadone use outside of treatment programs) was more common among women than men and more frequent among individuals not in a methadone program. This study suggests that older IDU females who are still using heroin may be using street methadone to treat signs of withdrawal. A fourth study reveals differential results by gender—specifically, that childhood victimization produced a greater likelihood of illicit drug use at age 40 among females, but not males. Such results underscore the need for differentiating study outcomes by gender—and for targeted interventions, especially victimized females.

- **Predictors of Drug Use in Females**
  Female-only studies are revealing important predictors, both of drug initiation and of continued drug use. For example, using data (collected 1994–2005) from 1,065 females who participated in both the baseline and followup wave of the Missouri Adolescent Female Twin Study interviews, researchers identified correlates of cannabis initiation. Specifically, multivariate stepwise modeling revealed significant influences of alcohol use at baseline as well as peer attitudes towards cannabis use related to starting marijuana use. The authors concluded that having peers with favorable attitudes toward alcohol, cigarette, and cannabis use is an important correlate of cannabis initiation in adolescent females and that prevention and intervention efforts need to take this into account when developing drug resistance training programs for adolescents. Another study explored the relationship between age of first menstrual period and daily smoking, and whether this relationship was influenced by weight concerns, which were reported by greater than 60 percent of the 71 females enrolled in a smoking cessation trial. Researchers found a significant association between age of first premenstrual period and onset of daily smoking—a relationship that was not modified by weight concerns. These findings support previous research showing that early maturation represents a risk factor for drug abuse.

- **Sex Differences in Predictors of Drug Abuse**
  For both boys and girls, advanced physical maturity was associated with a cluster of high-risk behaviors, including having sex for drugs or money. For females, the additional impact of having an older romantic partner, versus any partner at all, was substantial and particularly important for the high-risk cluster. Given that romantic partners elevate risk for young adolescent males and females, a need exists to identify and understand the various facts of adolescent romantic relationships that play a role in substance use and sexual decisions. Another study examined the effects of delinquency and depressed mood at ages 11, 12, 13, 14, and 16 years on problem substance use at age 18, with results stratified by gender. For girls, correlations were evident between depressed mood and problem drug abuse in middle adolescence, at ages 14 and 16. For boys, positive correlations occurred between delinquency and drug abuse. Another positive association was seen between parental problem drinking and the outcome for girls and between early-onset substance use and the outcome for boys. These findings have potential implications for specific targets of early prevention and how these may differ for boys and girls. A third study examined the association between dieting and smoking initiation among adolescents. Data were collected at two waves: (1) when students were in 7th through 11th grades and (2) when students were in 8th to 12th grades. Results show that inactive dieting—trying to lose weight at Time 1 but not trying to lose weight at Time 2—was a significant predictor of smoking initiation among males, but not among females. Results suggest the need to examine the association between dieting and regular smoking initiation.

Adolescents: Drug Problems, Risks, and Prevention

Drug use in adolescence is often associated with a variety of psychological problems

in ways that are not the same in boys and girls. In one study, among adolescents who engaged in light and moderate risk behavior patterns with respect to drug abuse and sexual behavior problems, females experienced significantly more depressive symptoms than males, whereas among those engaging in high-risk drug abuse and sexual behavior, there were few sex differences in the odds of depression. These findings support the need to screen for depression in female adolescents engaging even in experimental risk behaviors. In another study, researchers examined the relationship between onset of substance use and five risk factors related to suicide (high depressive symptoms, suicide ideation, suicide ideation with alcohol and/or drug use, endorsement of suicide as a personal option, and suicide attempt). Earlier onset of habitual drug use was associated with all five suicide risk factors for boys and four of the five risks for girls. Onset of regular smoking was associated with one of the five risk factors (suicide ideation) for boys, but with three risk factors for girls (suicide ideation, suicide ideation with alcohol and/or drug use, and personal endorsement of suicide). Onset of marijuana use was not associated with any suicide risk for either gender. These findings reinforce the importance of screening for drug abuse in early adolescence and underscore the need for research on intervention efforts that acknowledge and incorporate gender differences.

- **Mother's Relational Schema as Adolescent Risk Factors**
  Relational schema narratives are automatic, unconscious response tendencies that reflect the nature of a mother's relationship with her child. A NIDA-supported study measured these tendencies through interpreting speech samples in which a mother (biological, step, or adoptive) was describing her relationship with a target adolescent. Results provided unique information to predict adolescent externalizing behavior (e.g., drug abuse), and which could be considered in the assessment of family dynamics and the design of interventions to prevent and treat adolescent behavior problems.

- **Being a Sexual Minority Female (e.g., non-exclusively heterosexual) Increases Risk for Substance Abuse in Asian Americans Transitioning From Adolescence to Young Adulthood**
  Using data from the National Longitudinal Study of Adolescent Health (Wave I, 1996, and Wave II, 2001), researchers analyzed prevalence, incidence, and patterns of smoking, binge drinking, marijuana use, and other drug use among 1,108 Asian Americans and Pacific Islanders (AAPIs), by sexual orientation and gender. They found significant increases in the incidence and prevalence of all four types of substance use (tobacco, binge drinking, marijuana, and other drugs) among sexual minority AAPIs, and particularly among female sexual minorities, as compared to heterosexual young women, young men, or sexual minority young men. In fact, female sexual minorities' odds of having used marijuana and other drugs were two to nine times higher.

- **Long-Term Influence of Family Factors Among African-American Families Particularly Strong for Female Adolescents**
  A study using longitudinal data from a community cohort of African-American inner-city males and females identified substance abuse patterns from first grade through mid-adulthood, examining differences by gender, as well as the roles of early family structure and process in drug use initiation. Researchers found a long-term influence of early family factors on substance abuse onset, particularly for females—specifically, family discipline in childhood and family cohesion and parental rule setting in adolescence were key factors in predicting later substance use for females, but not for males. Such studies again highlight the need for tailored prevention and intervention solutions according to gender.

- **Family-, School-, and Community-Based Interventions**
  Prevention programs aimed at adolescents often yield results that are different in boys and girls, as seen in two recent studies. A school-based prevention program called "keepin' it REAL"—implemented in middle schools in Phoenix, AZ—was aimed at seventh graders, who were mostly from lower income Latino neighborhoods and

from some higher income non-Latino White neighborhoods. The program sought to reduce drug use and foster anti-drug norms. Results indicated that among Latino students who were more linguistically acculturated and among non-Latino Whites, the program was equally effective for boys and girls in reducing marijuana, cigarette, and alcohol use and in fostering anti-drug norms. Among Latino students who were less linguistically acculturated, however, it was more effective in reducing alcohol and cigarette use in boys than girls, and in fostering anti-drug norms. The greater effectiveness for boys is perhaps attributable to the relative lack of risk at baseline among less linguistically acculturated Latino girls vs. boys; thus, the intervention may have delayed positive effects on those girls as they acculturate. Another intervention—a family-focused universal preventive intervention called the IOWA Strengthening Families program—was equally effective for both boys and girls in reducing monthly polysubstance abuse (alcohol, tobacco, marijuana, and inhalants) in a sample of rural Midwestern adolescents followed from 6th to 12th grades; however, the program slowed the rate of increase in polysubstance use significantly more for girls than for boys.

Prescription Drug Abuse and Anabolic Steroids

When it comes to abuse of prescription drugs—a growing problem in this country—females and males behave differently, including displaying differences by age and drug type. The studies summarized below highlight examples of these differences, which relate to propensity to use, adverse effects, diversion rates, and symptoms of severity. Consequences of anabolic steroid use in females are also discussed.

- **Differing Prevalence Rates, Associated Behaviors, and Adverse Effects for Male and Female Prescription Drug Abusers**
  According to the National Comorbidity Survey data, collected 2001–2003 and reported in 2007, males were more likely than females to have engaged in "extramedical" drug use, cannabis use, and cocaine use. The latest National Survey on Drug Use and Health (NSDUH) data also reflect this finding when viewing the entire survey population aged 12 and older. However, another study analyzing 2002–2003 NSDUH data files found gender differences when examining development of dependence symptoms related to opioid analgesic abuse, with females aged 12 and older two times as likely as males to display more severe symptomatology as a result of their abuse. When it comes to diverting their prescription medications—sharing them with friends, for example—a higher percentage of 7th–12th grade girls reported doing so than boys in one study (n = 1,086). In another study of prescription drug use among college students, undergraduate females consistently overestimated the prevalence of nonmedical prescription drug and marijuana use by student peers, versus the estimates by males. This was true even though the past-year prevalence rates of actual use did not differ significantly as a function of gender. This finding prompts a deeper look into why drug use misperception is greater among females, given the important role that one's perceptions of social norms can play in decisions to use drugs. Gender differences were also seen in a study on prescription pain reliever abuse among adolescents 12–17 years old; 2005 NSDUH data showed that approximately 1 in 10 adolescents reported nonprescribed use of pain relievers in their lifetimes (9.3 percent in males and 10.3 percent in females). Further, treatment for psychological problems was associated with this use in females, whereas being booked for criminal activities was associated with such use among males. Such discrepancies suggest the need to consider different ways of intervening with young female vs. male abusers, and of potentially "catching" them as they enter other systems (e.g., mental health, juvenile justice).

- **More Health-Compromising Behaviors Seen in Female Users of Anabolic Steroids vs. NonUsers**
  A study analyzing data from the 2003 Centers for Disease Control and Prevention national school-based Youth Risk Behavior

Survey compared the self-reported anabolic steroid use of 7,544 female students in grades 9–12 with other health-related behaviors and with sports participation. The 5.3 percent of females reporting use had a marked increase in other health-compromising behaviors, including past 30-day use of alcohol, cigarettes, cocaine, and diet pills, over nonusers. They were also more likely to carry a weapon, have had sexual intercourse before age 13, and have had feelings of sadness or hopelessness almost every day for at least 2 consecutive weeks; they were less likely to play school-sponsored team sports than nonusers. While females are not the only or major abusers of steroids, such findings are useful in helping to better characterize this population and design more responsive interventions.

Prenatal Exposure to Drugs—Need for Ongoing Prevention and Treatment Efforts for Pregnant and Postpartum Women

Despite the well-established dangers of using licit and illicit drugs during pregnancy, pregnant women continue to abuse substances that cross the placenta and impact the fetus. The latest National Survey on Drug Use and Health data reveal that among pregnant women aged 15 to 44 years, 5.2 percent reported using illicit drugs in the past month (vs. 9.7 percent of nonpregnant women), and 16.4 percent of the women in this age category reported cigarette smoking in the past month (vs. 28.4 percent of nonpregnant). In addition, NSDUH reports some alarming data concerning pregnant youth aged 15–17: 24.3 percent of girls in this age group reported past-month cigarette smoking (vs. 16.1 percent for nonpregnant), and 22.6 percent reported past-month use of illicit drugs (vs. 13.3 percent of nonpregnant). Thus, among young women aged 15–17, there are higher rates of smoking and illicit drug use among those who are pregnant compared to those who are not pregnant.

While the past decade has witnessed declines in smoking during pregnancy, continuing abuse of legal and illegal drugs during pregnancy calls for vigilant and sustained prevention efforts. Ongoing research is continuing to identify specific and often subtle differences in development between exposed and nonexposed children, and is also striving to increase understanding of the mechanisms underlying the differences that occur. This is complex and challenging work, in large part because of the many confounding factors in these studies (e.g., parenting quality, polydrug use, socioeconomic status, exposure to stress and violence). The studies summarized below highlight findings with regard to effects of drug use on children exposed prenatally and on pregnant and postpartum women, suggesting promising prevention and treatment approaches—for example, for nicotine and other drug dependence—and identifying factors that may influence treatment outcomes.

One such factor is managed care (MC), which impacts both drug-dependent women and their children. A study using archival data looked at the effects of MC on a population of drug-dependent women and their children in a comprehensive care drug treatment facility in pre- and post-MC conditions. The MC group had more fetal deaths, decreased immunization rates, and a greater number of social services interventions. That MC has had such an unfavorable impact on drug-exposed children calls for consideration of an alternative to MC for this population.

Effects of Drug Abuse—On the Child

Research and real-life experience have clearly established the need to address drug abuse in pregnant women. Drug use during pregnancy, including nonillicit drugs like alcohol and nicotine, have been associated with potentially deleterious and even long-term effects on children exposed prenatally. That said, other evidence shows that negative outcomes in exposed children can be ameliorated by supportive home environments and good-quality parenting. The research summarized below underscores the importance of intervening with mothers before their babies are born.

- **Potential Effects of Prenatal Cocaine Exposure**
  Data collected on infants and children who were prenatally exposed to cocaine are beginning to reveal troubling potential associations with physiological, behavioral, and

cognitive deficits developmentally. However, these findings are preliminary and more studies must be done before drawing causal conclusions. Such findings include smaller mean head circumferences and lower mean cortical gray matter among exposed kids, as well as attention, language, and learning deficits from prenatal cocaine exposure. For example, one study has identified a possible relationship between prenatal cocaine exposure and language development for receptive, expressive, and total language scores, with cocaine exposure related to poorer performance. Behavioral outcomes, including aggression in young children, have also been associated with prenatal cocaine exposure. Research is needed to examine whether the effects of prenatal cocaine on health risk behaviors persist into adolescence, when such behaviors tend to increase. Cognitive functioning may also be affected. Several clinical studies have reported neurocognitive impairments and diminished executive functioning (e.g., problem solving, attention, and inhibitory control) as being associated with prenatal cocaine exposure. Conversely, another recent study of 17 prenatally cocaine-exposed adolescents and 17 nonexposed adolescents found similar outcomes in the two groups on an executive functioning task and in accompanying fMRI activation patterns. This speaks to the need to interpret the implications of these studies with caution and bolsters NIDA's continued commitment to study long-term effects in the child, as well as effective treatment and prevention approaches for pregnant women.

- **Methadone Mothers and Their Babies—Preliminary Studies**
  Methadone medication has been invaluable in helping opioid-addicted patients sustain abstinence. In examining potential predictors of Neonatal Abstinence Syndrome (NAS), researchers found that infants born to mothers on methadone maintenance during pregnancy frequently showed evidence of NAS, but their signs and symptoms varied widely. To zero in on why, investigators examined whether vagal tone responsivity—a measure of autonomic nervous system homeostasis, stress vulnerability, and self-regulation—to methadone administration in 50 pregnant women was a factor in how NAS affected the newborn. Findings showed that NAS expression was related to maternal vagal activity and that vagal tone, suppression, and activation were all associated with NAS symptomatology and treatment. Importantly, NAS expression was not related to histories of maternal substance use or methadone maintenance, or to psychotropic medication exposure. Another study found that among methadone-maintained breastfeeding mothers, concentrations of methadone in breastmilk sampled over 30 days postpartum were low and unrelated to maternal dose, even with significant increases in methadone concentrations in breastmilk over time. These results contribute to discussion of the current recommendation of breastfeeding for methadone-maintained women.

- **Gender, Substance Exposure, and Disease Progression in a Cohort of HIV-Exposed Children**
  Researchers from the Women and Infants Transmission Study analyzed blood samples from antiretroviral therapy (ART)-treated, HIV-infected children (n = 158) and HIV-uninfected children (n = 1,801) to examine gender and substance exposure differences in lymphocyte subsets and plasma RNA levels. In ART-treated children with HIV perinatal infection, those whose mothers used hard drugs during pregnancy showed a trend toward having lower CD4+ cell counts, with female children having lower plasma RNA levels than their male counterparts; however, despite males' higher plasma RNA levels, a greater proportion of them survived through 8 years of age. There were no gender differences with respect to the age of diagnosis of HIV, time to antiretroviral therapy after diagnosis of HIV, type of antiretroviral therapy, or overall mortality rates.

Promising Approaches for Addressing Drug Abuse and Other Mental Health Disorders During Pregnancy

- **Improving Treatment Outcomes for Pregnant Women Addicted to Opiates and/or**

Cocaine
Studies are illuminating ways in which treatment outcomes for pregnant women addicted to opiates and/or cocaine can be improved. NIDA-supported research that shows the effectiveness of behavioral incentive programs in increasing treatment retention and abstinence in men and women now extend to pregnant women. In a recent study, pregnant women in treatment for opiate and/or cocaine dependence who were assigned to a voucher reinforcement treatment program attended more treatment days than those in a standard treatment program. Although vouchers did not appear to differentially affect inpatient treatment participation, beginning it at this time appeared to have an important effect on pregnant women making the transition to outpatient treatment. Moreover, the voucher effect was sustained posttreatment. Another study points to the need to have long-term, consistent treatment programs for substance-abusing, methadone-maintained mothers with young children. Researchers at Yale tested a Relational Psychotherapy Mothers' Group (RPMG) approach with such a sample population. At 6 months posttreatment, women in the RPMG group (n = 60) showed less child maltreatment and cocaine abuse, with their children reporting greater improvements in emotional adjustment than other children; however, these treatment gains were not sustained once treatment was discontinued. Among another group of methadone-stabilized pregnant women, those with mood disorders were more likely to be positive for drug use while in treatment, compared with females without a mood or anxiety disorder, or those with a primary anxiety disorder. Findings highlight the need to conduct ongoing monitoring and intervention during pregnancy and after, and to treat cooccurring drug abuse and other mental disorders, particularly given the high rate of relapse among the dually diagnosed.

- **Marijuana Use and HIV-Related Risk Factors Among Previously Pregnant Teens**
  A NIDA-supported study examining a group of 279 young adult women (ages 18–24) in Pittsburgh, PA, who were previously pregnant as teens, found that early marijuana use, mental health problems, and African-American race were significant risk factors for sexually-transmitted infections (STIs). A dose-response pattern with regard to marijuana use and STIs was also identified, with marijuana use predicting a higher number of lifetime sexual partners. This finding suggests the need to screen pregnant teenage girls for early drug use and mental health problems, as they may benefit the most from the implementation of STI/HIV screening and skill-based STI and HIV prevention programs.

- **Effects of Comorbid Psychological Disorders on Pregnant Smokers**
  Several studies provide evidence of an association between having a mental disorder and cigarette smoking among pregnant women. One study found that among nearly 22 percent of pregnant women reporting cigarette use, about 45 percent met the criteria for at least one psychiatric disorder. Among those with nicotine dependence (12.4 percent), the comorbidity rate was 57.5 percent. This study found that nicotine dependence during pregnancy significantly predicted any mental disorder, any mood disorder, major depression, dysthymia (i.e., mild, chronic depression), and panic disorder. Importantly, no significant associations between cigarette use and mental disorders were found in nonaddicted smokers. Another study found the inverse also to be true—that smoking was more likely among pregnant women who met diagnostic criteria for a recent mood or anxiety disorder, or alcohol or substance abuse disorder. A third study, which examined psychiatric disorders as predictors of smoking outcomes among pregnant smokers, found that—compared with women without depressive disorders—women with dysthymia smoked a significantly greater average number of cigarettes per day during a targeted quit-date period. These studies all suggest the need for more research on the effects of depression on cigarette smoking, and vice versa, in pregnant women, including the need for mood-focused smoking cessation interventions.

- **Treatment Approaches to Improve Smoking Cessation Outcomes for Pregnant and Postpartum Women**
  Past research has shown a robust relationship between early resumption of smoking during a quit attempt and later smoking. Unknown was whether this predictor applies to women who quit during pregnancy, where smoking is contraindicated. A study at the University of Vermont sought to assess the smoking status of 129 women enrolled in smoking cessation studies who had attempted to quit during their pregnancies. Smoking status was assessed early in the cessation effort and again at the end of pregnancy. Women who smoked in the first 2 weeks of quitting had a greater than 80 percent chance of being classified as smokers at the end-of-pregnancy assessment. These findings suggest that clinicians should monitor smoking status during the initial weeks of a quit attempt and modify treatment if necessary. Another study investigated whether delay discounting (DD), a measure of impulsivity, can predict treatment outcome among postpartum women who had stopped smoking during pregnancy. Incentives were used to prevent relapse among the 48 participants. Findings showed that greater baseline DD measures were significant predictors of smoking status at 24 weeks postpartum. These results also extend previous treatment outcome findings to pregnant and recently postpartum cigarette smokers and suggest the need for monitoring during pregnancy for increased drug abuse risk. A third study tested contingent vouchers, earned for smoking abstinence, to see whether they could effectively decrease maternal smoking and improve fetal growth. Findings showed that contingent vouchers significantly increased abstinence at pregnancy end and at 12 weeks postpartum (24 percent vs. 3 percent). Significantly greater fetal growth also occurred with the contingent condition.

Drug Abuse Treatment Approaches and Health Services—"One Size" Approaches May Not Be Best

A major reason for understanding male–female differences in the constellation of contributory factors to female drug abuse is to develop more effective treatment programs. Factors such as how and when to intervene, the reasons and settings for seeking treatment, the treatments that are most effective, and the consequences of not receiving treatment can all vary by gender. Understanding these differences can help inform the tailoring of treatment approaches and increase the likelihood of positive outcomes. For example, a recent study suggests that males and females should perhaps be subject to different diagnostic criteria, both for identifying the presence of a drug abuse problem and for distinguishing between abuse and addiction. The researchers in this instance identified much gender heterogeneity with both drug abuse and drug dependence criteria provided by the DSM-IV for cannabis abuse and dependence. They concluded that these criteria function differently in men and women and require further refinement to make them more gender sensitive. Such findings need to be followed up on and eventually integrated in research and clinical settings—so that both genders can benefit from diagnosis and treatment most effective for them.

The Value of Gender-Specific Treatment Approaches

By and large, research confirms that tailoring drug abuse treatment to women's particular needs leads to more positive outcomes for women in treatment. Unfortunately, the availability of tailored programs seems to be decreasing, as reported by a NIDA-supported study showing recent changes in outpatient substance abuse treatment (OSAT) tailoring from 1995 to 2005. Using data from a national OSAT unit survey of approximately 600 women, this study found decreased availability of single-sex therapy—from 66 percentage to 44 percent of unit—and declines in percentage of staff trained to work with women—from 42 percent to 32 percent over the decade. This trend is not a positive one for women who need help with drug abuse problems.

Moreover, women are underrepresented among individuals seeking drug abuse treatment, even when their lower drug abuse prevalence rates are 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 healthcare settings and potentially contributing to different rates of drug abuse treatment entry. Moreover, predictors of treatment retention, completion, or outcomes (e.g., background characteristics) also vary by gender. For example, among cocaine-dependent individuals, severity of childhood emotional abuse was a predictor of cocaine relapse, but only for females, not males.

To help promote positive outcomes for women in treatment, gender-specific components may be valuable to include, as shown in the studies summarized below.

- **Gender-Specific Drug Abuse Treatment Promotes Continuity of Care for Women** Treatment duration is well established as an important factor in achieving positive outcomes—for both men and women. Now a NIDA-supported study shows the value of specialized services in furthering treatment duration for women. This retrospective study reports on the continuity of care for women with children who were admitted either to long-term residential substance abuse treatment offering specialized care or to standard mixed-gender treatment. It showed that women in "women-only" treatment programs were more likely than those in standard programs to continue care—37 percent vs. 14 percent. Children provide a valuable social support to women and can further their abstinence duration. One study reports that children were viewed as providing as much abstinence support to mothers as that provided by adult network members. Findings suggest that treatment providers should be aware of the reliance that women patients may have on their children and to focus on that relationship as well as the adult relationships in women's lives—particularly for women in residential treatment, where greater support may be necessary.

Gender Differences in the Efficacy of Drug Abuse Pharmacotherapies

Research has often revealed gender differences in medication efficacy, sometimes even opposite effects in males and females. In the two studies described below, pharmacotherapies were found to be effective in males, but not in females. These studies illustrate the need to differentiate outcomes of drug abuse and addiction pharmacotherapy trials by sex/gender.

In the first study, bupropion was tested against placebo for efficacy in prolonging abstinence in methamphetamine-dependent patients. Five clinics and 151 drug-dependent treatment seekers participated. Regression analysis found a statistically significant difference between bupropion and placebo groups in the probability of a nonuse week over the 12-week treatment period. However, these group differences occurred only for males, not females, among whom no differences were detected. The second study revealed gender differences with high-dose naltrexone in patients with cooccurring cocaine and alcohol dependence. In a clinical trial with 164 patients to test the efficacy of naltrexone taken for 12 weeks, significant gender-by-medication interactions were found for both cocaine and alcohol use, with naltrexone reducing drug use in men, but not in women. The researchers surmise that females taking this high daily dose of naltrexone will not benefit because of the medication's side effects for them. They note that the "increased sensitivity of opioid pathways between men and women is a viable explanation for the more dramatic gender differences in response to medication." Such differences are critical to consider when prescribing a treatment regimen for individual patients.

Subgroups of Women May Have Special Treatment and Services Needs

Findings that gender often plays a role in treatment has prompted NIDA to call on clinical researchers to address common and unique predictors of treatment outcomes for subgroups of women and men, and to devise strategies targeted at program characteristics associated with positive outcomes in both genders. Determining which treatment and

services approaches need to be tailored to integrate unique predictive factors is an important goal of treatment research.

One environment that is not meeting the particular needs of women 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. Unfortunately, few addiction treatment programs are designed to meet women's specific needs, especially the need to address physical or sexual abuse history and multiple comorbid psychiatric disorders. Findings from NIDA-supported criminal justice research studies show substantial differences in background characteristics for men and women, which call for more research on gender-specific paths of recovery to understand the degree to which these differences affect treatment and posttreatment needs and outcomes. Services that respond to gender-specific needs, which include child responsibilities, for example, may further enhance treatment outcomes. More 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. The following research synopses look at criminal justice populations as well as other subgroups of women and their treatment and services needs.

- **Criminal Justice-Involved Women in Treatment**
  The field of drug abuse treatment requires reliable and valid instruments to measure patient motivation, cognitive functioning, and other variables critical to treatment success. As part of NIDA's Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) initiative to examine performance indicators for criminal justice populations receiving treatment, a recent study examined psychometric properties of the 108-item Texas Christian University Criminal Justice Client Evaluation of Self and Treatment (CJ CEST). This tool is composed of 15 scales across 3 major domains, which assess treatment motivation (e.g., desire for help, treatment readiness), psychosocial functioning (e.g., depression, self-esteem), and treatment engagement (e.g., treatment participation, peer support). The study included 3,266 offenders from 26 corrections programs in 6 States. Differences among the various programs included those characterizing male- versus female-only programs; for example, women were more motivated and involved in their treatment and had stronger social support systems. Such tools offer a valuable means to measure client needs and functioning at intake and progress over time. Noted gender differences could suggest which aspects of treatment to enhance for males and females.

- **Older Women Show Better Long-Term Treatment Outcomes Than Older Men**
  A recent NIDA-supported study examined outcomes for women and men, 55 and older, who were in an outpatient addiction treatment program. At 7 years, 76 percent of women reported abstinence in the prior 30 days compared to only 54 percent of men. Regression analysis showed that longer treatment stay predicted abstinence, a finding supported by previous studies of addicted patients. Although findings showed that older women had better outcomes than older men, treatment length was actually more significant than gender in predicting outcome. Such studies are important given that older women constitute a fast-growing, yet understudied, subgroup. Future studies are needed to learn how to optimize successful treatment for older women and older men, and examine ways to engage older patients and to keep them in treatment longer.

- **Out-of-Treatment Women on Welfare**
  Researchers examined the effects of intensive case management (ICM) among 302 drug-dependent women who applied and were eligible for Federal welfare and who were not currently in drug abuse treatment. Those in the ICM group (which provided intensive treatment engagement), as compared to usual care, had more case manager contacts, better treatment engagement, and more self-help attendance than those in usual care. The preliminary findings suggest that case management may be an effective or ancillary intervention for drug-addicted women on welfare, even when they are not receiving formal drug abuse treatment.

- **Symptom Severity Patterns in Female Smokers and Relationship to Relapse**
  Data analyzed from 137 female smokers 18–40 years old revealed patterns of craving, withdrawal, and smoking urges that were important in predicting relapse. The female smokers completed 30 days of a protocol as part of a longitudinal smoking cessation trial, and were then followed post-quit date. Researchers collected measures of craving, withdrawal, and smoking urges at baseline and every day for 30 days from the quit date. All but 26 women relapsed, with a consistent symptom-severity pattern observed for the remaining 111, wherein all variables increased in intensity up to the day of relapse, then subsided quickly. This study suggests that frequent symptom monitoring could play a key role in relapse prevention.

- **Intervention for Female Sexual Assault Victims**
  An acute postsexual assault intervention to prevent drug abuse in women used a two-part video intervention for female sexual assault victims to specifically (1) minimize anxiety/discomfort during forensic examinations, thereby reducing risk of future emotional problems, and (2) prevent increased substance use and abuse following sexual assault. Results show that the video was associated with significantly lower frequency of marijuana use at each time point among women who reported use prior to the assault.

- **Mothers Who Use Drugs**
  Parenting moms need comprehensive treatment services for drug abuse problems. Several NIDA-supported studies substantiate this need in terms of the enduring effects seen in the children of mothers with untreated drug use disorders. For example, a multilevel modeling study of 108 mothers (with 208 children collectively) entering a methadone maintenance program identified the mother's drug abuse severity and psychological maladjustment as the strongest predictors of children's out-of-home placement. Such risks are not necessarily short lived and can have cross-generational effects. A longitudinal study using data obtained from interviews with a New York City sample of 149 African-American and Puerto Rican children, plus one of their parents, found that mothers' drug problems and compromised self-esteem posed long-term risks to their children's functioning as parents, thereby affecting their grandchildren's quality of life. Another study also found durable drug abuse effects, this time among a subgroup of adolescent childbearing mothers. Compared to a representative sample of same-aged women, this subgroup did not "age out" of their drug abuse as they transitioned into adulthood. All of these studies reflect a pressing need to address mothers' drug abuse problems before they are "passed on" to their children in one form or another.

HIV/AIDS—Changing Risks for Women

Among 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. But while all groups are affected by HIV/AIDS, not all are affected equally, with HIV/AIDS a growing issue for women. In 1990, women accounted for about 11 percent of all new reported AIDS cases, a percentage that increased to over 26 percent of cases in 2005. Most women are infected with HIV through sex with men or IDU. African-American women are especially vulnerable. In 2005, 66 percent of the 9,708 HIV/AIDS diagnoses were among Black women, compared to 17 percent among White women, and 14 percent among Hispanic women. In 2005, HIV was the third leading cause of death for Black women aged 25–44 and the fourth leading cause of death for Hispanic women aged 35–44.

To address these trends, NIDA's comprehensive HIV/AIDS research portfolio includes studies of gender-related differences in factors that contribute to and protect from HIV risk. Other studies are pursuing 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.

- **Geographic Populations of Drug-Using Women With High HIV Prevalence**
  HIV is increasingly affecting females through sexual contact with HIV+ males, with findings emerging across different geographic groups. For example, among Puerto Rican noninjecting heroin users residing in high drug traffic areas, females were found to have much higher HIV prevalence compared to males (4.3 vs. 0.06 percent), more sexual assaults (35.1 vs. 3.6 percent), and severe PTSD symptomatology (40.5 vs. 25.7 percent). Further, nearly one in four of the females (23 percent) reported a history of sexually transmitted infections, compared to 3 percent of the males ($p < 0.01$). This research shows that non-IDU female heroin users in Puerto Rico have a host of different needs than do male heroin users, and that these critical medical needs are going largely unmet. Another study revealed that female migrant IDUs in Tijuana, Mexico—the largest city on the U.S.–Mexico border—has a 2.5-fold higher HIV prevalence than males (8.3 vs. 3.3 percent, while representing just 13 percent of the sample of 1,056 IDUs. Moreover, only 7 percent were aware of their serostatus, highlighting the need for HIV testing and its integration with drug treatment. Finally, in a sample of street-recruited IDUs in Ukraine, HIV prevalence was 40 percent among women vs. 32 percent among men, with only roughly 15 percent knowing that they were HIV+. Further, women were more than twice as likely as men to have sex with another IDU (68.8 vs. 33.7 percent), which likely contributed to their higher HIV prevalence. This study highlights the urgent need for interventions that better address safe sex practices and self-efficacy for both males and females.

- **High-Risk Behaviors Among Subgroup Populations**
  Geographically and demographically diverse subpopulations of women exhibit risk behaviors that can lead to HIV. Multiple studies examine this phenomenon. For example, among homeless and marginally housed individuals in San Francisco, crack use was related to sex trade (exchanging sex for money or drugs) for both women and men, while many other correlates were gender specific. In a Houston, TX sample of 193 female African-American crack cocaine smokers living in neighborhoods with high rates of drug use, 66 percent reported currently trading sex for money. Compared to the women who never or who previously traded in sex, they were less likely to have a main sexual partner, more likely to have a casual sex partner, and more likely to smoke large quantities of crack. Among new IDUs in New York City, gender differences characterized injection risk behaviors and social circumstances at the first injection episode, with women more likely than men to cite social network influences and to have male sex partner initiators. Gender differences were also found in the association between descriptive social norms (norms that specify what most people do) versus injunctive social norms (people's perceptions of what behavior is approved or disapproved of by others) and needle sharing among heroin and cocaine IDUs in Baltimore, MD, findings suggesting the utility for both men and women of interventions that promote peer norms among IDUs. As with other studies, the data also support the need for gender-specific HIV prevention interventions, because injunctive norms were associated with needle sharing only among men. Extending these findings, another study of women IDUs in Baltimore found that women who believed their friends exchanged sex for money or drugs were more than two times as likely to have exchanged sex in the prior 90 days, versus 20 percent as likely if they believed their friends disapproved. Together, these studies highlight the need for drug abuse treatment and other services, such as mental health treatment, for subgroups of women at heightened risk for HIV. Such studies add to our understanding of HIV disease transmission and the need to develop gender-specific HIV prevention interventions.

- **Primary Care Benefits and Needs**
  A prospective 2-year study of nearly 300 individuals in a Boston residential detoxification program found that linkage to

primary care reduced sex risk behavior among females with addictions, but not males. Another study found that tailored health education programs to increase knowledge about menopause may be especially helpful for HIV-infected and drug-using women. Many peri- and post-menopausal drug-using women, especially those who are HIV+, fail to attribute their hot flashes and vaginal dryness (which may promote HIV transmission) to menopause, suggesting a need for menopause health education and treatment as part of integrated drug and HIV treatment.

- **Other Drug-Use–Related Infections**
  NIDA studies show that drug use behaviors and risky sexual behaviors that put drug users at risk for HIV also put them at risk for other medical conditions. Findings further point to the need for HIV prevention interventions and further highlight the medical needs among drug users. For example, in King County, WA, where human T-cell lymphotropic virus type 2 (HTLV-2) infection is endemic, HTLV-2 infection was 50 percent higher among women in a 2,500-member study sample of IDUs. Women were also more likely to share needles and to have sex with their needle-sharing partners, factors that may have contributed to the differential prevalence. Another study found that high rates of trichomonas vaginalis—the most prevalent nonviral sexually transmitted infection—among female African-American drug users in central Brooklyn correlated with drug use and more than one sexual partner in the prior 30 days. This disease, inexpensively treated, is associated with increased HIV transmission and negative reproductive outcomes. In the Women's Interagency HIV Study of HIV-infected and -uninfected women in six U.S. cities, presence and level of hepatitis C virus (HCV) viremia were also associated with HIV coinfection and with drug use and smoking. In another study among 462 noninjecting heroin and cocaine users in a drug detoxification program in New York City, genital herpes simplex virus-2 (HSV-2), also associated with HIV transmission, was more prevalent in women than men (86 percent vs. 51 percent); and although HIV rates were comparable, the relationship between HIV and HSV-2 was stronger in women: 100 percent of HIV-seropositive women were also HSV-2 seropositive, compared to 61 percent of males. Further, within a prospective sample of 253 noninjecting heroin users in New York City, gender differences characterized sexual risk behaviors for hepatitis B virus (HBV) and HCV seroconversion. Finally, among new drug injectors in New York City, HCV seroprevalence was higher in women than men (42 percent vs. 27 percent), with gender differences in sexual risk correlates, which calls for early and gender-sensitive intervention with new IDUs.

- **HIV Treatment**
  A recent NIDA-supported study of 1,605 HIV-infected, antiretroviral-naïve patients starting highly active antiretroviral therapy (HAART) in an HIV/AIDS drug treatment program in British Columbia found that being female and an IDU were predictors of hospitalization, along with factors related to adherence and previous hospitalizations. Within a longitudinal multisite cohort of HIV+ women, those who used drugs and reported accessing any drug abuse treatment program—whether medication based or medication free—were more likely to adhere to ART. This study supports the important role of drug abuse treatment in improving HIV outcomes. Finally, another study revealed a high rate of intimate partner violence against females among HIV+ male IDUs. Specifically, in a multicity intervention study aimed at reducing risky sexual and injection behaviors among HIV+ IDUs, 40 percent of the more than 300 males reported perpetrating violence against their female partners. This finding points to the need for HIV treatment for male IDUs to include interventions that help reduce their intimate female partner violence and HIV transmission among women.

Initiatives

NIDA seeks to promote and facilitate 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 funding opportunity announcements, travel awards, development and sponsorship of symposia and meetings, scientific presentations, and publications.

NIDA-Issued Funding Opportunity Announcements (FOAs)

The following are NIDA-issued FOAs, including Requests for Applications (RFAs), Program Announcements (PAs), and Notices (NOT) in effect during 2007 and 2008 that seek to promote research on sex/gender differences and issues specific to females:

NIDA-Issued FOAs Specific to Women & Sex/Gender Differences

- PAR-06-476, Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences (R36), July 10, 2006.
- PA-07-329, PA-330, PA-331, Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence, released Mar 15, 2007. Three mechanisms: R01 (329), R03 (330), R21 (331).
- NOT-DA-07-006, Update of Notice in Guide, Notice Regarding the Availability of Competitive Supplements To Study Sex/Gender Differences in Drug Abuse, released December 15, 2006.

Other NIDA-Issued FOAs With an Emphasis on Women & Sex/Gender Differences

- RFA-DA-09-020, Secondary Data Analyses for Substance Abuse Research, released November 5, 2008. Two mechanisms: R21, R33.
- RFA-DA-09-013, RFA-09-014, Interactions Between Physical Activity and Drug Abuse, released October 17, 2008. Two mechanisms: R01 (013), R03 (014).
- PA-09-020, PA-021, PA-022, International Research Collaboration on Drug Abuse and Addiction Research, released October 29, 2008. Three mechanisms: R01 (020), R21 (021), R03 (022).
- RFA-DA-09-012, Exploratory Centers for Translational Research on the Clinical Neurobiology of Drug Addiction (P20), released September 12, 2008.
- RFA-DA-09-008, RFA-DA-09-009, Brain Imaging Studies of Negative Reinforcement in Humans, released November 5, 2008. Two mechanisms: R01 (008), R21 (009).
- PA-08-263, PA-264, PA-265, Health Services Research on the Prevention and Treatment of Drug and Alcohol Abuse, released October 6, 2008. Three mechanisms: R01 (263), R21 (264), R03 (265).
- PA-08-253, PA-254, Unique Interactions Between Tobacco Use and HIV/AIDS, released August 26, 2008. Two mechanisms: R01 (253), R03 (254).
- PA-08-217, PA-218, PA-219, Drug Abuse Prevention Intervention Research, released July 25, 2008. Three mechanisms: R01 (217), R21 (218), R03 (219).
- PA-08-172, PA-173, PA-174, Economics of Treatment and Prevention Services for Drug & Alcohol Abuse, released June 6, 2008. Three mechanisms: R03 (172), R21 (173), R01 (174).
- PAR-08-145, Science Education Drug Abuse Partnership Award (R25), released April 11, 2008.
- PA-08-127, PA-128, PA-129, Prescription Drug Misuse, released April 3, 2008. Three mechanisms: R01 (127), R21 (128), R03 (129).
- PA-08-124, PA-125, PA-126, Epidemiology of Drug Abuse, released March 28, 2008. Three mechanisms: R01 (124), R21 (125), R03 (126).
- PA-07-409, Health Research With Diverse Populations (R01), released July 19, 2007.
- PA-07-374, PA-375, Psychopharmacology of Widely Available Psychoactive Natural Products, released June 4, 2007. Two mechanisms: R01 (374), R03 (375).
- PA-07-333, PA-334, Medications Development for the Treatment of Amphetamine and Amphetamine-Like Related Disorders,

released March 22, 2007. Two mechanisms: R01 (333), R21 (334).

- PA-07-307, PA-308, PA-309, Drug Abuse Aspects of HIV/AIDS, released January 17, 2007. Three mechanisms: R01 (307), R03 (308), R21 (309).
- PAR-07-221, NIDA Research Education Grants in Drug Abuse and Addiction (R25), released February 16, 2007.
- PA-06-487, PA-488, PA-07-111, Behavioral & Integrative Treatment Development Program (R01), released July 14, 2006 and December 2006. Three mechanisms: R21 (487), R03 (488), R01 (111).

Other Funding Opportunity Announcements in Which NIDA Participates

In addition to the above NIDA-issued FOAs, NIDA also participates with other ICs in the following announcements that seek to promote research on sex/gender differences and issues specific to females:

- PA-07-081, Women's Mental Health in Pregnancy and the Postpartum Period, released November 22, 2006.
- PAS-07-382 (R03) & PAS-07-381 (R21), Advancing Novel Science in Women's Health Research (ANSWHR), released June 11, 2007.
- PA-07-081, Women's Mental Health in Pregnancy and the Postpartum Period, released November 22, 2006.
- PA-07-154, Health Disparities Among Minority and Underserved Women, released December 13, 2006.
- PA-08-191, Supplements To Promote Reentry into Biomedical and Behavioral Research Careers, released July 1, 2008.

NIDA-Sponsored Travel Awards

- *Women & Gender Junior Investigator Travel Award Program for the Annual Meeting of the College on Problems of Drug Dependence*
  These $750 travel awards (approximately 30 per year) have been made annually beginning in 2000 and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. At the 2007 meeting, June 16–21 in Quebec City, Canada, there were 31 awardees. At the 2008 meeting, June 14–19 in San Juan, PR, there were 28 awardees.
- *Early Career Investigators Poster Session and Social Hour, cosponsored by NIDA, the National Institute on Alcohol Abuse and Alcoholism, and American Psychological Divisions 28 and 50 at the American Psychological Association Annual Meetings, August 17–20, 2007, San Francisco, CA, and August 14–17, 2008, Boston, MA*
  Eight of the 50 travel awardees in 2007 and 9 of the 51 travel awardees in 2008 sponsored by NIDA presented research on women or sex/gender differences in drug abuse.

NIDA Staff Presentations

- Invited workshop, "Sex/Gender Matters in Drug Abuse," at the annual Virginia Summer Institute for Addiction Studies, July 16–20, 2007, Williamsburg, VA.
- Invited talk, "Health Disparities: What It Means for Women of Color in Drug Abuse Treatment." Women's Alliance to Strengthen Treatment Access & Retention (WASTAR) conference, "Substance Abuse Treatment & Recovery," September 17–18, 2007, Lake Tahoe, NV.
- Invited talk, "Special Services for Women in Substance Abuse Treatment," Women's Alliance To Strengthen Treatment Access & Retention (WASTAR) conference, "Substance Abuse Treatment & Recovery," September 17–18, 2007, Lake Tahoe, NV.
- Invited talk, "Women and Substance Abuse: What Do We Know?" The Anita B. Roberts Lecture sponsored by ORWH, Bethesda, MD, October 23, 2007.
- Invited talk, "Leadership and Training for Women in Health Sciences in Latin America," sponsored by Fogarty, Bethesda, MD, December 3, 2007.
- Invited grand round, "The Pervasiveness of Sex/Gender Differences in Drug Abuse,"

Yale University School of Medicine, January 15, 2008.

- Invited talk, "Cerebrovascular Perfusion Correlates with Performance on a Neurobehavioral Test Battery: Gender Differences," Youth Science Fair, Washington, DC, March 19, 2008.
- Invited classroom lecture, "The Pervasiveness of Sex/Gender Difference in Drug Abuse," at The American University for the psychology course, Women & Mental Health, April 14, 2008.
- Invited discussant presentation, "Sex Differences in Causes and Consequences of Drug Abuse," in symposium, "Sex Differences in Causes and Consequences of Drug Abuse," Organization for the Study of Sex Differences Annual Meeting, New Orleans, LA, June 4–6, 2008.
- Invited talk, "Prenatal Drug-Exposed Cohorts: Gold Mines for Studying Sex/Gender Differences in Drug Abuse," at NIDA meeting, Adolescent Development Following Prenatal Drug Exposure: Research Progress, Challenges, and Opportunities, Rockville, MD, November 20–21, 2008.

NIDA-Organized Activities at Scientific Conferences

- Symposium, "A Translational Approach to Understanding Gender, Adolescence and Vulnerability to Nicotine Addiction," Society for Research on Nicotine and Tobacco Annual Meeting, February 21–24, 2007, Austin, TX.
- Symposium, "Drug Abuse and Homelessness Among Women at Risk for HIV," American Psychological Association, August 17–20, 2007, San Francisco, CA.
- Symposium, "Women's Issues and Substance Abuse Treatment," American Psychological Association Annual Meeting, August 17–20, 2007, San Francisco, CA.
- Symposium, "Family Violence and Drug Use Trajectories," American Psychological Association Annual Meeting, August 17–20, 2007, San Francisco, CA.
- Roundtable, "Gender Differences in Psychopathology as Drug Abuse Predictors and Consequences," American Psychological Association Annual Meeting, August 17–20, 2007, San Francisco, CA.
- Symposium, "A Translational Approach to Nicotine, Smoking and Weight." National Conference on Tobacco and Health, October 24–26, 2007, Minneapolis, MN.
- Symposium, "Issues in Drug Abuse Treatment of Women: Translation from the Lab to the Clinic," 3rd International Congress on Women's Mental Health, March 16–21, 2008, Melbourne, Australia.
- Symposium, "Women and Substance Abuse Treatment: Exploring Women-Focused Treatments and Services," American Psychiatric Association Annual Meeting, May 3–7, 2008, Washington, DC.
- Symposium, "Sex Differences in Causes and Consequences of Drug Abuse," Organization for the Study of Sex Differences Annual Meeting, June 4–6, 2008, New Orleans, LA.
- Poster, "Women and Sex/Gender Differences Program," presented at the NIDA International Program meeting at the College on Problems of Drug Dependence Annual Meeting, June 14–19, 2008, San Juan, PR.
- Symposium, "Biological Basis of Sex Differences in Drug Abuse: A Translational Perspective," American Psychological Association Annual Meeting, August 14–17, 2008, Boston, MA.
- Symposium, "The Impact of Criminalization on Women's Identity and Treatment Needs," American Psychological Association Annual Meeting, August 14–17, 2008, Boston, MA.
- Symposium, "Women in Violent Relationships: Trauma and HIV Risk," American Psychological Association Annual Meeting, August 14–17, 2008, Boston, MA.
- Symposium, "Girls in the Juvenile Justice System: Health Disparities in Substance Abuse and HIV/STI Risk," American Academy of Child and Adolescent Psychiatry

Annual Meeting, October 28–November 2, 2008, Chicago, IL.

NIDA Meetings & Seminars

- NIDA seminar, "Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering," Jo Handelsman, Ph.D., University of Wisconsin, July 24, 2007, Rockville, MD.
- NIDA cosponsorship of conference, "American Psychological Association Summit on Abuse and Trauma and Violence in Relationships: Connecting Agendas and Forging New Directions," February 28–29, 2008, Bethesda, MD.
- NIDA-organized seminar, "Sex and Gender Research: Substance Abuse," sponsored by the NIH Office of Research on Women's Health, March 27, 2008, NIH, Bethesda, MD.
- NIDA-funded conference, "Women and Smoking: Understanding Socioeconomic Influences," April 9–10, 2008, Westin Annapolis Hotel, Annapolis, MD.
- NIDA seminar, "Why Is It More Difficult for Women than Men To Quit Smoking? Potential Mechanisms and Possible Solutions," Sherry McKee, Ph.D., Yale, May 12, 2008, Rockville, MD.
- NIDA meeting, "Maternal Lifestyles Study Annual Meeting," November 19, 2008, Bethesda, MD.
- NIDA meeting, "Adolescent Development Following Prenatal Drug Exposure: Research Progress, Challenges, and Opportunities," November 20–21, 2008, Bethesda, MD.

NIDA Publications

- *Mini-Program: Focus on Women & Sex/Gender Differences (2007) (2008)*
  This publication 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 & Gender Junior Investigator Travel Awardees, announcement of the travel award program for the following year's CPDD meeting, and information on current NIDA funding opportunities relative to women and sex/gender differences.
- *A Collection of NIDA Notes: Articles That Address Women & Sex/Gender Differences Research (1996, 1997, 1999, 2002, 2004, 2006, 2008; NIH Pub. No.: NN0013)*
  This publication is a compilation of research articles from the NIDA Notes newsletter. Originally published in 1996, it is revised periodically, most recently in July 2008.
- *Monitoring the Future National Results on Adolescent Drug Use—Overview of Key Findings: 2007 (NIH Pub. No.: 08-6418)*
  Provides a summary of drug use trends from a survey of 8th, 10th, and 12th grade students nationwide, including analysis by gender. Also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.
- *National Survey Results from Monitoring the Future 2007, Volume I: Secondary Students (NIH Pub. No.: 08-6418A)*
  Reports on the prevalence of drug use among students in 8th, 10th, and 12th grades, including analysis by gender. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.
- *National Survey Results from Monitoring the Future 2007, Volume II: College Students and Adults Ages 19–40 (NIH Pub. No.: 08-6418B)*
  Reviews trends in drug use by populations based on gender, college plans, regions of the country, population density, race/ethnicity, and parents' education. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.
- NIDA created and has maintained the Web site, Women and Sex/Gender Differences Research Program, since 1998 (http://www.nida.nih.gov/WHGD/WHGDHome.html).

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Health Disparities Among Special Populations of Women

NIDA recognizes that the causes and consequences of drug abuse and addiction, as well as prevention and treatment needs, often vary among population groups. New approaches are needed to address special populations 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, plus members of particular ethnic or minority groups, sexual minorities, and more. Ongoing NIDA-supported research targets these and other groups, reflecting our belief that ongoing research into population-specific needs related to preventing and treating drug abuse and addiction will help keep more people from abusing drugs in the first place, and for those who do, will lead them into treatment and eventual recovery. Recent research on some of these groups has been described in Section B, Treatment Studies Focused on Subgroups of Women and HIV/AIDS—Changing Risks for Women, with additional studies scattered throughout this report. These include studies that have examined drug use patterns among Native Americans and African-Americans, where striking health disparities exist, particularly with regard to drug abuse and addiction consequences. For example, a study examining neurological correlates of marijuana addiction in Native Americans revealed greater toxicity associated with females' marijuana dependence. These findings highlight the need for studies focused on high-risk special populations.

Gender Analysis

NIDA has emphasized sex/gender analysis research for more than 10 years, and many of the research findings described above result from our efforts to actively promote the study of sex/gender differences in drug abuse in all areas of research. This research is suggesting 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 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.

Traditional one-size-fits-all, unisex research approaches to drug abuse are giving way to recognizing the value of taking a sex/gender-based research approach and analyzing data separately for males and females. Indeed, findings from all of NIDA's research areas—basic, clinical, and epidemiological research studies—are increasingly showing sex/gender to be a major determinant of outcome, and that studies using gender-blind intervention approaches often yield results that occur only in one gender. Although effective interven-

tions 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.

National Institute of Environmental Health Sciences

Executive Summary

Environmental agents play a role in a number of female-predominant diseases. These likely include breast cancer, osteoporosis, ovarian dysfunction, uterine fibroids, and autoimmune diseases, among others. The National Institute of Environmental Health Sciences (NIEHS) approaches women's health research through defining underlying susceptibilities to these diseases, investigating the role of estrogenic and other endocrine-active compounds in their etiology, indentifying important environmental triggers for their development and important nutritional factors that can reduce risk, and determining the importance of timing of exposure to disease risk. As results of these studies become available, women can better determine how to alter lifestyle factors leading to these diseases. The medical and public health communities have a better understanding in treating, diagnosing and preventing these diseases, and regulators can better define standards that protect women from environmental triggers.

Working Groups Focused on Women's Health

NIEHS has several groups focused entirely or in part on women's health. Dr. Donna Baird heads the Women's Health group within the Epidemiology Branch, which studies genetic susceptibility in chronic disease, the molecular genetics of cancer, women's health, autoimmune disease, and neuroepidemiology. Dr. Baird's work is focused on fertility, early pregnancy, and the epidemiology of uterine fibroids. Also within the Division of Intramural Research, the staff who conduct science at the headquarters in Research Triangle Park (as opposed to through grants to outside investigators) is the Laboratory of Reproductive and Developmental Toxicology. The lab conducts basic research on reproductive and developmental health, including developmental biology, gene regulation, pharmacogenetics, and receptor biology. 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 glands. The Chromatin and Gene Expression group has a strong interest in the epigenetic regulation of the human susceptibility gene BRCA1, the IKK promoter and the estrogen-regulated cathepsin D, a protease whose over expression is closely associated with poor clinical outcome for patients with breast cancer.

Accomplishments

Notable Studies and Research Programs

- **The Sister Study: Environmental Risk Factors for Breast Cancer**
  The NIEHS Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. Such sisters have about twice the risk of developing breast cancer as other women. The frequency of relevant genes and shared risk factors will be greater among sisters, increasing the statistical power of the study to detect risks. Sisters selected for the study are highly motivated, and study leaders predict high response rates and compliance over time. Thus, studying sisters will enhance the researcher's ability to assess the interplay of genes and environment in breast cancer risk and to identify potentially preventable risk factors. The prospective design will allow them to assess exposures before the onset of disease and avoid biases common to retrospective studies. The study—projected to last 10 or more years—will also allow them to examine a wide range of health outcomes of

relevance to women, and to create a framework from which to test new hypotheses as they emerge.

Cancer-free sisters are being recruited nationally through health professionals, breast cancer advocates, the Internet, a network of trained recruitment volunteers, and a national advertising campaign. Recruitment strategies are designed to maximize inclusion of minorities and high-risk women. Study materials are available in English and Spanish. Study researchers will collect data on potential risk factors and current health status using computer-assisted telephone interviews and mail questionnaires. The scientists will collect and bank blood, urine, and environmental samples for future use in nested studies of women who develop breast cancer (or other diseases) compared with those who do not. Annual tracking and biannual questionnaires will update contact information, vital status, and changes in medical history and exposures. Researchers may retrieve medical records and tumor tissue, if feasible, for those who develop breast cancer or other diseases. Analyses of incident cases will assess the independent and combined effects of environmental exposures and genetic polymorphisms that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors (e.g., smoking, occupational exposures, alcohol, diet, and obesity) and include measurement or analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. Ancillary studies will investigate the risk for other diseases (e.g., heart disease, osteoporosis, other hormonal cancers, respiratory disease, and autoimmune diseases) and explore genetic and environmental effects on breast cancer prognosis by continuing to follow women in the cohort who develop breast cancer.

- **Uterine Regression Study**
  The purpose of the Postpartum Uterine Regression Study is to document any fibroids present in early- to midpregnancy and to measure fibroid size after postpartum uterine regression. Study collaborators hypothesize that small fibroids will have disappeared and large fibroids will remain essentially unchanged in size. In epidemiologic studies of uterine fibroids, parity tends to be protective. The researchers hypothesized that a protective effect could arise from loss of early tumor lesions during postpartum remodeling of the uterus (Baird and Dunson, 2003). To test this hypothesis, the researchers developed a collaborative study with Dr. Katherine Hartmann at the University of North Carolina at Chapel Hill. In her miscarriage study, women enroll very early in pregnancy and have an ultrasound examination around the seventh gestational week. Hartmann searches for fibroids and records the size and location of any tumors. With NIEHS support, the women with fibroids are given another ultrasound examination 3 months after their pregnancy ends. Size and location of all fibroids are again recorded. The collaborators will look for disappearance of fibroids, as well as change in size or location. They anticipate collecting data from 300–400 women. If the data suggest that fibroids tend to disappear, further investigation of the mechanisms involved may lead to new strategies for nonsurgical fibroid treatment.

- **The Agricultural Health Study (AHS)**
  This is a prospective study of licensed pesticide applicators from North Carolina and Iowa recruited in 1993–1997 at the time of license renewal. The cohort includes 4,916 commercial applicators from Iowa and 52,395 private applicators, mostly farmers, from both States. More than 75 percent or 32,347 spouses of married private applicators also enrolled in the cohort. The study has generated publication on pesticides and atopic and nonatopic asthma among farm women, as well as chronic bronchitis among nonsmoking farm women—see entries below—among other issues related to women's health. The study is a collaboration of NIEHS, the National Cancer Institute (NCI), the Environmental Protection Agency (EPA), and the National Institute for Occupational Safety and Health (NIOSH). Applicators completed a short enrollment questionnaire on farming, personal pesticide

use, and lifestyle factors. Applicators who completed the questionnaire received a set of take-home questionnaires, including two to be completed by the female spouse of farmers and a third to be completed by the applicator that obtained additional details on pesticide exposure and health status. During 1999–2003, a followup telephone interview updated exposure information and changes in health status. Participants who completed the interview were asked to provide a buccal-cell DNA sample—for future analyses of gene and environment interactions—and a food frequency questionnaire by mail. A second followup telephone interview, expected to be completed in 2009, is underway. Questionnaires provided self-reported information on demographic factors, medical characteristics, history of smoking and alcohol use, and a lifetime use of pesticides, including 50 specific compounds. Over 68 percent of applicators (33,450) and 75 percent of spouses (23,775) completed the first followup interview. Approximately 40 percent of participants returned buccal cell samples.

In addition to studying changes in health that are reported through the followup questionnaire, the researchers annually link the cohort to State cancer registries and vital records to monitor cancer incidence and mortality. As an occupational group, farmers, male and female, are unique in that they often live where they work and their family members often participate in farming activities and may have inadvertent exposure to potential farm hazards. The AHS is the largest study of farmers and their families in the world and has provided Epidemiology Branch investigators and collaborators with an invaluable source of information. The study collects comprehensive data on pesticide exposure and factors that might modify exposures and has developed and validated improved methods for pesticide exposure assessment. Information provided by spouses about their children has facilitated studies on the health of children who live on farms. Topics of specific interest to NIEHS investigators, trainees, and collaborators include neurobehavioral function and neurodegenerative diseases, respiratory health, reproductive health, and cancer.

- **The Breast Cancer and the Environment Research Centers (BCERC)**
  The BCERC is a network of four national centers created in September 2003 by NIEHS and NCI to support transdisciplinary teams of scientists, clinicians, and breast cancer advocates to study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer. The research at each center includes a biology study, an epidemiology study, and a Community-based Outreach and Translation Core (COTC). The joint research being conducted by the centers is based on the hypothesis that chemical, physical, and social factors in the environment interact with genetic factors to affect mammary gland development during puberty and across the lifespan in ways that can alter breast cancer risk in later life. The overall outcomes of BCERC will be used to develop public health messages designed to educate young girls and women who are at high risk of breast cancer about the role(s) of specific environmental stressors in breast cancer and how to reduce exposures to those stressors.

Scientific Advances

- **GATA-3 Links Tumor Differentiation and Dissemination in a Mouse Model of Luminal Breast Cancer**
  How breast cancers are able to move through the body to other organs and metastasize, creating tumors in other organs, is poorly understood. Using a hyperplasia transplant system, this study showed that the movement of tumor cells and their establishment in other organs occur in distinct steps during tumor progression. Bioinformatic analysis revealed that loss of the transcription factor GATA-3 marked progression from precancer adenoma to early carcinoma and onset of the movement of tumor cells. Restoration of GATA-3 in late carcinomas induced tumor differentiation and suppressed movement of tumor cells to other sites. When GATA-3 was deleted in a targeted way in early tumors, it led to apoptosis, programmed

cell death typical of normal cells rather than tumor cells. This indicated that loss of GATA-3 is not sufficient for converting cells to malignancy. Rather, malignant progression occurred with an expanding GATA-3-negative tumor cell population. These data indicate that GATA-3 regulates tumor differentiation and suppresses tumor dissemination in breast cancer (Kouros-Mehr, H., et al. *Cancer Cell* 13(2):141-152, 2008).

- **HOXA11 Is Critical for Development and Maintenance of Uterosacral Ligaments and Deficient in Pelvic Prolapse**
  Pelvic organ prolapse (POP) is a common, debilitating disorder affecting millions of women. Uterosacral ligaments (USLs) are the main supportive structures of the uterus and vagina and are often attenuated in women with POP. Although the mechanical strength of USLs is known to be dependent on collagen synthesis and catabolism and the degradation protein MMP2 has been implicated in POP, the molecular mechanisms involved in the development of POP are currently unknown. Homeobox (HOX) genes are transcriptional regulators that orchestrate embryonic development of the urogenital tract. This study demonstrated that HOXA11 is essential for organogenesis of the USL by showing that USLs were absent in HOXA11-null mice. Researchers compared expression of HOXA11, collagen type I, collagen type III, MMP2, and MMP9 in USLs of women with and without POP. Expression of HOXA11 and both collagens was dramatically decreased while MMP2 was increased in women with POP. Constitutive expression of HOXA11 in murine fibroblasts resulted in significantly increased expression of collagen type III and decreased expression of MMP2. These results identified HOXA11 as an essential gene for the development of the USL and suggested that women with POP might have weakened connective tissue due to changes in a signaling pathway involving HOXA11, collagen type III, and MMP2 (Connell, K.A., et al. *Journal of Clinical Investigation* 118(3):1050-1055, 2008).

- **Isolation and the Timing of Mammary Gland Development, Gonadarche, and Ovarian Senescence**
  Implications for Mammary Tumor Burden:
  In this study of Norway rats, researchers hypothesized that lifelong psychosocial experiences, social isolation, or group living trigger different developmental trajectories in the ovarian system, contributing to predisease pathways for spontaneous mammary tumors. Epidemiological studies indicate that early puberty and delayed menopause are risk factors for breast cancer. To that end, researchers took a cross-sectional, prospective approach and examined the ovarian system at two different developmental points, young adulthood and middle age. Investigators assessed ovarian function at both points, as well as mammary gland development at puberty and mammary tumor burden in middle age. Social isolation dissociated two components of puberty; it accelerated maturation of ovarian function while it simultaneously delayed mammary tissue development thereby increasing the exposure of developing breast parenchyma to high levels of estrogen. By midlife, socially isolated rats had greater tumor burden despite having entered estropause prematurely, demonstrating that isolation did not increase tumorigenesis by promoting ovarian function. These findings are discussed in the context of facultative lifespan strategies for rats born at different times of year and those living in isolation or in a large burrow community (Hermes, G.L., et al. *Developmental Psychobiology* 50(4):353-360, 2008).

- **Collective Epithelial Migration and Cell Rearrangements Drive Mammary Branching Morphogenesis**
  Epithelial organs are built through the movement of groups of interconnected cells. Researchers observed cells in elongating mammary ducts reorganize into a multilayered epithelium, migrate collectively, and rearrange dynamically, all without forming leading cellular extensions. Duct initiation required proliferation, Rac, and myosin light-chain kinase, whereas repolarization to a bilayer depended on Rho kinase. Investigators observed that branching morpho-

genesis results from the active motility of both luminal and myoepithelial cells. Luminal epithelial cells advanced collectively, whereas myoepithelial cells appeared to restrain elongating ducts. Significantly, researchers observed that normal epithelium and neoplastic hyperplasias are organized similarly, suggesting common mechanisms of epithelial growth (Ewald, A.J., et al. *Developmental Cell* 14(4):570-581, 2008).

- **Pesticides and Atopic and Nonatopic Asthma Among Farm Women in the Agricultural Health Study**
  Risk factors for asthma among farm women are understudied, so researchers evaluated pesticide and other occupational exposures as risk factors for adult-onset asthma. Studying 25,814 farm women in the Agricultural Health Study, investigators used self-reported history of doctor-diagnosed asthma with or without eczema and/or hay fever to create two case groups: patients with atopic asthma and those with nonatopic asthma. They assessed disease-exposure associations with polytomous logistic regression. At enrollment (1993–1997), 702 women (2.7 percent) reported a doctor's diagnosis of asthma after age 19 years (282 atopic, 420 nonatopic). Growing up on a farm (61 percent of all farm women) was protective for atopic asthma (odds ratio [OR], 0.55; 95 percent confidence interval [CI], 0.43–0.70) and, to a lesser extent, for nonatopic asthma (OR, 0.83; 95 percent CI, 0.68–1.02; p value for difference = 0.008). Pesticide use was almost exclusively associated with atopic asthma. Any use of pesticides on the farm was associated only with atopic asthma (OR, 1.46; 95 percent CI, 1.14–1.87). This association with pesticides was strongest among women who had grown up on a farm. Women who grew up on farms and did not apply pesticides had the lowest overall risk of atopic asthma (OR, 0.41; 95 percent CI, 0.27–0.62) compared with women who neither grew up on farms nor applied pesticides. A total of 7 of 16 insecticides, 2 of 11 herbicides, and 1 of 4 fungicides were significantly associated with atopic asthma; only permethrin use on crops was associated with nonatopic asthma. These findings suggest that pesticides may contribute to atopic asthma, but not nonatopic asthma, among farm women (Hoppin, J.A., et al; *American Journal of Respiratory and Critical Care Medicine* 177(1):11-18, 2008; Epub 2007, Oct 11).

- **Maternal Heparin-Binding-EGF (HB-EGF) Deficiency Limits Pregnancy Success in Mice**
  An intimate discourse between the blastocyst and uterus is essential for successful implantation. However, the molecular basis of this interaction is not clearly understood. Exploiting genomic HB-EGF mutant mice, researchers showed that maternal deficiency of HB-EGF-like growth factor defers on-time implantation, leading to compromised pregnancy outcome. Investigators also demonstrated that amphiregulin, but not epiregulin, partially compensates for the loss of HB-EGF during implantation. In search of the mechanism of this compensation, they found that reduced preimplantation estrogen secretion from ovarian HB-EGF deficiency is a cause of sustained expression of uterine amphiregulin before the initiation of implantation. To explore the significance specifically of uterine HB-EGF in implantation, researchers examined this event in mice with conditional deletion of uterine HB-EGF and found that this specific loss of HB-EGF in the uterus still defers on-time implantation without altering preimplantation ovarian estrogen secretion. The observation of normal induction of uterine amphiregulin surrounding the blastocyst at the time of attachment in these conditional mutant mice suggests a compensatory role of amphiregulin for uterine loss of HB-EGF, preventing complete failure of pregnancy. Our study provides genetic evidence that HB-EGF is critical for normal implantation. This finding has high clinical relevance because HB-EGF signaling is known to be important for human implantation (Xie, H.H., et al. *Proceedings of the National Academy of Sciences of the United States of America* 104(46):18315-18320, 2007; Epub 2007, Nov 6).

- **Spontaneous Airway Hyperresponsiveness in Estrogen Receptor-Alpha-Deficient Mice**
  Airway hyperresponsiveness is a critical feature of asthma. Substantial epidemiologic evidence supports a role for female sex hormones in modulating lung function and airway hyperresponsiveness in humans. The objective of this study was to examine the role of estrogen receptors in modulating lung function and airway responsiveness using estrogen receptor-deficient mice. Lung function was assessed by a combination of whole-body barometric plethysmography, measurement of airway resistance, and isometric force measurements in isolated bronchial rings. M2 muscarinic receptor expression was assessed by Western blotting, and function was assessed by electrical field stimulation of tracheas in the presence/absence of gallamine. Allergic airway disease was examined after ovalbumin sensitization and exposure. Estrogen receptor-alpha knockout mice exhibit a variety of lung function abnormalities and have enhanced airway responsiveness to inhaled methacholine and serotonin under basal conditions. This is associated with reduced M2 muscarinic receptor expression and function in the lungs. Absence of estrogen receptor-alpha also leads to increased airway responsiveness without increased inflammation after allergen sensitization and challenge. These data suggest that estrogen receptor-alpha is a critical regulator of airway hyperresponsiveness in mice (Carey, M.A., *American Journal of Respiratory and Critical Care Medicine* 176(2):215, 2007).

- **Network-Based Classification of Breast Cancer Metastasis**
  Mapping the pathways that give rise to metastasis is one of the key challenges of breast cancer research. Recently, several large-scale studies have shed light on this problem through analysis of gene expression profiles to identify markers correlated with metastasis. Here, researchers applied a protein-network-based approach that identifies markers not as individual genes, but as subnetworks extracted from protein interaction databases. The resulting sub-networks provide novel hypotheses for pathways involved in tumor progression. Although genes with known breast cancer mutations are typically not detected through analysis of differential expression, they play a central role in the protein network by interconnecting many differentially expressed genes. Researchers found that the subnetwork markers are more reproducible than individual marker genes selected without network information, and that they achieve higher accuracy in the classification of metastatic versus nonmetastatic tumors (Chuang, H.Y., et al. *Molecular Systems Biology* 3 :141, 2007).

- **Sensitization to Mouse Allergen and Asthma Morbidity Among Women in Boston**
  Recent studies have shown that mouse allergen is prevalent and potentially important in both urban and suburban environments, particularly in homes of subjects with asthma sensitized to this allergen. However, little is known about the relation of sensitization to mouse allergen to asthma morbidity in adults with asthma outside the occupational laboratory setting. In this study, researchers evaluated whether sensitization to mouse allergen is a cause of morbidity in women with asthma from a range of socioeconomic backgrounds from a large metropolitan area in the United States. This study found that, regardless of race, ethnicity, or socioeconomic status, women sensitized to mouse allergen have higher rates of a physician's diagnosis of asthma and asthma morbidity. Although the effect of mouse allergen sensitization on asthma and asthma morbidity was somewhat lower in minorities, mouse sensitization was present in a higher proportion of the minority population. Thus, the population at risk for mouse allergy-associated asthma may be greater among the African-American and Hispanic population compared with non-Hispanic White women of childbearing age (Phipatanakul, W. *Journal of Allergy and Clinical Immunology* 120(4):954-956, 2007).

- **Short Telomere Length and Breast Cancer Risk**
  A Study in Sister Sets: Telomeres consist of a tandem repeats of the sequence TTAGGG at the ends of chromosomes and play a key role in the maintenance of chromo-

somal stability. Previous studies indicated that short telomeres are associated with increased risk for human bladder, head and neck, lung, and renal cell cancer. We investigated the association between White blood cell telomere length and breast cancer risk among 268 family sets (287 breast cancer cases and 350 sister controls). Telomere length was assessed by quantitative PCR. The mean telomere length was shorter in cases (mean, 0.70; range, 0.03−1.95) than in unaffected control sisters (mean, 0.74; range, 0.03−2.29), but no significant difference was observed (p = 0.11). When subjects were categorized according to the median telomere length in controls (0.70), affected sisters had shorter telomeres compared with unaffected sisters after adjusting for age at blood donation and smoking status [OR, 1.3; (95 percent CI), 0.9−1.8], but the association was not statistically significant. The association by quartile of telomere length (Q4 shortest versus Q1 longest) also supported an increase in risk from shorter telomere length, although the association was not statistically significant (OR, 1.6; 95 percent CI, 0.9−2.7). This association was more pronounced among premenopausal women (OR, 2.1; 95 percent CI, 0.8−5.5) than postmenopausal women (OR, 1.3; 95 percent CI, 0.5−3.6 for Q4 versus Q1). If these associations are replicated in larger studies, they provide modest epidemiologic evidence that shortened telomere length may be associated with breast cancer risk (Shen, J., et al. *Cancer Research* 67(11):5538-5544, 2007).

- **Green Tea Polyphenols Reverse Cooperation Between c-Rel and CK2 that Induces the Aryl Hydrocarbon Receptor, Slug, and an Invasive Phenotype**
  Exposure to and bioaccumulation of lipophilic environmental pollutants, such as polycyclic aromatic hydrocarbons (PAHs), has been implicated in breast cancer. Treatment of female rats with the prototypic xenobiotic PAH 7,12-dimethylbenz(a) anthracene (DMBA) induces mammary tumors with an invasive phenotype. In this study, researchers found that green tea prevents or reverses loss of the epithelial marker E-cadherin on the surface of DMBA-induced in situ cancers. To investigate the mechanism(s) leading to a less invasive phenotype, the effects of the green tea polyphenol epigallocatechin-3 gallate (EGCG) on mammary tumor cells were assessed. EGCG reversed epithelial to mesenchymal transition (EMT) in DMBA-treated NF-kappaB c-Rel-driven mammary tumor cells and reduced levels of c-Rel and the protein kinase CK2. Ectopic coexpression of c-Rel and CK2alpha in untransformed mammary epithelial cells was sufficient to induce a mesenchymal gene profile. Mammary tumors and cell lines derived from MMTV-c-Rel x CK2alpha bitransgenic mice displayed a highly invasive phenotype. Coexpression of c-Rel and CK2, or DMBA exposure induced the aryl hydrocarbon receptor (AhR) and putative target gene product Slug, an EMT master regulator, which could be reversed by EGCG treatment. Thus, activation of c-Rel and CK2 and downstream targets AhR and Slug by DMBA induces EMT; EGCG can inhibit this signaling (Belguise, K., et al. *Cancer Research* 67(24):11742-11750, 2007).

- **Estrogen Receptor Regulation of Carbonic Anhydrase XII Through a Distal Enhancer in Breast Cancer**
  The expression of carbonic anhydrase XII (CA12), a gene that encodes a zinc metalloenzyme responsible for acidification of the microenvironment of cancer cells, is highly correlated with estrogen receptor alpha (ER alpha) in human breast tumors. In this study, researchers found that CA12 is robustly regulated by estrogen via ER alpha in breast cancer cells, and that this regulation involves a distal estrogen-responsive enhancer region. Upon the addition of estradiol, ER alpha binds directly to this distal enhancer in vivo, resulting in the recruitment of RNA polymerase II and steroid receptor coactivators SRC-2 and SRC-3, and changes in histone acetylation. Mutagenesis of an imperfect estrogen-responsive element within this enhancer region abolishes estrogen-dependent activity, and chromosome conformation capture and chromatin immunoprecipitation assays show that this distal enhancer communicates with the transcriptional start site of

the CA12 gene via intrachromosomal looping upon hormone treatment. This distal enhancer element is observed in the homologous mouse genomic sequence, and the expression of the mouse homologue, CA12, is rapidly and robustly stimulated by estradiol in the mouse uterus in vivo, suggesting that the ER regulation of CA12 is mechanistically and evolutionarily conserved. These findings highlight the crucial role of ER in the regulation of the CA12 gene, and provide insight into the transcriptional regulatory mechanism that accounts for the strong association of CA12 and ER in human breast cancers (Barnett, D.H., et al. Cancer Research 68(9):3505-3515, 2008).

- **Comprehensive Analysis of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 Loci and Squamous Cell Cervical Cancer Risk**
  Variation in human major histocompatibility genes may influence the risk of squamous cell cervical cancer (SCC) by altering the efficiency of the T-cell-mediated immune response to human papillomavirus (HPV) antigens. Researchers used high-resolution methods to genotype human leukocyte antigen (HLA) class I (A, B, and Cw) and class II (DRB1 and DQB1) loci in 544 women with SCC and 542 controls. Recognizing that HLA molecules are codominantly expressed, investigators focused on cooccurring alleles. Among 137 allele combinations present at >5 percent in the case or control groups, 36 were significantly associated with SCC risk. All but one of the 30 combinations that increased risk included DQB1*0301, and 23 included subsets of A*0201-B*4402-Cw*0501-DRB1*0401-DQB1*0301. Another combination, B*4402-DRB1*1101-DQB1*0301, conferred a strong risk of SCC (OR, 10; 95 percent CI, 3–33.3). Among the six combinations that conferred a decreased risk of SCC, four included Cw*0701 or DQB1*02. Most multilocus results were similar for SCC that contained HPV16; a notable exception was A*0101-B*0801-Cw*0701-DRB1*0301-DQB1*0201 and its subsets, which were associated with HPV16-positive SCC (OR, 0.5; 95 percent CI, 0.3–0.9). The main multilocus associations were replicated in studies of cervical adenocarcinoma and vulvar cancer. These data confirm that T helper and cytotoxic T-cell responses are both important cofactors with HPV in cervical cancer etiology and indicate that cooccurring HLA alleles across loci seem to be more important than individual alleles. Thus, certain cooccurring alleles may be markers of disease risk that have clinical value as biomarkers for targeted screening or development of new therapies (Madeleine, M.M., et al. *Cancer Research* 68(9): 3532-3539, 2008).

- **Epithelial Progeny of Estrogen-Exposed Breast Progenitor Cells Display a Cancer-Like Methylome**
  Estrogen imprinting is used to describe a phenomenon in which early developmental exposure to endocrine disruptors increases breast cancer risk later in adult life. The researchers propose that long-lived, self-regenerating stem and progenitor cells are more susceptible to the exposure injury than terminally differentiated epithelial cells in the breast duct. Mammospheres, containing enriched breast progenitors, were used as an exposure system to simulate this imprinting phenomenon in vitro. Using MeDIP-chip, a methylation microarray screening method, investigators found that 0.5 percent (120 loci) of human CpG islands were hypermethylated in epithelial cells derived from estrogen-exposed progenitors compared with the nonestrogen-exposed control cells. This epigenetic event may lead to progressive silencing of tumor suppressor genes, including RUNX3, in these epithelial cells, which also occurred in primary breast tumors. Furthermore, normal tissue in close proximity to the tumor site also displayed RUNX3 hypermethylation, suggesting that this aberrant event occurs in early breast carcinogenesis. The high prevalence of estrogen-induced epigenetic changes in primary tumors and the surrounding histologically normal tissues provides the first empirical link between estrogen injury of breast stem/progenitor cells and carcinogenesis. This finding also offers a mechanistic explanation as to why a tumor suppressor gene, such as RUNX3, can be heritably silenced by epigenetic mechanisms in breast cancer

(Cheng, A.S., et al. *Cancer Research* 68(6): 1786-1796, 2008).

- **A Human Breast Cell Model of Preinvasive to Invasive Transition**
  A crucial step in human breast cancer progression is the acquisition of invasiveness. There is a distinct lack of human cell culture models to study the transition from preinvasive to invasive phenotype as it may occur "spontaneously" in vivo. To delineate molecular alterations important for this transition, researchers isolated human breast epithelial cell lines that showed partial loss of tissue polarity in three-dimensional reconstituted basement membrane cultures. These cells remained noninvasive; however, unlike their nonmalignant counterparts, they exhibited a high propensity to acquire invasiveness through basement membrane in culture. The genomic aberrations and gene expression profiles of the cells in this model showed a high degree of similarity to primary breast tumor profiles. The xenograft tumors formed by the cell lines in three different microenvironments in nude mice displayed metaplastic phenotypes, including squamous and basal characteristics, with invasive cells exhibiting features of higher grade tumors. To find functionally significant changes in transition from preinvasive to invasive phenotype, investigators performed attribute profile clustering analysis on the list of genes differentially expressed between preinvasive and invasive cells. They found integral membrane proteins, transcription factors, kinases, transport molecules, and chemokines to be highly represented. In addition, expression of matrix metalloproteinases MMP9, MMP13, MMP15, and MMP17 was up-regulated in the invasive cells. Using small interfering RNA-based approaches, researchers found these MMPs to be required for the invasive phenotype. This model provides a new tool for dissection of mechanisms by which preinvasive breast cells could acquire invasiveness in a metaplastic context (Rizki, A. *Cancer Research* 68(5):1378-1387, 2008).

Gender Analysis

- **Genetic Polymorphisms, Hormone Levels, and Hot Flashes in Midlife Women**
  Hot flashes disrupt the lives of millions of women each year. Although hot flashes are a public health concern, little is known about risk factors that predispose women to hot flashes. Thus, the objective of this study was to examine whether sex steroid hormone levels and genetic polymorphisms in hormone biosynthesis and degradation enzymes are associated with the risk of hot flashes. In a cross-sectional study design, midlife women aged 45–54 years (n=639) were recruited from Baltimore and its surrounding counties. Participants completed a questionnaire and donated a blood sample for steroid hormone analysis and genotyping. The associations between genetic polymorphisms and hormone levels, as well as the associations among genetic polymorphisms, hormone levels, and hot flashes, were examined using statistical models. A polymorphism in CYP1B1 was associated with lower dehydroepiandrosterone-sulfate (DHEA-S) and progesterone levels, while a polymorphism in CYP19 (aromatase) was associated with higher testosterone and DHEA-S levels. Lower progesterone and sex hormone binding globulin levels, lower free estradiol index, and a higher ratio of total androgens to total estrogens were associated with experiencing hot flashes. A polymorphism in CYP1B1 and a polymorphism in 3betaHSD were both associated with hot flashes. Some genetic polymorphisms may be associated with altered levels of hormones in midlife women. Further, selected genetic polymorphisms and altered hormone levels may be associated with the risk of hot flashes in midlife women (Schilling, C., et al. *Maturitas* 57(2):120-131, 2007; Epub 2006 Dec 21).

- **Gender-Specific Effects of Endogenous Testosterone: Female Alpha-Estrogen Receptor-Deficient C57BI/6J Mice Develop Glomerulosclerosis**
  Young female mice on a C57Bl/6J (B6) background are considered glomerulosclerosis (GS) resistant, but aging B6 mice develop mild GS. Estrogen deficiency accel-

erates while estrogen replacement retards GS in young sclerosis-prone oligosyndactyly mutant mice on an ROP background. To explore the effects of sex hormones on glomerular structure and function in the context of gender and genetic background, researchers studied mice in which the estrogen-receptor (ER) genes alpha- or -beta were deleted (alpha- or betaER knockout [KO]) and crossed into the B6 background. They also studied ovariectomized (Ovx) B6 mice given testosterone. Male and female betaERKO and male alphaERKO mice had no glomerular dysfunction at 9 months of age; however, alphaERKO female mice displayed albuminuria and GS. Ovx prevented glomerular dysfunction in alphaERKO female mice by eliminating endogenous testosterone production while exogenous testosterone induced GS in Ovx B6 mice. Androgen receptor (AR) expression and function was found in microdissected glomeruli and cultured mesangial cells. Testosterone compared to placebo increased both AR expression and TGF-bet mRNA levels in glomeruli isolated from female B6 mice. Estrogen deficiency had no deleterious effects on the glomeruli in B6 mice. The study shows that genetic traits strongly influence the GS-promoting effects of estrogen deficiency while testosterone induces GS in a gender-specific manner (Elliott, S.J., *Kidney International* 72(4):464-472, 2007; Epub 2007 May 9).

- **Disruption of the Developing Female Reproductive System by Phytoestrogens: Genistein as an Example**
  Studies have shown that exposure to genistein causes deleterious effects on the developing female reproductive system. Mice treated neonatally on days 1–5 by subcutaneous injection of genistein (0.5–50 mg/kg) exhibited altered ovarian differentiation, leading to multioocyte follicles (MOFs) at 2 months of age. Ovarian function and estrous cyclicity were also disrupted by neonatal exposure to genistein, with increasing severity observed over time. Reduced fertility was observed in mice treated with genistein (0.5, 5, or 25 mg/kg) and infertility was observed at 50 mg/kg. Mammary gland and behavioral endpoints were also affected by neonatal genistein treatment. Further, transgenerational effects were observed; female offspring obtained from breeding genistein-treated females (25 mg/kg) to control males had increased MOFs. Thus, neonatal treatment with genistein at environmentally relevant doses caused adverse consequences on female development, which is manifested in adulthood. Whether adverse effects occur in human infants exposed to soy-based products such as soy infant formulas is unknown, but the neonatal murine model may help address some of the current uncertainties because we have shown that many effects obtained from feeding genistin, the glycosolated form of genistein found in soy formula, are similar to those obtained from injecting genistein (Jefferson, W.N. *Molecular Nutrition and Food Research* 51(7):832-844, 2007).

- **Evidence for Sex Differences in the Determinants of Homocysteine Concentrations**
  A high homocysteine phenotype, often accompanied by low folate, is associated with several pathologies, including cardiovascular disease and birth defects. This phenotype appears to be influenced by both genetic and environmental factors, which may act in a sex-dependent manner. The present analyses were undertaken to identify the determinants of homocysteine concentrations in young men and women, and are based on data from a cohort of young, reproductive age (20–26 years old) individuals in Northern Ireland. Multivariate modeling indicated that homocysteine concentrations are associated with red blood cell (RBC) folate, vitamin B(12), MTHFR 677C > T genotype, and smoking status in both males and females. However, the interrelationships between these variables appear to differ between the sexes. Specifically, homocysteine levels in males were significantly associated with interactions between MTHFR 677C > T genotype and both RBC folate and smoking status. In contrast, homocysteine levels in females were significantly associated with interactions between smoking status and RBC folate. These results suggest that the characteristics of individuals who are at the highest risk for a high

homocysteine phenotype differ for males and females. Among males, those with the MTHFR 677TT genotype appear to be at the highest risk and to be the most vulnerable to factors (e.g., smoking, low RBC folate) that are associated with homocysteine-raising effects. Among females, smokers (regardless of MTHFR genotype) appear to be at the highest risk, and to be the most vulnerable to a single factor (i.e., RBC folate) that is associated with homocysteine-raising effects (Stanislawksa-Sachadyn, A., *Molecular Genetics and Metabolism* 93(4):355-362, 2008; Epub Jan 2008).

Initiatives/Workshops and Conferences

2007

- 2007 Keystone Symposia "Reproduction: Advances and Challenges," Feb. 20–25, 2007, Santa Fe, NM.
- 8th Annual Women's Health Research Conference, April 1, 2007, UNC Chapel Hill, NC.
- Environmental Health is a VERB: Building Healthy Children, April 16, 2007, Houston, TX.
- Heavy Metal Exposures in Women and Children, the Role of Nutrients, April 30, 2007, Washington, DC.
- 4th International Conference on Female Reproductive Tract, Frauenworth, Germany, June 8–12, 2007.
- Mammary Gland Biology GRC, June 10–15, 2007, Newport, RI.
- International Neurotoxicology Association meeting, June 10–15, 2007, Pacific Grove, CA.
- GRC on Hormone Action in Development & Cancer, July 15–20, 2007, New London, NH.
- Sixteenth Ovarian Workshop, July 19–21, 2007, San Antonio, TX.
- 40th Annual Meeting, Society for the Study of Reproduction, July 21–25, 2007, San Antonio, TX.
- 2007 Epigenetics GRC, August 6–9, 2007, Holderness, NH.
- Aspen Perinatal Biology Symposium, August 25–28, 2007, Aspen, CO.
- Susan G. Komen for the Cure 10th Annual Mission Conference, August 26–28, 2007, Washington, DC.
- 19th Annual ISEE Meeting, September 5–9, 2007, Mexico City, Mexico.
- 1st International Congress on Breast Development, September 27–30, 2007, Turin, Italy.
- A1HRA Pharma Bi-Annual Seminar on Emergency Contraception, October 11–12, 2007, Paris, France.
- The 17th Annual Conference of the International Society of Exposure Analysis, October 14–18, 2007, Durham, NC.
- Environmental Mutagen Society 38th Annual Meeting, October 19–25, 2007, Atlanta, GA.
- Breast Cancer and Environment Research Centers Annual Meeting, November 8–9, 2007, Cincinnati, OH.
- 24th International Neurotoxicology meeting, November 11–15, 2007 San Antonio, TX.
- World Assembly on Tobacco Counter's Health (WATCH), December 2–5, 2007, New Dehli, India.

2008

- Sexual Maturation and Puberty, February 23, 2008, Research Triangle Park, NC.
- Cancer Disparities: Biennial Symposia and Education Forums, March 6–8, 2008, Washington, DC.
- 9th Annual Women's Health Research Conference, April 1, 2008, UNC Chapel Hill, NC.

- 41st Annual Society for Study of Reproduction Meeting, May 25–31, 2008, Kauai, HI.
- Environmental Endocrine Disruptors 2008 GRC, June 8–13, 2008, Waterville Valley, NH.
- Neurobehavioral Teratology Society (NBTS) Annual Meeting, June 28–July 2, 2008, Monterey, CA.
- Teratology Society, June 28–July 2, 2008, Monterey, CA.
- NBTS Symposium: Fetal Behavior and Neurotoxicology, June 29, 2008, Monterey, CA.
- Joint ISEE–ISEA Meeting , October 12–16, 2008, Pasadena, CA.
- Environmental Etiologies of Neurological Disorders: Scientific, Translational, and Public Implications, October 12–15, 2008, Rochester, NY.
- 7th International Conference on Urban Health, October 29–31, 2008, Vancouver, BC, Canada.
- Fibrosis, January 20–25, 2009, Keystone, CO.
- Frontiers in Reproductive Biology and Regulation of Fertility–Keystone, February 1–6, 2009, Santa Fe, NM.

Health Disparities Among Special Populations of Women

- **Chronic Bronchitis Among Nonsmoking Farm Women in the Agricultural Health Study**
  The purpose of this study was to examine agricultural risk factors for chronic bronchitis among nonsmoking farm women. Researchers used self-reported enrollment data from the 21,541 nonsmoking women in the Agricultural Health Study to evaluate occupational risk factors for prevalent chronic bronchitis among farm women. ORs for chronic bronchitis for occupational exposures were adjusted for age, State, and related agricultural exposures. Results: Applying manure and driving combines were independently associated with chronic bronchitis. Off-farm job exposures associated with chronic bronchitis were organic dusts, asbestos, gasoline, and solvents. Five pesticides were associated with chronic bronchitis after multivariate adjustment and sensitivity analyses: dichlorvos (OR=1.63, 95 percent CI=1.01, 2.61), DDT (OR=1.67, 95 percent CI=1.13, 2.47), cyanazine (OR=1.88, 95 percent CI=1.00, 3.54), paraquat (OR=1.91, 95 percent CI=1.02, 3.55), and methyl bromide (OR=1.82, 95 percent CI=1.02, 3.24). Pesticides as well as grain and dust exposures were associated with chronic bronchitis among nonsmoking farm women (Valcin, M. *Journal of Occupational and Environmental Medicine* 49(5):574-583, 2007).
- **Are We Failing Vulnerable Workers? The Case of Black Women in Poultry Processing in Rural North Carolina**
  In 1989, North Carolina Occupational Safety and Health Administration inspectors cited two poultry processing plants in northeastern North Carolina for serious repetitive motion problems. In 1990, investigators from the National Institute for Occupational Safety and Health confirmed significant upper extremity musculoskeletal symptoms and disorders among workers. This study now reports on analyses of baseline data collected from a cohort of women employed in one of these plants. The plant, which is the largest employer of women in the area, is located in a sparsely populated area with a Black majority where nearly one-third of the population lives below the poverty level. Conditions we report suggest failure of existing health and safety systems, both regulatory and consultative, to prevent morbidity among vulnerable women in this industry, as well as social and economic conditions that influence availability of work and use of benefits to which they are entitled (Lipscomb, H.J. *New Solutions : A Journal Of Environmental And Occupational Health Policy* 17(1-2):17-40, 2007).
- **Upper Extremity Musculoskeletal Symptoms and Disorders Among a Cohort of Women Employed in Poultry Processing**
  Researchers evaluated musculoskeletal problems among women employed in poultry processing in rural northeastern North Carolina. Poultry processing is the

largest single employer of women in this economically depressed region with a Black majority population. Data were collected from a cohort of 291 women through interviews and physical exams conducted at 6-month intervals over 3 years. An index of cumulative exposure, based on departmental rankings and work history, was the primary exposure variable. Other variables of interest included work organization factors, other medical conditions, depressive symptoms, children in the home, and hand-intensive home activities. Poisson regression with generalized estimating equations was used to evaluate factors associated with occurrences of upper extremity symptoms and incidence of disorders at followup. Symptoms making it difficult to maintain work speed or quality and depressive symptoms at baseline were associated with symptoms at followup; age, being overweight, and job insecurity at baseline were associated with incident disorders. After considering these factors, the exposure response pattern was J-shaped, with risk decreasing in the second quartile of cumulative exposure and then going steadily up; the effect was stronger for disorders. The pattern of risk is consistent with onset of early musculoskeletal problems among women new to the industry followed by a later increase with continued exposure. Among this highly exposed population, the effects of depressive symptoms and work organization factors were diminished when cumulative exposure was considered, illustrating the contextual nature of the complex relationships between physical work exposures and psychosocial factors (Lipscomb, H. *American Journal of Industrial Medicine* 51(1):24-36, 2008).

- **Difference in Airflow Obstruction Between Hispanic and Non-Hispanic White Female Smokers**

  Smoking-related respiratory diseases are a major cause of morbidity and mortality. However, the relationship between smoking and respiratory disease has not been well studied among ethnic minorities in general and among women in particular. The objective of this cross-sectional study was to evaluate the risk of airflow obstruction and to assess lung function among Hispanic and non-Hispanic White (NHW) female smokers in a New Mexico cohort. Participants completed a questionnaire detailing smoking history and underwent spirometry testing. Outcomes studied included airflow obstruction, selected lung function parameters, and chronic mucus hypersecretion. Chi square, logistic, and linear regression techniques were utilized. Of the 1,433 eligible women participants, 248 (17.3 percent) were Hispanic; and 319 had airflow obstruction (22.3 percent). Hispanic smokers were more likely to be current smokers, and report fewer pack-years of smoking, compared to NHW smokers ($p < 0.05$ for all analyses). Further, Hispanic smokers were at a reduced risk of airflow obstruction compared to NHW smokers, with an OR of 0.51, 95 percent CI 0.34, 0.78 ($p = 0.002$) after adjustment for age, body mass index, pack-years, and duration of smoking, and current smoking status. Following adjustment for covariates, Hispanic smokers also had a higher mean absolute and percentage predicted post-bronchodilator FEV(1)/FVC ratio, as well as higher mean percent predicted FEV(1) ($p < 0.05$ for all analyses). Hispanic female smokers in this New Mexico-based cohort had lower risk of airflow obstruction and better lung function than NHW female smokers. Further, smoking history did not completely explain these associations (Sood, A. *COPD* 5(5):274-281, 2008).

- **Genomic DNA Methylation Among Women in a Multiethnic New York City Birth Cohort**

  One plausible mechanism for the environment to alter cancer susceptibility is through DNA methylation. Alterations in DNA methylation can lead to genomic instability and altered gene transcription. Genomic DNA methylation levels have been inversely associated with age, suggesting that factors throughout life may be associated with declines in DNA methylation. Using information from a multiethnic New York City birth cohort (born between 1959 and 1963), we examined whether genomic DNA methylation, measured in peripheral blood mononuclear cells, was associated with

smoking exposure and other epidemiologic risk factors across the life course. Information on prenatal and childhood exposures was collected prospectively through 1971, and information on adult exposures and blood specimens were collected in adulthood from 2001 to 2007. Methylation levels of leukocyte DNA were determined using a [(3)H]-methyl acceptance assay where higher values of disintegrations per minute, per microgram DNA indicate less DNA methylation. Genomic methylation of leukocyte DNA differed by ethnicity (66 percent of Blacks, 48 percent of Whites, and 29 percent of Hispanics were above the median level of disintegrations per minute, per microgram DNA; $p = 0.03$). In multivariable modeling, DNA methylation was statistically significantly associated with maternal smoking during pregnancy, longer birth length, later age at menarche, nulliparity, and later age at first birth. These data, if replicated in larger samples, suggest that risk factors across the life course may be associated with DNA methylation in adulthood. Larger studies and studies that measure within-individual changes in DNA methylation over time are a necessary next step (Terry, M.B. *Cancer Epidemiology, Biomarkers & Prevention* 17(9):2306-2310, 2008).

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Executive Summary

The National Institute of General Medical Sciences (NIGMS) supports research and research training for the basic biomedical sciences. Studies supported by NIGMS do not necessarily target any particular disease or condition, but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, genetics, developmental biology, drug discovery, pharmacology, physiology, bioinformatics, computational biology, and selected areas of behavioral sciences. NIGMS-supported research is often applicable to a wide variety of diseases or organ systems, including those specific to, or which disproportionately affect, women.

Interindividual drug responses depend on genetic variation as well as modifying factors such as environment, diet, other medications, age, and gender. NIGMS supports investigations of critical candidate proteins and genes that may contribute to pharmacogenetic and pharmacogenomic variations in drug metabolism and clearance. For example, many women with hormone receptor-positive breast cancer receive tamoxifen at some point in their treatment course. Tamoxifen is biotransformed to the potent antiestrogen endoxifen almost exclusively through the cytochrome P450 (CYP) 2D6 isoform. The balance of evidence available currently suggests that a single nucleotide polymorphism in the CYP2D6 gene, particularly the presence of 2 null alleles, predicts reduced tamoxifen metabolism and possibly poorer outcome than expected in patients with a wild-type genotype. This is called the "no pain-no gain" phenomenon, where women have to experience uncomfortable side effects in order for the therapy to be working, and effectively blocking estrogen receptors. Until data are available from retrospective examinations of the large prospective trials already conducted, or adequately powered prospective analyses, transforming this information into guidelines for individual patients remains challenging. The Food and Drug Administration does not currently recommend routine testing for CYP2D6 genotype for making clinical decisions regarding the use of tamoxifen. Use of concomitant strong or intermediate inhibitors of CYP2D6 should also be avoided when alternate medications are available. The ongoing research of Dr. David Flockhart, Indiana University, is directed toward identifying other polymorphisms that may influence the efficacy and safety of tamoxifen, other hormonal agents, and chemotherapies used to treat breast cancer. The International Tamoxifen Pharmacogenetics Consortium is forming (ITPC, http://www.pharmgkb.org/views/project.jsp?pId=63) at the NIGMS-sponsored PharmGKB in order to reconcile discrepant conclusions from clinical studies already conducted.

NIGMS also supports the work of structural biologists who seek to determine the three-

dimensional structures of enzymes. One such investigator, Dr. Debashis Ghosh at the Hauptman-Woodward Medical Research Institute (HWI) in Buffalo, NY, studies the molecular details of aromatase, the key enzyme required for the body to make estrogen. Dr. Ghosh has solved the three-dimensional structure of this enzyme, which will now facilitate the development of drugs for treatment of estrogen-dependent breast tumors. In total, NIGMS provides over $12 million per year in support of basic research related to breast cancer.

NIGMS supports the interdisciplinary research training of predoctoral and postdoctoral scientists. Predoctoral training programs focused in cell biology, molecular biology, and biochemistry prepare researchers to study cellular mechanisms, enzymology, and molecular mechanisms relevant to understanding cell growth, activation, division, and motility. NIGMS-supported training in genetics at the predoctoral level prepares future scientists to understand inheritance of genetic factors, transcriptional control, mutagenesis, DNA structure, recombination and repair, and the role of genes in cell division and differentiation. Training programs in molecular biophysics focus on the development of scientists who are able to determine the three-dimensional structures of biologically active molecules and the relationship of structure to function. 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 preparing more chemists with a knowledge and understanding of biological systems. This is an area of study critical to the design of new drugs, and diagnostic and preventive approaches. This program complements the NIGMS 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. NIGMS supports the training of dual-degree candidates through the Medical Scientist Training Program (MSTP). Training students with both a medical and scientific background, the MSTP program graduates doctors who can address basic research problems and relate their findings to clinical areas.

Accomplishments

NIGMS is actively involved in the NIH Directors "Working Group for Women in Science." Recognizing the importance of a diverse workforce in maintaining the U.S. strength in science and engineering, NIGMS has led efforts to address the paucity of women in academic chemistry careers. To this end, NIGMS/NIH, the National Science Foundation, and the Department of Energy sponsored an historic meeting of chemistry department chairs and other academic leaders to identify specific strategies that chemistry departments, universities, and Federal agencies can implement, to encourage and enable broader participation by women in the chemical sciences.

Chemistry department chairs in attendance were asked to make changes at their university employing the strategies learned at this workshop (http://chemchairs.uoregon.edu/). A followup survey of the chairs conducted by Geri Richmond, University of Oregon, has revealed that the workshop had a significant impact on attitudes of the chairs who attended (http://coach.uoregon.edu/coach/documents/Impact.pdf). The report of the meeting titled "Building Strong Academic Chemistry Departments Through Gender Equity" can be found at http://www.seas.harvard.edu/friend/GenderEquity_report+cover.pdf. NIGMS now has a committee in place that is planning a workshop to address issues of gender equity and the advancement of women in academic medical careers.

NIGMS is taking part in the funding opportunity, "Advancing Novel Science in Women's Health Research (ANSWHR)," http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html, which seeks to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences.

NATIONAL INSTITUTE OF MENTAL HEALTH

Executive Summary

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. Additionally, some women are at increased risk of depression during certain times of reproductive change, such as in 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. NIMH has also 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 crosscutting programs such as the Women's Mental Health Team, NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, services and the prevention of mental disorders in women. This 2007–2008 NIMH report highlights offices and groups designated to focus on women's mental health, 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.

Office and Groups Designated To Focus on Women's Mental Health

The Women's Mental Health Program is located organizationally 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 working with the NIH Office of Research on Women's Health and other governmental and nongovernmental organizations interested in women's issues. The Office coordinates NIMH activities that serve to fulfill the congressional mandate for tracking the inclusion of women and minorities in clinical research.

The Women's Mental Health Team serves as the focal point for coordination of NIMH scientific activities related to women's health and sex/gender differences research. Members of the 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 together across disciplinary boundaries to plan workshops, prepare/review science reports, and create funding opportunities related to women's mental health.

Accomplishments/ Research Highlights

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 U.S. adults. 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. The following

examples of NIMH-supported research illustrate the Institute's efforts in this area.

Sex Differences in the Vulnerability to Mental Disorders Induced by Stress

NIMH-supported investigators participated in a 2007 Society for Neuroscience symposium titled, "Stress and Disease: Is Being Female a Predisposing Factor?" A summary of the data presented was published and included discussion of current knowledge of sex differences in stress response as a vulnerability factor in mental and substance abuse disorders. Highlights included elucidation of possible mechanisms contributing to the onset of greater stress sensitivity of females during and post puberty. Additional new data suggested that prenatal and early postnatal factors can differentially affect female sensitivity to the later development of anxiety or substance abuse disorders. (Becker, J.B., et al. *Journal of Neuroscience* 27(44):11851-11855, 2007).

Role of Estrogen Receptor Beta in Mediating Antidepressant Effect of Estrogens in Model System

Study results revealed sex differences in stress-related immobility in mice. Female animals with higher circulating estrogens (proestrous) demonstrated less immobility than did mice with lower estradiol (diestrous). This difference in susceptibility across the estrous cycle was eliminated in mice with genetic deletion of the estrogen receptor (ER) beta. Administration of an ER beta selective ligand decreased immobility scores in normal ovariectomized mice, but not in ovariectomized mice with deletion of the ER beta receptor. These data suggest that ER beta may be required for some of the stress-related anti-depressant effects of estrogens. They further suggest the possibility of developing ER beta receptor selective ligands with potential mood-elevating effects that do not carry the adverse effects associated with activation of the alpha ERs (Walf, A.A., et al. *Journal of Psychopharmacology* 23(4):442-450, 2009

Differential Neurotrophin Roles in Anxiety and Depression-Related Behaviors in Females

Acute and chronic stress decrease levels of brain-derived neurotrophic factor (BDNF), a signaling molecule believed to play a role in depression and antidepressant treatment mechanisms. Using mice in which BDNF was selectively deleted from forebrain, this study showed sex-dependent effects on behavior. BDNF deletion in forebrain increased the general activity of male, but not female, mice relative to mice expressing normal levels of BDNF. In contrast, female but not male BDNF-deficient mice showed decreases in anxiety-like behaviors relative to controls. However, the female, but not male, BDNF-deficient mice also demonstrated more behaviors associated with depression. Consistent with previous findings, the behavioral actions of an antidepressant were prevented in both the male and female BDNF-deficient mice. These results support a possible specific role of forebrain BDNF in expression of anxiety and depression-related behaviors in females. They further demonstrate the importance of examining both sexes for potential genetic effects on behaviors in model systems because previous studies examining only male BDNF-deficient mice did not reveal mood-related effects (Monteggia, L.M., et al. *Biological Psychiatry* 61(2):187-197, 2007).

Gender Differences in Genetic Linkage and Association on 11p15 in Families With Obsessive-Compulsive Disorder

Gender differences in obsessive-compulsive disorder (OCD) have been reported by several research groups. This family-based OCD genetic study features a linkage genome scan using multipoint allele-sharing methods to test for linkage in 219 families participating in the OCD Collaborative Genetics Study. When these families were stratified by gender, suggestive linkage to chromosome 11p15 at a genetic marker D11S2362 ($p = 0.00012$) was revealed in families with affected males, but not in the ones with affected females. The researchers further conducted fine mapping with a denser genetic marker panel in the region of 11p15, and detected a significant linkage signal ($p < 0.00001$) in the families of males affected with

OCD. Subsequently, 632 additional genetic markers were genotyped spanning a 4.0 Mb region surrounding the linkage peak in the original families and an additional 165 families. Six markers were associated with OCD ($p < 0.001$): two of them were identified when all the families were included, and four markers only in male-specific families. Again, no genetic marker showed significant association with the OCD phenotype only in the families with females who are affected with OCD. This research suggests a possible gender effect in the etiology of OCD using a well-designed molecular experiment. Further research is needed to understanding the mechanisms underlying these gender differences, and may provide hints as to why males and females are differentially vulnerable at a particular genetic region to the development of OCD (Wang, Y., et al. *American Journal of Medical Genetics. Part B* Epub 2008 April 18).

Women and Men Process Unpleasant Stimuli in Different Brain Hemispheres

Studies of the neural circuits that process emotional stimuli have previously revealed differences in the brains of men and women. Specifically, memories for emotional stimuli are correlated with activity in the left amygdala in women, but in the right amygdala for men. In a new study, Gasbarri et al. (2007) have extended this finding into the cortex. The investigators measured event-related brain potentials at frontal and parietal sites while men and women viewed sets of pleasant, neutral, or unpleasant pictures. They found that responses to unpleasant, highly arousing pictures were larger and faster on the left in women and on the right in men. This study adds further evidence for the importance of controlling for sex and gender effects in studies of emotional processing and emotional memory. It also provides a starting point for investigating the role of lateralized cortico-amygdala circuits in patients with affective disorders (Gasbarri, A., et al. *Brain Research* 1138:176-186, 2007).

Early Touch Affects Parenting and Pair-Bonding in a Sexually Dimorphic Manner

Because prairie voles sustain monogamous relationships and cooperate in the care of their offspring, these rodents have been used as an ethologically valid model of human social behavior. How these animals are handled in the laboratory, however, may affect their later behavior. Bales et al. (2007) have now shown that differences in handling during the first 2 weeks of life can change postweaning alloparental care (care directed toward the offspring of others) and adult pair bonding in prairie voles. Moreover, these effects are sexually dimorphic. Males who were handled as infants increased their alloparental behavior, but females did not. Females who were handled as infants showed increased partner preferences, but males did not. Previous handling decreased adult anxiety in a nonsocial setting (an elevated plus-maze) for both males and females. These findings emphasize the sensitivity of voles to environmental manipulations, such as touch/handling, during early postnatal development. The different findings in males versus females indicate that the vole may be a useful model animal in which to study sex differences in the development of psychiatric disorders (Bales, K.L., et al. *Developmental Psychobiology* 49(4):335-342, 2007).

Social Isolation Disrupts Neuroendocrine Systems and Causes "Anhedonia" in Females More Than Males

Prairie voles have a reliance on their social environment that closely resembles that of humans. Because a sense of isolation may be a chronic stressor that contributes to the development of depression, Grippo et al. (2007) studied the neuroendocrine and affective impact of social isolation on male and female voles. Adult voles were socially isolated (housed singly, rather than in pairs) for four weeks. Neuroendocrine measures were made from blood samples and immunoreactivity patterns examined in the paraventricular nucleus (PVN). The degree to which voles preferred drinking a sucrose solution to water served as an operational behavioral measure of "anhedonia," a core feature of clinical depression in

humans. Social isolation resulted in a set of female-specific neuroendocrine and behavioral responses. Only females had increased circulating oxytocin levels, increased numbers of oxytocin-producing cells in the PVN, and reduced sucrose preference. After an acute stressor, only females had increased levels of circulating adrenocorticotropic hormone and corticosterone and increased activity in corticotropin releasing factor (CRF)-producing cells in the PVN. The authors suggest that oxytocin acts as a buffer, to compensate for the effects of the corticosteroid-related hormones released from the hypothalamic-pituitary axis (HPA). In female voles, the increase in oxytocin levels may not fully compensate for the hypersensitivity of the HPA axis. This imbalance may, in turn, lead to a greater vulnerability to depression-like symptoms in females than males (Grippo, A.J., et al. *Psychoneuroendocrinology* 32(8-10):966-980, 2007).

Sex-Specific Social Behavior Regulated By Mecp2, a Gene Implicated in Autism Spectrum Disorders

Pervasive developmental disorder is a classification covering five related conditions, including the neurodevelopmental disorder Rett syndrome (RTT) and autism. RTT has a known genetic cause with mutations in Methyl-CpG-binding protein 2 (MeCP2), a global repressor of gene expression, responsible for the majority of RTT cases. However, reduced MeCP2 is also implicated in autism and related disorders that have a gender bias in incidence. Previous studies from the Auger lab found that, during a transient steroid-sensitive period of newborn brain development, male rats express less MeCP2 than females within the amygdala and the ventromedial hypothalamus. In this present study, the Auger lab reports that experimentally reducing MeCP2 in the amygdala during this sensitive period of brain sexual differentiation reduced juvenile social play behavior in males, but not females. Reduced MeCP2 expression did not change juvenile sociability or anxiety-like behavior, suggesting that this disruption is associated with subtle behavioral modification. This suggests that MeCP2 may have an overlooked role in the organization of sexually dimorphic behaviors and that male juvenile behavior is particularly sensitive to MeCP2 disruption during this period of development (Kurian, J.R., et al. *Journal of Neuroscience* 28(28):7137-7142, 2008).

A Novel Mechanism of Hypothalamic Synaptic Development Regulated by the Sex Hormone Estradiol

The hypothalamus is a brain region with known anatomical sex differences that may relate to its role in regulating the release of hormones such as growth hormone. However, the mechanism by which these differences are established is not known. Previous studies had shown hypothalamic sex differences in the number of dendritic spines, microscopic components of neuronal synapses that are critical for establishing and maintaining electrical transmission. In this study, newborn female rats were treated with the sex hormone estradiol, during a critical steroid-sensitive period of brain development, in order to induce the male phenotype (increased number of dendritic spines) in the hypothalamus. The development of dendritic spines was then closely followed at the molecular level. In contrast to other brain regions, where an initial overabundance of spines is later pruned back, the activation of estrogen receptors in the hypothalamus by estradiol resulted in the growth of new synapses on dendritic spines. This involved the presynaptic release of the neurotransmitter glutamate, activation of postsynaptic glutamate receptors, which resulted in the changes in dendritic spines and synaptic function. This novel mechanism may help explain how long-lasting sexually dimorphic changes occur during the steroid hormone-sensitive period of hypothalamus development (Schwarz, J.M., et al. *Neuron* 58(4):584-598, 2008).

Estrogen and Progesterone Decrease Corticotrophin-Releasing Hormone in the Paraventricular Nucleus of the Hypothalamus of Nonhuman Primates: Implications for Stress Resilience

Stress is known to increase the level of CRH in the hypothalamic paraventricular nucleus. This hormone has also been suggested to play a key role in processes underlying depression. Here the ovarian hormones, estrogen and progesterone, were chronically given to adult

monkeys whose ovaries were removed surgically to determine how this treatment changes the expression of CRH protein and messenger RNA in the paraventricular nucleus. Levels of both CRH protein and gene expression were found to decrease. These results suggest that ovarian hormone-dependent decreases in CRH expression in the paraventricular nucleus enhance stress resilience in nonhuman primates (Bethea, C.L., et al. *Neuropsychopharmacology* 33(3):546-556, 2008).

Research on Specific Mental Disorders

According to the National Co-morbidity 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. Eating disorders, while 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. The following examples demonstrate NIMH-supported research on specific mental disorders.

GABA-A Receptors May Play a Role in Postpartum Depression

Levels of estrogen and progesterone markedly change following pregnancy and are thought to underlie postpartum depression, a disorder affecting about 15 percent of women after they give birth. However, treating women with these hormones, to mimic the hormonal changes that occur during pregnancy, leads to depression only in women with a history of this disorder. As a result, the mechanisms underlying postpartum depression do not simply reflect the changing hormone levels that occur with pregnancy. Previous studies have shown that delta-subunit-containing GABA-A receptors fluctuate as ovarian hormone levels fluctuate across the estrous cycle in rodents. In a recent study, researchers investigated changes in GABA-A receptors during pregnancy and the postpartum period. They found that expression of the delta subunit of the GABA-A receptor in the mouse hippocampus decreased significantly during pregnancy and returned to control levels postpartum. Postpartum mice deficient in the GABA-A receptor delta subunits showed an increase in depression-like behaviors compared with controls. Mice deficient in the GABA-A receptor delta subunits also showed abnormal maternal behavior during the postpartum period. This abnormal maternal behavior was reversed by treating the mice with THIP, a GABA-A receptor delta-subunit-preferring agonist that pharmacologically enhances the tonic inhibition mediated by this type of GABA-A receptor. These results highlight the potentially important role of GABA-A receptor dysfunction during pregnancy and postpartum and suggest that the delta subunit may be a potential target for development of new treatments for postpartum depression (Maguire, J., et al. *Neuron* 59(2):207-213, 2008).

Pain and Depression in Preadolescent Girls

Although the cooccurrence of pain and depression is common in adults, little is known about this link in children and about the mechanisms that explain this association. This study showed that response to a controlled pain stimulus was prospectively associated with later depressive symptoms at ages 10 and 11. Pain and depression were more strongly linked among girls in the advanced stages of pubertal development and among European-American girls. These results inform the developmental timing of the association between depression and pain response and suggest that systems that trigger the adrenal and gonadal axes (during pubertal development) may be part of the circuitry linking pain and depression (Keenan, K., et al. *Journal of Pediatric Psychology* Epub 2008 Oct 28).

Excessive Problem Talk Among Girlfriends Linked to Symptoms of Anxiety and Depression

Close friendships are often considered essential sources of social support, protective against symptoms of depression and anxiety in children and adolescents. Although corumination, the act of excessively discussing problems, with friends can increase perception of social support, it may also result in too much focus on problem salience and contribute to

symptoms of anxiety and depression. In a recent 6-month longitudinal study of middle childhood to midadolescent youth, researchers reported that corumination has both costs and benefits for young girls. Corumination predicted increased positive friendship quality as well as increased depressive and anxiety symptoms 6 months later. Additionally, positive friendship quality and symptoms predicted increased corumination over time, suggesting a continuous cycle. Corumination was not associated with later depression and anxiety among boys, however. The findings have implications for the identification of girls at risk for developing depressive/anxiety symptoms despite close, supportive friendships and suggest the need to evaluate peer support when intervening with youth at risk (Rose, A.J., et al. *Developmental Psychobiology* 43(4):1019-1031, 2007).

Parenting and Adolescent Behavior in Girls: A Two-Way Street

The Pittsburgh Girls Study is a large-scale, longitudinal study of assessing risk and protective factors for the development of conduct disorder and other psychopathologies in girls. In the past year, this project has generated several articles on the reciprocal relationship between parenting and early adolescent behavior. For example, during development, conduct problems in young girls increased the likelihood of harsh punishment by parents, which in turn led to more conduct problems as the girls grew up. Parenting styles characterized as being low in warmth were associated with increased conduct problems and increased symptoms of depression in girls from 7 to 12 years of age. Furthermore, early symptoms of depressed mood were associated with a decrease in the warmth of parental interactions at older ages. This two-way street between parenting style and early adolescent behavior suggests a need for early interventions that target both parents and children in order to decrease the likelihood of developing conduct problems or depression in adolescent girls (Hipwell, A., et al. *Journal of Abnormal Child Psychology* 36(5):663-677, 2008; Epub 2008 Jan 3; Miller, S., et al. *Journal of Abnormal Child Psychology* Epub 2008 Sep 7).

Adolescent Mothers' Exposure to Intimate Partner Violence and Trajectories of Depressive Symptoms Over Time

Adolescent mothers are at high risk of experiencing intimate partner violence (IPV), which may increase their likelihood of depressive symptoms in adulthood, yet little is known about the long-term effects of IPV on adolescent mothers' trajectories of depressive symptoms. The study reported here uses prospective data spanning 14 years from a study of 229 adolescent mothers to evaluate the effects of adolescent exposure to IPV on the trajectories of depressive symptoms over time, as well as the likelihood of depressive symptoms at age 28. After controlling for levels of economic insecurity, the results indicate that adolescent IPV and an early vulnerability to depression were significantly related to the starting level, but not the change over time of adult depressive symptom trajectories. Both cumulative and concurrent IPV predicted the likelihood of depressive symptoms at age 28. Followup analyses indicate that adolescent IPV is associated with greater levels of adult IPV, and that women who report both adolescent and adult IPV have the highest mean levels of depressive symptoms. These findings suggest that exposure to IPV in adolescence may alter the life course of young women, increasing their risk for continuing exposure to intimate partner violence in adulthood and its concomitant negative mental health effects. Efforts aimed at prevention and at early intervention regarding IPV among adolescent mothers are important components of the clinical care of young mothers (Lindhorst, T., et al. *Social Science & Medicine* 66(6):1322-1333, 2008)..

Lamotrigine in Bipolar Disorder: Efficacy During Pregnancy

Medications used to treat bipolar disorder may pose risk to the fetus during pregnancy and clinicians may recommend discontinuation of such medications. Thus, alternative treatments for bipolar disorder are needed. Lamotrigine is an antiseizure medication that may be effective for the treatment of bipolar disorder with minimal risk to the fetus. A recent study examined risk of recurrence among pregnant women diagnosed with bipo-

lar disorder, comparing those who continued treatment with lamotrigine to those who discontinued traditional medications for mood stabilization. Those who continued treatment with lamotrigine were at much less risk for recurrence of a mood episode, suggesting that lamotrigine may effectively manage bipolar disorder during pregnancy while offering greater fetal safety than other medications typically used to treat the disorder (Newport, D.J., et al. *Bipolar Disorders* 10(3):432-436, 2008).

Risk of Recurrence in Women With Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation

The authors in this study estimated the risk of recurrence of depressed or manic mood episodes among women during pregnancy, comparing those who either continued or discontinued treatment with mood stabilizers. Overall, the risk was substantial with 71 percent of women suffering recurrence of a mood episode. However, compared to those who continued medication, the risk for recurrence among patients who discontinued treatment doubled, the time to recurrence was quartered, and the proportion of weeks in episode during pregnancy was five times greater. Among those who discontinued, it appeared that the risk of recurrence was partially attenuated by a gradual discontinuation of a mood stabilizer. Factors that increased the risk for recurrence included bipolar II diagnosis, earlier onset, more recurrences per year, a recent episode, use of antidepressants, and the use of anticonvulsants compared to lithium. Clearly, discontinuation of a mood stabilizer during pregnancy poses risks and this risk should be weighed against the risk of recurrence (Viguera, A.C., et al. *American Journal of Psychiatry* 164(12):1817-1824, 2007).

Depression Linked to Bone Thinning in Premenopausal Women

Researchers compared premenopausal depressed (n = 89) and nondepressed women (n = 44) and found that premenopausal women with even mild depression have less bone mass than do their nondepressed peers. The level of bone loss is at least as high as that associated with recognized risk factors for osteoporosis, including smoking, low calcium intake, and lack of physical activity. Hip bones, the site of frequent fractures among older people, were among those showing the most thinning in depressed premenopausal women. Except for depression, the two groups were similar in risk factors, including calcium, caffeine, and alcohol intake; smoking; level of physical fitness; use of oral contraceptives; and age of first menstrual period. One difference was that the depressed women were taking antidepressant medications. A previous study suggested that older adults taking antidepressants called selective serotonin reuptake inhibitors had more bone fractures than others. However, the current study showed that these medications were not linked to low bone mass in premenopausal women. There was no significant link between the degree of bone loss and the severity of depression or the cumulative number of depressive episodes. Blood and urine samples showed that depressed women have imbalances in immune-system substances, including those that produce inflammation, compared to their healthy peers. This additional finding strengthens the case for a suspected link between depression-induced imbalances in the immune system and accelerated bone loss. Compared to the others, the depressed women in this study had higher levels of immune-system proteins that promote inflammation, and lower levels of those that prevent it (Eskandari, F., et al. *Archives of Internal Medicine* 167(21):2329-2336, 2007).

Prenatal Hormone Exposure and Risk for Eating Disorders: A Comparison of Opposite-Sex and Same-Sex Twins

Although the sex difference in eating disorder prevalence has typically been attributed to psychosocial factors, biological factors may also play a role. Prenatal testosterone exposure is a promising candidate because it masculinizes behavior in animals and humans via its permanent effects on the central nervous system. The purpose of this study was to examine whether in utero testosterone exposure has masculinizing effects and protective effects on disordered eating (DE) by comparing opposite-sex (OS) and same-sex (SS) twins. Twin

type (SS vs. OS) is considered a proxy measure of prenatal hormone exposure because females from OS pairs are exposed to more testosterone in utero than females from SS pairs. The results of this study indicated that SS female twins exhibited the highest levels of disordered eating followed by OS female twins, OS male twins, and SS male twins. These results could not be accounted for by levels of anxiety or socialization effects. The results also suggest that masculinization of DE in OS female twins is unlikely to be due to socialization effects alone. Biological factors, such as the masculinization of the central nervous system by prenatal testosterone exposure, may also contribute to sex differences in DE prevalence (Culbert, K.M., et al. *Archives of General Psychiatry* 65(3):329-336, 2008).

A Preventive Intervention for Eating Disorders

Researchers have developed a brief (3 hours) school-based program that takes a "dissonance based" approach to eating disorder prevention. Adolescent girls (n = 481) who expressed body dissatisfaction were randomly assigned to a dissonance-thin-ideal internalization reduction program, a healthy weight control program, an expressive writing control condition, or an assessment-only control condition. The dissonance intervention targets the thin ideal internalized by young women with body image concerns. The women who participated in the program engaged in verbal, written, and behavioral exercises during which they critiqued the thin ideal (e.g., write an essay that is counterattitudinal). The investigators theorized that participating in these types of activities produces a psychological discomfort that motivates the young women to reduce their internalization of the thin ideal. This would then decrease their body dissatisfaction, dieting, negative affect, and symptoms of eating disorders. The 3-hour healthy weight intervention focuses on teaching healthy improvements to dietary intake and exercise as a way of achieving body satisfaction in order to decrease risk for unhealthy weight control behaviors. Compared to the assessment-only condition, women who participated in the dissonance program showed greater reductions in three targeted risk factors (thin-ideal internalization, body dissatisfaction, and negative affect), eating disorder symptoms, and psychosocial impairment, with effects continuing 2 to 3 years after participation in the program. These women also demonstrated reduced risk for onset of eating disorders through the 3 year followup period. Effects were also found for the healthy weight intervention condition (Stice, E., et al. *Journal of Consulting and Clinical Psychology* 76(2):329-340, 2008).

Gender and Age Differences in Associations Between Peer Dieting and Drive for Thinness

The purpose of this study was to examine associations between peer dieting and drive for thinness (DT) in men and women of three age groups and to compare rates of perceived vs. reported peer dieting. The data came from an epidemiological study in which surveys were completed by women (n = 1,468) and men (n = 592) from three age groups: late adolescent (mean +/- SD age: 20 +/- 1.6 years), adult (30 +/- 1.6), and midlife (40.1 +/- 2). The results of the study indicated there were significant associations found between perceived peer dieting and DT in women and men. For women, associations were strongest in late adolescents for same-sex peers. Associations in men did not differ by age group or peer sex. Expected gender differences in the strength of associations were not found. These results may partially account for why DT has been found to decline with age in women, but not men. Longitudinal research is needed to support cross-sectional findings (Gravener, J.A., et al. *International Journal of Eating Disorders* 41(1):57-63, 2008).

Baclofen Treatment for Binge Eating Disorder

This clinical study explores the idea that baclofen, a drug acting upon y-amino butyric acid B (GABA-B) receptors that showed encouraging results in the treatment of cocaine, opiate, and alcohol dependence, may be efficient in female patients suffering from binge eating. Participants in this study were seven women ranging from 18 to 45 who met clinical criteria for binge eating disorders. Upon conducting formal interviews, patients were administered either baclofen or placebo

at increasing doses from 15 to 60 mg/day during 11 weeks of treatment. The results demonstrate that five out of seven patients exhibited 50 percent or more reduction in their binge eating episodes, while three out of seven patients demonstrated a complete cessation of binge eating episodes at the end of the trial. Although the sample size was quite small, these data are encouraging because baclofen reduced their frequency of binge eating and produced a small but statistically significant effect on the ratings of food craving. The ability of baclofen to reduce intake, craving, and anxiety for drug abuse in both human and animal studies suggests that it might act on reward-linked circuitry that may be dysfunctional in both substance abuse and binge eating. The results obtained on a small population in this study suggest a possibility that baclofen may be useful in treatment of female patients suffering from binge eating as well as warrant better controlled studies in a larger population (Broft, A.I., et al. *International Journal of Eating Disorders* 40(8):687-691, 2007).

The Genetics of Anorexia Nervosa Collaborative Study: Methods and Sample Description

This research consists of a 12-site international collaboration designed to identify genetic variants that affect risk for anorexia nervosa (AN). Specifically, 400 families will be ascertained with 2 or more individuals affected with AN. The assessment battery produces a rich set of phenotypes comprising eating disorder diagnoses and psychological and personality features known to be associated with vulnerability to eating disorders. To date, the investigators report attributes of the first 200 families, comprising 200 probands and 232 affected relatives. The results gained from this international collaboration will provide context for the genotyping of the first 200 families by the Center for Inherited Disease Research. The investigators will then analyze the first 200 families for linkage, complete recruitment of roughly 400 families, and then perform final linkage analyses on the complete cohort. DNA, genotypes, and phenotypes will form a national eating disorder repository maintained by the NIMH and be available to qualified investigators (Kaye, W.H., et al. *International Journal of Eating Disorders* 41(4):289-300, 2008).

Altered Reward Processing in Women Recovered from Anorexia Nervosa

Individuals with anorexia nervosa are known to be ascetic and able to sustain self-denial of food as well as most comforts and pleasures in life. Building on previous findings of altered striatal dopamine binding in anorexia nervosa, the authors sought to assess the response of the anterior ventral striatum to reward and loss in this disorder. Striatal responses to a simple monetary reward task were investigated using event-related functional magnetic resonance imaging. The results of the study suggest that individuals who have recovered from anorexia nervosa may have difficulties in differentiating positive and negative feedback. The exaggerated activation of the caudate, a region involved in linking action to outcome, may constitute an attempt at "strategic" (as opposed to hedonic) means of responding to reward stimuli. The authors hypothesize that individuals with anorexia nervosa have an imbalance in information processing, with impaired ability to identify the emotional significance of a stimulus, but increased traffic in neurocircuits concerned with planning and consequences (Wagner, A., et al. *American Journal of Psychiatry* 164(12):1842-1849, 2007).

Cortisol Low and PTSD Risk High in Children of Holocaust-Survivor Mothers With PTSD

People with posttraumatic stress disorder (PTSD) tend to have low levels of cortisol, a hormone that puts the brakes on the body's reaction to stress, so that it does not go on for too long and cause damage. A series of studies funded by NIMH suggest that the children of people with PTSD inherit the tendency to have low cortisol levels and increased vulnerability to PTSD. In these investigations, researchers studied adult children born to parents who had gone through the Holocaust and had developed PTSD and community control subjects. They found that children whose mothers had PTSD had the low-cortisol trait far more often than did children whose fathers had PTSD. This suggests that the passing on

of the trait to the next generation may involve genes—but not in the classic way that genes transmit traits from parents to offspring. In the womb, fetuses already have the genes they inherited from their parents; they inherited them at conception, laying the foundation for all of their traits. But the environment in the uterus—including the mother's stress-related hormone levels—can cause changes in the activity patterns of the fetus' genes, such as when and for how long a gene is "switched on." These changes may alter a multitude of traits and, once set in motion, may persist throughout life. This could explain why the adult children of Holocaust-surviving mothers with PTSD, far more than children of fathers, had low cortisol levels. Another explanation could be that the children may have spent more time with their mothers early in life, and that the mothers' behaviors influenced the children's responses to stress. These same researchers also found that the presence of maternal PTSD was associated with PTSD in adult offspring—whereas other psychiatric diagnoses did not show specific effects associated with maternal PTSD. Low cortisol levels—something that appears to be transmitted from mothers to children and predisposes to PTSD—may provide additional clues to a better understanding of who will develop PTSD and methods for early intervention (Yehuda, R., et al. *Archives of General Psychiatry* 64(9):1040-1048, 2007; Yehuda, R., et al. *Journal of Psychiatric Research* 42(13):1104-1111, 2008; Epub 2008 Feb 20).

History of Interpersonal Violence Exposure Clue to Risk Architecture for PTSD in Women

In a study attempting to shed light on two separate but interrelated findings in the epidemiology of PTSD, women's greater PTSD risk following traumatic events and the sensitizing effects of a prior trauma on the PTSD response to a subsequent trauma, researchers confirmed that women's risk for PTSD following assaultive violence was higher than men's and further observed that when assaultive violence preceded a later nonassaultive trauma, there was an increased risk (relative risk = 4.9) for PTSD, which was not observed in men. Data come from a representative sample of 1,698 young adults from a large U.S. city and revealed that the relative risk in women was significantly higher than in men. These findings suggest that assaultive violence elicits women's PTSD response directly by sensitizing them to the effects of subsequent traumatic events of lesser magnitude (Breslau, N., et al. *Journal of Pediatric Psychology* 32(3):338-342, 2007; Epub 2006 May 22).

Borderline Personality Disorder: Brain Differences Related to Disruptions in Cooperation in Relationships

Different patterns of brain activity in people with borderline personality disorder were associated with disruptions in the ability to recognize social norms or modify behaviors that likely result in distrust and broken relationships. Researchers evaluated cooperation among pairs of participants playing an investment game. Compared with the control group, trust and cooperation faltered over time in pairs that included a person with borderline personality disorder. Moreover, they were half as likely as healthy trustees to try to repair the relationship through coaxing. To determine whether a neural basis exists for this behavior, the researchers analyzed brain activity in the bilateral anterior insula. In addition to other functions, this region responds when we sense unfairness or violations of social norms. In healthy participants, insula activity increased as offers or returned amounts decreased. By comparison, in participants with borderline personality disorder, insula activity increased only in response to low amounts they sent back to the investor; insula activity remained at an average level regardless of the amount offered to them by investors. The findings suggest that either people with borderline personality disorder are not persuaded by rewards of money in the same ways as healthy people, or that they do not regard low investment offers as a violation of social norms. The researchers also found that people with borderline personality disorder reported lower levels of trust in general, compared with healthy participants. In other words, untrustworthy behavior by the investors would not be seen as a violation of social norms because the participants with borderline personality disorder had less trust in their partners to begin with. Using concepts from game theory,

this study offers a new way of studying and understanding interpersonal relationships and mental illnesses that impair social interactions (King-Casas, B., et al. *Science* 321(5890):806-810, 2008).

Unpleasant Words Trigger Strong Startle Response in People with Borderline Personality Disorder

Researchers measured the startle eye-blink response, a measure of emotional reactivity, in 27 people with borderline personality disorder (BPD) and 21 healthy people. During the study, each participant was shown a random series of words, some with neutral emotional meaning (e.g., "collect," "regular," "actually") and some with unpleasant meanings, particularly for people with BPD (e.g., "hate," "lonely," "abandon"). The participants would hear a brief startling burst of static noise at unpredictable intervals—sometimes while a word was shown, sometimes between words, and sometimes not at all. The researchers found that both groups of participants had similar startle reactions when viewing neutral words. But people with BPD were more startled than healthy adults by the static burst when looking at unpleasant words. Also, people with more BPD symptoms showed a greater difference in startle reaction when viewing unpleasant words vs. neutral words compared to people with less severe BPD. This finding suggests that unstable emotions and impulsiveness in people with BPD may be related to an exaggerated startle reflex. The researchers' study presents an objective way to measure the problems with mood and emotional responses that are hallmark symptoms of BPD, suggesting a potentially useful adjunct to self-reported information when diagnosing and treating the disorder (Hazlett, E.A., et al. *Biological Psychiatry* 62(3):250-255, 2007).

Research on Health Behavior, AIDS, and Mental Health Disparities

Research on health behaviors related to AIDS is increasingly important to the reduction of health disparities in minority populations, for example, the disproportionate increase in HIV infection experienced by African-American women. Healthcare disparities can also occur as a function of age, geographic location, socioeconomic status, and other factors The following examples highlight FY 2007–2008 NIMH-funded research addressing AIDS and health disparities.

Prevalence of Eating Disorders within the U.S. Black Population Varies

Few studies have examined eating disorders among Blacks. Those studies with such a focus have found that binge eating disorder (BED) occurs with equal or greater frequency for African-American and White women, while anorexia nervosa is rarely found among African-American women. These findings come from a national probability sample of households drawn based on adult population estimates and power calculations for detecting differences in the two adult samples, using the African-American sample as the primary core sampling base for the study. The findings show that among adults, women had higher lifetime prevalence of any binge eating and 12-month prevalence of bulimia nervosa (BN) and BED than men. Marginally significant gender differences were found for adults with lifetime prevalence of BN and any binge eating with women experiencing higher prevalence than men. No significant gender differences were found among adolescents; however, it is notable that more cases of boys than girls were reported with 12-month prevalence for AN, BN, and any binge eating (Taylor, J., et al. *International Journal of Eating Disorders* 40(Suppl):S10-S14, 2007).

Acculturation Plays an Important Role in Understanding Eating Disorders Among Latinos

Research on eating disorders has primarily focused on young, White female populations from relatively affluent backgrounds. Information about the prevalence of eating disorders in ethnic minority groups, particularly Latinos, is virtually unknown. Data come from the National Latino and Asian American Study (NLAAS), a national epidemiological household survey of Latinos in the United States. Compared to men, women tended to have higher lifetime and 12-month prevalence rates for BN, BED, and any binge eating, but differences were not statistically significant. Consistent with previous studies, the investigators

observed some support for the risk effect of acculturation for Latinos. Specifically, foreign nativity is associated with decreased risk for binge eating, and those who spent more than 70 percent of their lifetime in the United States reported the highest rate of lifetime BN. Preoccupation with slimness might be increasingly adopted as Latinos integrate American conceptions of beauty, losing their defense against eating disorders. Less time spent in the United States (perhaps especially during adolescence, the developmental period of highest risk for developing an eating disorder) most likely means less exposure or cultural adaptation to U.S. norms and expectations (Alegria, M., et al. *International Journal of Eating Disorders* 40(Suppl):S15-S21, 2007).

Despite Low Prevalence Estimates, Eating Disorders Are Present Among Asian-American Men and Women

This research contributes to the eating disorders literature by providing epidemiological data on prevalence and correlates of eating disorders among Asian American adults. Using data from the NLAAS, researchers determined whether eating disorders are common among Asian Americans by comparing lifetime and 12-month prevalence of eating disorders between men and women. The results show that only lifetime prevalence for BED is significantly higher for Asian women compared to Asian men. This finding on gender differences supports the existing literature that indicates women exhibit more disordered eating problems compared to men, and men are less likely to develop and engage in disordered eating behaviors (Nicado, E., et al. *International Journal of Eating Disorders* 40(Suppl):S22-S26, 2007).

Concerns about Stigma May Partly Account for the Low Rate of Mental Health Care Seeking Among Disadvantaged Ethnic Minority Immigrant Women

In a study aimed at better understanding the low rate of mental health service use among economically disadvantaged immigrant and U.S.-born Black and Latina women, the authors examined the relationship of stigma concerns to wanting and getting mental health care. All participants in the research were screened for depression and were then asked in either Spanish or English whether any of a series of stigma concerns and logistical barriers would keep them from getting professional health. Women who screened positive for depression and Black immigrant groups and U.S.-born Blacks were more likely than U.S.-born Whites to endorse stigma concerns about care. U.S.-born and immigrant Latinas did not differ significantly from Whites. Women without depression in all immigrant groups were more likely than U.S.-born White women to report stigma concerns. Women with stigma-related concerns were less likely than those without such concerns to indicate an interest in treatment. The authors suggest that settings providing care for immigrant women should be alert to the substantial concerns these women might have about entering mental health care, and consider such strategies as client education about mental health treatment to help alleviate these concerns (Nadeem, E., et al. *Psychiatric Services* 58(12):1547-1554, 2007).

Self-Destructive Behaviors and Substance Use Predict Risky Sexual Behavior Among HIV Positive Women with a History of Childhood Sexual Abuse

Among individuals with HIV, there is a high prevalence of childhood sexual abuse (CSA). There are few data on factors that predict risky sexual behavior among individuals living with HIV who have a history of CSA. This study interviewed over 250 men and women living with HIV who had experienced sexual abuse before the age of 18. Among women, sexual risk was predicted by the presence of self-destructive behaviors, cocaine or crack use, and behavioral difficulties. Results indicate that HIV-prevention interventions for persons with HIV and CSA histories should address trauma-related behavioral difficulties and enhance coping skills to reduce sexual transmission risk behavior (Sikkema, K.J., et al. *Archives of Sexual Behavior* Epub 2007 Nov 13).

HIV Positive Survivors of Sexual Abuse Who Receive Coping Intervention Less Likely to Engage in Unprotected Sex

People who are HIV positive and have experienced childhood sexual abuse are less likely to engage in risky sexual behavior if they receive a group intervention designed to help them cope with their traumatic history. Previous research has found that people living with HIV are more likely than the general population to have experienced sexual abuse during childhood. Those with a history of sexual abuse are also more likely to engage in unprotected sexual behavior that can contribute to the spread of HIV and AIDS. In addition, the psychological consequences of childhood sexual abuse, such as low self-esteem, avoidance, and self-destructiveness, are associated with risky sexual behavior. Researchers developed a structured, manual-based intervention designed to help participants cope not only with HIV but also with the impact and consequences of their childhood trauma. The researchers randomly assigned 247 men and women with HIV positive status and a history of childhood sexual abuse to either a 15-session coping group intervention, or to a 15-session social support group. Sexual behavior was measured at the beginning of the intervention period, and at 4, 8, and 12 months postintervention. Across all of the followup periods, the researchers found more of a decrease in the frequency of unprotected sexual activity among the coping intervention group than the support group. By 12 months postintervention, those in the coping intervention group had reduced their rate of unprotected sexual behavior by an average of 54 percent compared with the support group. Researchers conclude that risky behavior among adults who are HIV+ and have abuse histories can be reduced more effectively by addressing trauma-related factors such as shame, coping difficulties, and relationship issues than by just providing general social support (Sikkema, K.J., et al. *Journal of Acquired Immune Deficiency Syndromes* 47(4):506-513, 2008).

Innovative Approach to Assessing Mood and Behaviors in Adolescents Used To Examine Reasons Youth Have Sex

Existing research on adolescent affect has been limited by self-report measures of global mood, which are subject to retrospective recall biases and do not fully capture the day-to-day experiences of adolescents. In order to address these biases, researchers used handheld computers with adolescents to capture real-time measures of daily mood. Adolescents were instructed to report when they had sex as soon as possible after the event. Adolescents were also asked to respond to a series of questions related to the event, including their mood and their reasons for engaging in sex. Overall, higher levels of anxiety were associated with external reasons for sex, while younger age and lower self-esteem were associated with affect management reasons. Among adolescent women, those with higher impulsiveness reported more external reasons for having sex and fewer intimacy/desire reasons. These findings may aid healthcare providers and researchers in understanding the differences in young people's motivations for sex, in particular, how affect management may play a role in young people's motivation to engage in risky behavior (Dawson, L.H., et al. *Journal of Sex Research* 45(3):225-232, 2008).

Women With HIV Report Higher Rates of Adherence During Pregnancy than During the Postpartum Period

Among women with HIV infection, pregnancy is a time when maintenance of maternal health and reduction of vertical HIV transmission are primary concerns. Few studies have examined adherence to antiretroviral treatment during pregnancy and in the postpartum period when the demands of childcare may significantly interfere with women's self-care behaviors. This study examined antiretroviral therapy use and adherence in pregnant and postpartum women with HIV infection participating in the Women and Infants Transmission Study. During the third trimester visit, 61 percent (188/309) reported complete adherence, while at the 6-month postpartum visit, only 44 percent (97/220) of these women reported complete adherence. Fewer women were also found to be taking antiretroviral

medications in the postpartum period. Factors associated with nonadherence across both of the visits included higher HIV-RNA viral load and increased alcohol use. These analyses indicate that the postpartum period is associated with increased rates of nonadherence and may present an excellent opportunity for intervening to maintain adherence after pregnancy (Mellins, C.A., et al. *AIDS Care* 20(8):958-968, 2008).

Maternal HIV Status Not Related to Risky Sexual Behavior Among Youth

HIV-negative, inner-city adolescents with parents with HIV infection are considered to be at high risk for acquiring HIV infection themselves. This study examined the effects of maternal HIV infection and psychosocial variables on the onset of sexual risk behavior in 144 HIV-negative adolescents, some of whom had a mother with HIV infection. Youth were first interviewed at 10–14 years of age, at which time 5 percent of the youth were sexually active. Youths were interviewed again at 13–19 years of age, at which time 42 percent reported being sexually active. Factors associated with risky behavior included youth and family psychosocial variables, but not maternal HIV status (Mellins, C.A., et al. *Journal of Youth and Adolescence* 36(3):265-278, 2007).

Higher Rates of Depression Among Women Who Have Disclosed Their HIV Status to Their Children

Given the effectiveness of antiretroviral medications, more and more mothers are living with HIV infection and raising children. This study evaluated the rates of mental health problems in mothers and children in families affected by maternal HIV infection as compared to those not affected by maternal HIV infection, but living in similar inner-city, low socioeconomic status, primarily ethnic-minority neighborhoods. Interviews with over 200 mother/child dyads were conducted looking at a range of mental health symptoms. Participants included early adolescents who were HIV negative (ages 10 through 14 years) and their mothers, approximately half of whom were HIV positive. Overall, mothers with HIV infection exhibited more depressive symptom profiles than uninfected mothers. There were no significant differences, however, in depressive symptom profiles between children of mothers who were HIV positive and children of mothers who were HIV negative. Among families directly affected by HIV, mothers who disclosed their status to their children endorsed greater depressive symptom profiles than those who did not disclose, and children who had been disclosed to were more likely to score in the clinically depressed range on the Child Depression Inventory than those who did not know. The results corroborate previous findings with women with HIV infection that highlight the mental health needs of mothers with HIV infection and their children, particularly children who know their mothers' status (Brackis-Cott, E., et al. *Journal of Early Adolescence* 27(1):67-89, 2007).

Initiatives

The announcements listed below were active in FY 2007–2008 and had a significant focus on women's mental health and/or sex differences research.

Requests for Applications (RFAs)

- **Innovative Trials for the Treatment of Anorexia Nervosa in Late Adolescence and Adulthood (RO1)**

  http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-07-090.html

Program Announcements (PAs)

- **Women's Mental Health and Sex/Gender Differences Research (R21)**

  http://grants1.nih.gov/grants/guide/pa-files/PA-06-334.html

- **Women's Mental Health in Pregnancy and the Postpartum Period (R21)**

  http://grants.nih.gov/grants/guide/pa-files/PA-06-377.html

- **Neurodevelopment and Neuroendocrine Signaling in Adolescence: Relevance to Mental Health (R21)**

  http://grants.nih.gov/grants/guide/pa-files/PA-09-009.html

- **Neurodevelopment and Neuroendocrine Signaling in Adolescence: Relevance to Mental Health (R01)**

  http://grants.nih.gov/grants/guide/pa-files/PA-09-008.html

- **Women's Mental Health in Pregnancy and the Postpartum Period (R01)**

  http://grants.nih.gov/grants/guide/pa-files/PA-06-376.html

- **Women's Mental Health and Sex/Gender Differences Research (R01)**

  http://grants.nih.gov/grants/guide/pa-files/PA-06-333.html

- **Mental Health Consequences of Violence and Trauma (R03)**

  http://grants.nih.gov/grants/guide/pa-files/PA-07-313.html

- **Mental Health Consequences of Violence and Trauma (R21)**

  http://grants.nih.gov/grants/guide/pa-files/PA-07-314.html

- **Mental Health Consequences of Violence and Trauma (R34)**

  http://grants.nih.gov/grants/guide/pa-files/PAR-07-315.html

- **Mental Health Consequences of Violence and Trauma (R01**

  http://grants.nih.gov/grants/guide/pa-files/PA-07-312.html

- **Translational Research in Eating Disorders**

  http://grants.nih.gov/grants/guide/pa-files/PA-07-312.html

In FY 2007–2008, NIMH also participated in the following Office of Research on Women's Health program announcements and requests for applications.

Requests for Applications

- **Research on Causal Factors and Interventions That Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (R01)**

  http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-09-012.html

Program Announcements

- **Supplements To Promote Reentry into Biomedical and Behavioral Research Careers**

  http://grants1.nih.gov/grants/guide/pa-files/PA-08-191.html

- **Advancing Novel Science in Women's Health Research (ANSWHR) (R03)**

  http://grants.nih.gov/grants/guide/pa-files/PAS-07-382.html

- **Advancing Novel Science in Women's Health Research (ANSWHR) (R21)**

  http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html

Conferences and Workshops

- **Research Roundtable: Heterogeneity in Child and Adolescent Depression**

The purpose of this workshop was to discuss empirical evidence for sources of heterogeneity in child and adolescent depression, evaluate the significance of known heterogeneity, and identify promising research directions in this area. One of the major topics was to discuss different processes that might influence the emergence of gender differences in rates of depression during the transition to adolescence.

- **Roundtable on Mood Disorders and Hormonal Transitions**

NIMH cosponsored the roundtable with the Society for Women's Health Research. The meeting brought together experts in the areas of postpartum and perimenopause-related depression, in order to share information regarding research in mood disorders associated with reproductive hormone change. NIMH-funded investigators, along with NIMH Intramural researchers, participated in the event.

Research and Other Efforts on Health Disparities in Women

NIMH encourages research on special populations of women who may experience healthcare disparities based on age, race, geographic location, sexual preference, socioeconomic status, physical disabilities, etc. Research involving women from these diverse groups is encouraged in the program announcements entitled, "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, NIMH encourages research in special populations of both men and women through the following announcements:

- **Research on Rural Mental Health and Drug Abuse Disorders**

  http://grants.nih.gov/grants/guide/pa-files/PA-06-478.html

- **Clinical Research on Mental Illness in Older Adults**

  http://grants.nih.gov/grants/guide/pa-files/PA-06-422.html

- **Community-Based Participatory Research**

  http://grants.nih.gov/grants/guide/pa-files/PAR-07-004.html

Highlights of individual research projects on special populations of women can be found in Section B, under "Accomplishments/Research Highlights."

Gender Analysis

NIMH encourages research through two program announcements on sex/gender research. 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. Highlights of individual studies focused on sex differences can be found under "Accomplishments/Research Highlights."

National Institute of Neurological Disorders and Stroke

Executive Summary

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, pain, stroke, epilepsy, and Rett syndrome. NINDS supports basic, translational, and clinical research on these disorders as well as targeted research to understand sex-based differences in normal behavior, development, cognition, and perception.

Epilepsy is characterized by chronic, recurring seizures caused by abnormal electrical activity in the brain. Although antiepileptic drugs (AEDs), brain stimulation, or surgery can help many patients control the disorder, for others, treatments are ineffective or 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.

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. The disorder, which can have progressive or relapsing-remitting forms, is characterized by attacks of muscle weakness, coordination, vision problems, abnormal sensations, and sometimes cognitive impairments. Hormonal factors may influence some forms of MS, making them more common in women.

Chronic pain is abnormal pain that persists for weeks, months, or even years. It is caused by the improper functioning of neuronal

pain circuits. Treatments for chronic pain can include medication, acupuncture, or relaxation techniques; local electrical stimulation or brain stimulation; psychotherapy or behavior modification therapies; or surgery. Some chronic pain conditions, like migraine headaches or fibromyalgia, tend to be diagnosed more often in women than in men and it is now widely believed that pain affects men and women differently. While the sex hormones estrogen and testosterone certainly play a role in this phenomenon, psychology and culture, too, may account at least in part for differences in how men and women receive pain signals.

Rett syndrome is a childhood neurological impairment that causes severe cognitive impairment, autistic behavior, stereotypic movements, and frequently seizures. The disease, which is considered an autism spectrum disorder, 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 disease is almost exclusively seen in females because male fetuses carrying the mutation are unviable.

Stroke is the third leading cause of death in the United States, and a major cause of disability in both women and men. It is caused by a rapid disruption in the blood supply to part of the brain as a result of either 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. Although women in general have a lower risk of stroke than men, because of their longer life expectancy they account for 60 percent of stroke fatalities. The NINDS stroke research program ranges from basic investigation of stroke mechanisms through large clinical trials aimed at prevention and treatment. Research is also targeted to special issues of stroke in various populations, including women. The NINDS Know Stroke public awareness campaign aims to educate the public about the symptoms of stroke and the importance of getting to the hospital quickly. The NINDS has partnered with several national organizations, including the General Federation of Women's Clubs, to distribute Know Stroke materials.

Women's Health Research at NINDS

Management of extramural research at NINDS is organized by "Clusters," which are teams of program directors organized around scientific and disease areas. Women's health research is covered across a number of the NINDS clusters. In addition, the Office of Clinical Research manages most aspects of clinical studies, including the recruitment of women and minorities. NINDS participates actively in NIH women's health research initiatives through its Director-appointed representative to the NIH Coordinating Committee for Research on Women's Health.

Accomplishments

Epilepsy

Female Rats as a Proxy for Studying the Effect of Epilepsy on the Hormonal System

Chronic seizures in women may lead to adverse effects on reproductive function, such as polycystic ovarian syndrome, an endocrine disorder that produces ovarian cysts and affects hormone levels, periods, weight, and ovulation. It has been difficult to dissociate the effects of epilepsy from those stemming from the chronic use of antiepileptic drugs. To distinguish between these two factors, NINDS-funded researchers induced persistent seizures in rats and tracked their ovarian cycles, weight gain, and hormone levels. Even in the absence of anticonvulsant therapy, epileptic rats showed higher disruptions to their ovarian cycles, increased levels of testosterone, weight gain, and higher incidence of ovarian cysts. The results support the theory that chronic epilepsy can lead to disruptions in the endocrine system and establish that the female rat may be used as a model to test issues related to hormone dysfunction in women with epilepsy (Scharfman, H.E., et al. *Annals of Neurology* 64:687-697, 2008).

An Estrogen-Dependent Mechanism that Protects from Epilepsy-Induced Cognitive Disturbances

An area of the brain known as the hippocampus is important in learning and memory.

A subset of neurons in this brain region has been shown to be susceptible to damage induced by seizures, which may lead to cognitive deficits associated with certain types of epilepsy. It had been previously shown that pretreatment with estradiol, a naturally occurring estrogen produced by the ovaries, protects neurons in the hippocampus from seizure-related lesions in rats that had had their ovaries removed. NINDS-funded scientists have now shown that the protective effect of estradiol works by increasing the levels of a protein known as neuropeptide Y in the hippocampus, which in turn silences aberrant neural activity related to seizures. The results shed light on how menopause (medical or natural) may affect learning and memory in patients with epilepsy and provide therapeutic leads to explore better treatments of epilepsy in menopausal women (Velísková, J., et al. *Journal of Neuroscience* 27:6054-6063, 2007).

Multiple Sclerosis

A Potential Estrogen-Mediated Strategy to Protect Neurons from Degeneration in MS

MS is largely believed to be an autoimmune disease in which the immune system mistakenly attacks healthy tissue in the brain and nervous system. In recent years, researchers have focused on estrogen as a potential therapy after observing that the disease goes into remission during pregnancy. In the body, estrogen binds to two types of receptor proteins, estrogen receptors alpha (ERα) and beta (ERβ). In women, both estrogen and therapies with drugs that target ERα are associated with breast and uterine cancer. Therapies that target ERβ have not been associated with cancer. An NINDS-funded study has recently shown that, if administered early, a drug that targets ERβ protects neurons from the harmful effects of MS in female mice. The drug was not effective in reducing inflammation, and mice still developed motor defects characteristic of MS, but after a few weeks of treatment, mice regained the ability to walk normally. This is the first time that a hormone treatment has been found that works against MS without reducing inflammation. Because ERβ does not cause feminization, there is a possibility that this treatment could also work in men (Tiwari-Woodruff, S., et al. *Proceedings of the National Academy of Sciences of the United States of America* 104(37):14813-14818, 2007).

Insights on How Pregnancy Induces the Immune System to Suppress MS

Women with MS often experience a decrease in relapse rate during pregnancy, most notably during the third trimester, and a subsequent flare of the disease 3–6 months postpartum. This observation had led investigators to explore the changes that occur within the immune system between late pregnancy and the postpartum period with the hopes of gaining a better understanding about the causes of the disease and to identify potential therapies. Using mice with experimentally induced MS, a group funded by NINDS has found that improvement during pregnancy is not due to a decrease in the number of White blood cells—the cells that under normal circumstances respond to foreign materials but that during MS mistakenly attack the nervous system. Rather, pregnancy changed the levels of specific immune system molecules. If the same type of immune system "environment" could be replicated in nonpregnant women with MS, it could lead to significant improvement in the burden of the disease (McClain, M.A., et al. *Journal of Immunology* 179:8146-8152, 2007).

Pain

A Biological Mechanism for Increased Gut Pain in Women

Pain from the visceral organs, such as that produced from irritable bowel syndrome, is one of the most common forms of pain in the clinical setting, and one of the most frequent reasons why patients seek medical attention. Pain from irritable bowel syndrome is more prevalent in women and has been observed to fluctuate with the menstrual cycle. NINDS-funded researchers have recently made progress in understanding how estrogen may modulate sensitivity to gut pain. Experiments in female rats have shown that estrogen may produce molecular changes in pain-sensing neurons that alter the function of the N-methyl-d-aspartate (NMDA) receptor. The NMDA

receptor is an important protein in neurons because it produces long-lasting changes that increase the activity of the neurons and that may sensitize them to harmful and even non-harmful stimuli. Developing a more complete understanding of the myriad ways that estrogen can modulate pain will enable researchers to develop better ways to prevent and treat pain in both women and men (Tang, B., et al. *Pain* 137(3):540-549, 2008).

The Analgesic Beta-Endorphin Lowers Chest Pain in Men, But Not in Women

Chest pain, a predominant symptom of ischemic heart disease, is a major cause of hospital admission. In clinical practice, opioids are the most common analgesics for treating moderate to severe pain, and these agents are frequently used to treat severe chest pain and acute myocardial infarction. To study whether opioids have the same analgesic effect on chest pain between men and women, researchers induced chest pain in healthy volunteers and in patients with heart disease. Pain perception was tested with or without treatment with the opioid beta-endorphin. No differences were observed in pain perception or sensitivity without beta-endorphin, but treatment with the drug had an analgesic effect on men but no pain-relieving effect on women. These results call for changes in common clinical treatment of chest pain in women (Sadigh, B., et al. *Clinical Journal of Pain* 2:750-755, 2007).

Rett syndrome (RTT)

Dissecting the Origins of Rett Syndrome Deficits, One Group of Neurons at a Time

Patients with classic RTT suffer from many different types of behavioral deficits, ranging from cognitive and behavioral impairments, to movement disorders, to sleep disturbances and abnormal physiological responses to stress. The majority of RTT cases are caused by mutations in the gene for the MeCP2 protein, which is widely expressed throughout the brain. To study which phenotypes arise from loss of MeCP2 in specific brain regions, researchers genetically removed the MeCP2 gene from a subset of neurons in the hypothalamus, a brain region important for the regulation of metabolic processes such as stress responses and control of food intake. Loss of MeCP2 in these neurons resulted in mice that performed normally in numerous behavioral and cognitive assays, but that had the same abnormal stress response as mice that lacked the MeCP2 gene in the entire brain. Surprisingly, researchers observed that mice without MeCP2 in the hypothalamus were also aggressive and obese, similar to patients with mild forms of RTT. The researchers plan to use the same strategy to investigate the other brain regions that might be involved in the expression of Rett-associated behaviors (Fyffe, S.L., et al. *Neuron* 59(6):947-958, 2008).

Different Mutations in the Gene for Rett Syndrome Produce Different Levels of Clinical Severity

More than 200 mutations and other DNA aberrations in the MeCP2 gene have been found to cause the neurodevelopmental disorder RTT. Although the features of RTT are distinctive, the presentation of RTT may vary in severity. In a study funded by NINDS, the MeCP2 mutations of 245 girls diagnosed with typical RTT were identified and were associated to the level of disease severity as quantified using a clinical scale. The group found that specific MeCP2 mutations confer differential severity, particularly in ambulation, hand use, and language behaviors. These results allow the design of personalized therapies and counseling strategies targeted toward expected problems and suggest that the distinct effects of MeCP2 mutations should be considered in clinical intervention trials (Neul, J.L. *Neurology* 70(16):1313-1321, 2008).

Stroke

Strong Relationship Between Smoking and Stroke in Young Women

While cigarette smoking is a known risk factor for ischemic stroke (the type caused by blood clots), the relationship between cigarette dose and stroke risk had not been examined in a young (aged 15–50), ethnically diverse population of women. Researchers from the Stroke Prevention in Young Women Study (SPYWS), a large clinical study of the genetic and environmental risk factors for ischemic

stroke funded by NINDS, found a strong relationship between the number of cigarettes per day and the probability of ischemic stroke in young women. The findings support the need to target smoking as a preventable and modifiable risk factor for cerebrovascular disease in young women. This study was also supported in part by the U.S. Department of Veterans Affairs (VA), the Centers for Disease Control and Prevention (CDC), the Office of Research on Women's Health (ORWH), the National Institute on Aging (NIA), and the National Center for Research Resources (NCRR) (Bhat, V.M., et al. *Stroke* 39:2439-2443, 2007).

Variants in the Gene Neuroserpin May Place White Women at Risk for Early-Onset Ischemic Stroke

SPYWS researchers have also examined the relationship between mutations in the neuroprotective gene neuroserpin and risk of ischemic stroke, or stroke caused by a blood clot. Variations in the sequence of the neuroserpin gene were compared between healthy volunteers and young (15–49) White and African-American women who had suffered ischemic stroke. One gene variant was found to have strong association with stroke among White women, but not African-American women. Although results are preliminary and to be replicated, the study provides the first evidence that neuroserpin is associated with early-onset stroke among White women. This study was also supported in part by the VA, CDC, ORWH, NIA, and NCRR (Cole, J.W., et al. *BMC Neurology* 7:37, 2007).

Women With Visual Aura During Migraine Are at Higher Risk for Ischemic Stroke

The SPYWS has also helped elucidate the clinical features of migraine that place women at a greater risk for stroke. Researchers have found that women who frequently have a visual aura during migraine have 1.5 greater odds of having an ischemic stroke than women without migraine or women with migraines and without auras. Migraines with visual aura did not further increase the risk of stroke for women who already had a history of diabetes, hypertension, and myocardial infarction. However the combined use of oral contraceptives and smoking placed women with visual auras during migraine at the highest risk for stroke, increasing the odds of suffering ischemic stroke by sevenfold compared to women with visual aura who did not smoke or use oral contraceptives. This study was also supported in part by the VA, CDC, ORWH, NIA, and NCRR (MacClellan, L.R., et al. *Stroke* 38:2438-2445, 2007).

A Type of Vascular Disease Puts Women at a Higher Risk for Stroke Than Men

Symptomatic intracranial atherosclerotic disease is an aggressive form of vascular disease that puts both men and women at a high risk of recurrent stroke. Researchers have used data from the NINDS-funded Warfarin–Aspirin Symptomatic Intracranial Disease trial to understand the extent that this condition predisposes men and women to stroke and vascular disease outcomes. Women with intracranial arterial stenosis (narrowing of the blood vessels) were found to have a significantly higher risk for ischemic stroke and for a combined outcome of stroke or vascular death than men. These data support much more proactive screening of women with risk factors for this type of stenosis and aggressive management when risk factors are present (Williams, J.E., et al. *Stroke* 38:2055-2062, 2007).

Trends in Stroke Diagnosis Are Positive for Women

The NINDS-funded Ischemic Stroke Genetics Study (ISGS) has found that the clinical presentation of stroke in women and men is quite similar. Stroke severity, stroke subtype, the location and extent of brain tissue damage, and most of the stroke symptom profile were comparable between men and women. One difference found was that more women exhibited weakness as a symptom of stroke. The same study group also explored the extent to which clinicians perform a variety of stroke diagnostic tests, including brain and blood vessel imaging, and tests of heart function on men and women. In contradistinction with older studies, no differences were found between men and women in clinical evaluations received, and the team suggested that the use of advanced stroke care centers may be helping to reduce sex-based disparities. Together, these findings

suggest that strokes should not be difficult to diagnose in women and that women are receiving the same diagnostic tests as men (Barrett, K.M., et al. *Journal of Stroke and Cerebrovascular Diseases* 16:34-39, 2007; Leslie-Mazwi, T.M., et al. *Journal of Stroke and Cerebrovascular Diseases* 16:187-193, 2007).

Efforts in Public Outreach and the Know Stroke Campaign

Since 2001, NINDS has developed "Know Stroke: Know the Signs. Act in Time," a public awareness campaign to disseminate knowledge of the warning symptoms of stroke and the importance of seeking urgent treatment. NINDS partners with the CDC, the National Council of La Raza (NCLR), the National Alliance for Hispanic Health (NAHH), the General Federation of Women's Clubs (GFWC), the American Stroke Association (ASA), and the National Stroke Association (NSA) to distribute Know Stroke materials. In 2008, as part of Stroke Awareness Month activities (May), NINDS reached out to its partner organizations to promote stroke awareness. The GFCW, the world's oldest and largest women's community service organization, placed a Know Stroke feature on its Web site. NINDS program directors also participate in many outreach events to educate the public about stroke. For example, in 2008 NINDS deputy director Dr. Walter Koroshetz and Dr. John Lynch, a program director in the NINDS Office of Minority Health and Research, conducted a radio media tour and gave interviews to radio networks and stations across the country to an estimated audience of 1.5 million listeners. Dr. Koroshetz also was interviewed by NIH Radio for a feature on stroke that aired on 1,000 stations through XM Radio and is available on the NIH Web site. In June, Dr. Lynch was interviewed by Dr. Vivian Pinn, director of the NIH Office of Research on Women's Health, for the podcast "Pinn Point on Women's Health: Women and Strokes." The program is available on the NIH Web site and has an average of 300 downloads a week.

Gender Analysis

All NIH-funded Phase III clinical trials are required to include sufficient numbers of males and females to perform an analysis of sex differences in treatment outcomes, when appropriate to the condition under study. The NINDS also supports targeted research to understand sex-based differences in neurological disorders and normal behavior, cognition, and perception. More basic studies are investigating the effects of sex hormones on nervous system development and function, and evaluating their potential neuroprotective and regenerative effects. Special advances resulting from sex/gender analyses or plans for upcoming studies are highlighted below.

Stroke

- **Carotid Endarterectomy and Angioplasty/ Stenting**

The Carotid Revascularization Endarterectomy vs. Stenting (CREST) study is a randomized, multicenter clinical trial that is comparing the efficacy of two procedures in preventing stroke, heart attack, and/or death in patients who have had a temporary or a nondisabling stroke and who also have high-grade carotid stenosis, or narrowing of the arteries of the neck. The gold standard for treating carotid stenosis is an endarterectomy—a surgical procedure that involves "cleaning" the inside of the clogged vessel. Stent-assisted carotid angioplasty—a newer procedure that involves widening the narrowed vessel and inserting a device to hold it open—may offer a less invasive means of treating carotid stenosis. A comparison of the efficacy of the two procedures in men and women is a secondary outcome of the study. Previous studies (including analyses of two past NINDS-funded trials) have suggested that carotid endarterectomy may not be the best procedure for women.

- **Cognitive Decline and Stroke**

The NINDS-funded REasons for Geographic and Racial Differences in Stroke (REGARDS) study is an observational study of over 24,000 study participants—59 percent of whom are women—that is exploring the role of geographic differences on stroke risk factor prevalence, stroke incidence, and stroke mortality. The study is also exploring race, gender, genetics, and lifestyle choices as stroke risk factors. Recent analysis of the REGARDS data showed links between cognitive impairment and a history of stroke symptoms even after adjust-

ing for age, gender, and race. Although this analysis did not identify differences between men and women in the cross-sectional association between history of stroke symptoms and cognitive function, the REGARDS study will examine gender differences in cognitive change over time after experiencing stroke symptoms or overt stroke events.

Initiatives

Requests for Applications

- **Central Nervous System (CNS) Intersections of Drug Addiction, Chronic Pain, and Analgesia (R01, R03, and R21), RFA-DA-09-017, RFA-DA-09-019**
  Seeks to investigate CNS changes that occur with chronic pain, and how these changes parallel those that occur with drug addiction. Of interest will be how chronic pain changes the CNS, how analgesics of various classes impact pain-induced CNS changes, and how analgesics in the absence of pain (some of which have abuse potential) produce CNS changes. Cofunded by the National Institute on Drug Abuse (NIDA).

Program Announcements

- **Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01, R21), PA-08-246, PA-08-247**
  Encourages investigator-initiated proposals to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME/CFS), in diverse groups and across the lifespan. Issued by ORWH. Cofunded by 11 other Institutes and Centers (ICs).

- **Mechanisms, Models, Measurement, & Management in Pain Research (R01, R03, R21), PA-07-282, PA-06-542, PA-06-543**
  Seeks proposals to investigate the causes, costs, and societal effects of both acute and chronic pain and the relationships between the two, as well as proposals that link such understandings to the development of better approaches to therapeutic interventions. Interdisciplinary and multidisciplinary teams are strongly encouraged, as is research from underrepresented, minority, disabled, or women investigators. Cofunded by 11 other ICs in the Pain Consortium.

- **Neurobiology of Migraine (R01, R21), PA-07-305, PA-07-306**
  Seeks innovative research that will expand our current knowledge of susceptibility to migraine, pathophysiology of the disorder, neurobiological mechanisms underlying the phases of migraine, and the role of neuromodulators such as sex hormones, and genetic influences in migraine onset and duration. Cofunded by the National Institute on Deafness and Other Communication Disorders, the National Institute of Dental and Craniofacial Research, and the National Institute of Environmental Health Sciences (NIEHS).

- **Advancing Novel Science in Women's Health Research (ANSWHR) [R03, R21], PAS-07-381, PAS-07-382**
  Promotes innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences. Issued by ORWH. Cofunded by 22 other ICs.

Conferences and Workshops

- **Shared Neurobiology of Autism and Related Disorders, University of Southern California, June 10–13, 2007, Los Angeles, CA**
  This conference presented a model to facilitate research on multiple rare diseases, in which findings across diseases are conceptually integrated to identify shared pathophysiologic mechanisms. Diseases included autism and related neurodevelopmental disorders such as Rett Syndrome. The meeting was cosponsored by the National Institute of Mental Health, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIEHS, and private foundations.

- **Second Annual Research Symposium for Advances in Pain Research: Generalized Pain Conditions, May 1, 2007, NIH, Bethesda, MD**
  Sponsored by the NIH Pain Consortium, this conference explored recent research advances in the understanding of the

mechanisms of inflammatory, neuropathic, visceral, and treatment-induced pain (either chronic or acute) and in the development of management or therapeutic approaches. One session of the symposium focused on the role of the sex hormones in the processing of visceral pain.

Health Disparities Among Special Populations of Women

Stroke Risk Factors Are More Prevalent Among Black Men and Women

The research team leading the NINDS-funded REGARDS study continues to make great strides in analyzing data from the population-based group of nearly 24,000 individuals to explore the geographical and racial differences in the estimated 10-year stroke risk. Analysis of the levels of stroke risk in this cohort confirmed that both male and female African-Americans have a higher risk of stroke than their White counterparts regardless of their geographic location. Factors that contributed to increased risk included higher rates of hypertension, diabetes, smoking, and left ventricular hypertrophy. Although researchers surprisingly did not find differences in initial stroke risk based on geographic location, geography did play a major role in the prevalence of diabetes among Black women. The REGARDS results suggest that it may be possible to reduce racial differences in first stroke in both men and women through risk factor management (Cushman, M., et al. *Annals of Neurology* 64(5):507-513, 2008).

Subarachnoid Hemorrhage Disproportionately Affects Mexican-Americans and Women

Mexican-Americans comprise the largest component of the largest minority group in the United States. To study aspects of the epidemiology, presentation, and outcomes of stroke in this population, investigators from the NINDS-funded Brain Attack Surveillance in Corpus Christi (BASIC) project have collected data on almost 5,000 Mexican-Americans and non-Hispanic White men and women who have suffered stroke. A recent analysis showed that subarachnoid hemorrhage (SAH), or bleeding in the area between the brain and the thin tissues that cover the brain, was significantly more common in Mexican-Americans of either sex and in women in general. Mexican-American women had the highest risk of all. SAH is a devastating event that is associated with a high rate of morbidity and mortality. The results suggest that healthcare providers should consider women and Mexican-American high-risk groups for diagnosis and risk-factor reduction efforts (Eden, S.V., et al. *Neurology* 71(10):731-735, 2008).

Defining the Burden of Stroke in Mexican-American Women

The BASIC study was also used to examine the prevalence of general stroke risk among Mexican-American women and found that compared to non-Hispanic White women, they have elevated risk of stroke at younger ages (ages 45–59) and were more likely to have hypertension, diabetes, or the presence of both risk factors. Mexican-American women stroke cases were also more likely to report use of antihypertensive medications and to be aware of hypertension risk than non-Hispanic White women cases (Lisabeth, L.D., et al. *American Journal of Hypertension* 21(7) :778-783, 2008).

Genetic Differences Between Black and White Women Who Suffer Early-Onset Stroke

As described above (Accomplishments Section), Stroke Prevention in Young Women Study researchers have shown that certain gene variants are associated with ischemic stroke in White but not Black women (Cole, J.W., et al. *BMC Neurology* 7:37, 2007).

Efforts in Public Outreach and the Know Stroke Campaign in Special Communities

Since 2004, NINDS has collaborated with the CDC to implement the Know Stroke in the Community (KSIC) public awareness program. KSIC recruits "Stroke Champions" who are trained to use NINDS Know Stroke education materials and charged with bringing campaign messages to their communities. KSIC's target audiences are those at high risk for stroke—primarily African-Americans, Hispanics, and people over the age of 50—and their family members, caregivers, and healthcare providers.

As part of the 2008 Stroke Awareness Month activities, NINDS reached out to the National Council of La Raza to promote the NINDS Spanish-language toolkit for promotores (lay health educators) in its affiliate member services e-newsletter. The messages reached health educators in more than 300 Hispanic community-based clinics and organizations, with information on how to order and use the toolkits. In addition, NINDS provided informational releases to networks of more than 10,000 national and community newspapers, 500 African-American-focused newspapers, and more than 700 Hispanic-focused newspapers. The Institute also scripted, produced, and distributed a Spanish-language radio release to 500 Hispanic stations, including community and public outlets across the United States.

National Institute of Nursing Research

Executive Summary

The National Institute of Nursing Research (NINR) supports clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, and enhance end-of-life and palliative care. Confronting these issues requires shifting to a patient management paradigm that is increasingly person centered rather than disease oriented, that focuses on preventing the development of chronic illness rather than treating it, and that features the person as an active participant in his or her own health. The Institute's scientific focus spans multiple disciplines and unites the biological and behavioral sciences to better understand the complex interactions between the physiological factors of health and disease and the knowledge, beliefs, and behavior of the individual. Across all scientific programs, NINR's research addresses the special needs of at-risk and underserved populations with particular emphasis on health disparities.

The research goals of NINR's Strategic Plan, Changing Practice, Changing Lives, emphasize areas of public health in which NINR can have the greatest impact. Developed in 2006 in close consultation with representatives of the extramural community, this Plan details NINR's scientific priorities for research in 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 emphasizes four crosscutting strategies to advance science: integrating biological and behavioral science, adopting and adapting new technologies, improving methods for future scientific discovery, and developing the next generation of research investigators. The full text of the Strategic Plan can be found on NINR's Web site at http://www.ninr.nih.gov.

The breadth and depth of NINR's research portfolio is ideally suited to explore some of the most important challenges affecting the health of women, including the following:

- The growth of an aging female population faced with chronic diseases requiring complex management
- The growth of diverse racial and cultural populations of women and the associated issues of health disparities in these at-risk, underserved populations
- The emergence of new technologies driving biomedical discoveries in gender research, new challenges in perinatal care, genetics, and accessible telecommunication and Internet interventions for rural, low-income women
- The need to build a cadre of next-generation scientists and practitioners in women's health

In advancing the science of women's health, NINR funds and cofunds meritorious initiatives with specific attention to research that focuses on unique issues surrounding pain, aging, pregnancy, childcare, health disparities, and the participation and promotion of women in biomedical and behavioral research. Central to the themes within its strategic plan, NINR seeks to strengthen and enhance research dedicated to the study of diseases and disorders specific to women, whether as patients, caregivers, or communities. The Institute actively ensures that diverse

populations of women are represented in its studies and that disparities experienced by women in minority, rural, immigrant, and other underserved populations are addressed. NINR-supported investigators have contributed to new knowledge by addressing women's health across the lifespan. Numerous findings during fiscal years 2007 and 2008 have furthered understanding of issues uniquely relevant to women's health, including the following:

- Pregnancy, preterm birth, lactation, postpartum depression, and childrearing
- Aging and menopause
- Heart disease and stroke
- Breast cancer
- Diabetes, incontinence, and irritable bowel syndrome
- Pain management
- Promotion of healthy lifestyles for obesity, nutrition, and depression

In 2007 and 2008, NINR investigators made significant contributions to these research areas, including the design of new ways to improve health services among minority and underserved women, the promotion of cost-effective interventions for mothers and their premature infants, increasing understanding of menopause and aging effects, and developing new methods to assist women with breast cancer, heart disease, and diabetes. In addition, NINR remained committed to improving the science of women's health through the development of leaders in nursing science and the promotion of careers for women in biomedical science and clinical research. 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. NINR will continue to support innovative studies in research areas highlighted in its strategic plan, including self-management, symptom management, and caregiving; health promotion and disease prevention; research capacity development; technology integration; and end-of-life science. Results from these studies will inform future strategies as NINR begins to consider its strategic plan beyond 2010. In addition, input from stakeholders; trans-National Institutes of Health planning and priority-setting processes such as the NIH Roadmap, Neuroscience Blueprint, and Pain Consortium; and changing public health concerns will continue to shape the future directions of NINR research.

NINR Designated Focus on Research on Women's Health

NINR is committed to the development of science that addresses women's health. Through its funding of the University of Washington's Center on Women's Health and Gender Research (P30), NINR has expanded the cadre of collaborations among interdisciplinary investigators in basic and clinical research related to women's health across the lifespan. The program is a focused effort to enhance an understanding of the biobehavioral and sociocultural dimensions of women's health; advance knowledge of genetics and gender differences; expand understanding of health disparities, and close the gap among vulnerable subpopulations of women. Through additional support to the Center's training program under a T32 award, NINR continues to build research capacity to enable the study of diverse populations of women in culturally competent ways and to promote the development of research skills and opportunities for scholarship in women's health. In addition, NINR remains active in supporting NIH programs that promote research on women's health. Dr. Patricia Grady, Director of NINR, is a member of the NIH Working Group on Women in Biomedical Careers and participates in a number of internal NIH subcommittees within this program. A feature article on "Women in Science at the National Institutes of Health" by the Office of Research on Women's Health in 2007–2008 highlighted NINR's Director and Deputy Director. NINR has also supported and participated in the planning of the NIH State-of-the-Science Conference on "Prevention of Fecal and Urinary Incontinence in Adults" in December 2007. This important conference emphasized the challenges many women face in experiencing incontinence and the benefits of creating effective programs in prevention and management.

Accomplishments

Pregnancy, Childbirth, and Perinatal Health

Health issues surrounding pregnancy and the perinatal period compose a significant part of NINR's overall research portfolio in women's health. As part of a focus to translate research into public use, a program was designed to help nurses teach mothers and caregivers about risk factors and protective practices for Sudden Infant Death Syndrome (SIDS). The "Back to Sleep" continuing education program, developed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the NINR in collaboration with national nursing and health organizations, focuses on providing nurses with answers to many of the most typical questions asked by parents about safe infant sleeping practices along with practical ways in which nurses can provide information about SIDS in appropriate multicultural environments. More information is available through the NICHD Web site at http://www.nichd.nih.gov/sidsnursesce/.

Within its own portfolio, NINR investigators continue to make important contributions to improve pregnancy outcomes and ensure the health of both mothers and their infants. Pregnancy is a time when many women who smoke give up cigarettes, at least temporarily. A survey of a racially diverse group of low-income new mothers who stopped smoking during their pregnancy found that most quit to protect the health of their infants. But while almost two-thirds said they planned to remain nonsmokers after delivery, by the end of the second postpartum week, 69 percent returned to prepregnancy habits. Infant irritability, not knowing what to do, or how to seek help contributed to both thoughts of and a return to previous smoking behaviors. These findings stress the need to develop effective, culturally sensitive programs to educate mothers about the adverse health effects of smoking on their children and provide training on useful coping skills that will enable them to continue to refrain from harmful behaviors.

NINR supports research that seeks to understand maternal stress, psychological well-being, and caretaker support. Almost half a million premature infants are born in the United States each year, and most require hospitalization in a neonatal intensive care unit (NICU). The ongoing physical and developmental problems of many premature infants contribute to high levels of parental stress, anxiety, and depression. To identify and manage the needs of these parents, researchers developed a parental educational program, Creating Opportunities for Parental Empowerment (COPE), for mothers and fathers of premature infants. Compared to parents in a control group, COPE parents reported higher beliefs in their parenting role, exhibited more positive interactions with their babies, and had a better understanding of expected characteristics and behaviors of premature infants. In fact, infants of COPE program parents averaged 3.8 fewer days in the NICU than those of parents in a control group. This translated to a savings of about $5,000 per infant. This intervention could potentially save about $2.5 billion in healthcare costs annually.

Breastfeeding Practices

While the American Academy of Pediatrics recommends breastfeeding for all newborns, mothers of premature, low birthweight (LBW) infants face numerous obstacles in starting and maintaining such practices. The challenges faced with these infants may contribute to only one-third of mothers with LBW infants initiating breastfeeding and fewer than half continuing breastfeeding efforts after their infants are discharged from the hospital. However, researchers have found that supporting and encouraging mothers to begin and maintain breastfeeding may be an important intervention that makes a difference in the long-term developmental outcomes of their children. Infants who received some form of breastmilk until 6 months (corrected age) scored approximately 10 points higher in mental development and nearly 15 points higher in motor development than those who did not receive human milk over the same period of time. In fact, breastfeeding may also provide long-term benefits to the health of mothers.

Metabolic Syndrome (or MetSyn) is a clustering of metabolic abnormalities that includes insulin resistance, dyslipidemia, hypertension,

and obesity. Women with MetSyn are thus at increased risk for diabetes, cardiovascular events, and even death. Interestingly, breastfeeding (lactation) increases high-density lipoprotein (HDL) levels, decreases triglycerides, and improves insulin sensitivity, suggesting that there may be a protective association between a woman's history of lactation and the development of MetSyn. In a study that examined the association of lactation duration and the prevalence of MetSyn in 2,516 midlife women participating in the Study of Women's Health Across the Nation (SWAN), results indicated that women who had breastfed their children were significantly less likely to have impaired fasting glucose, elevated blood pressure, and abdominal obesity. In addition, the rate of MetSyn was significantly lower in women who had breastfed for longer periods of time with particular protective effects occurring after the first and second pregnancies. These maternal effects, in addition to the pediatric benefits of breastfeeding, may encourage more women to initiate and maintain breastfeeding practices.

Postpartum Depression

Postpartum depression (PPD) is a potentially debilitating disorder that occurs in a significant percentage of women during the first year after giving birth. Characterized by sadness, guilt, and despair, PPD can be a devastating disorder that may carry long-term consequences for these women. While several psychosocial risks for PPD have been identified, its biological contributions are unclear. A group of researchers focused on the role of elevated inflammatory cytokines (IL-6 and IL-1beta) in women with PPD recruited after delivery and followed for several postpartum days. Early increases in IL-1beta levels occurred on Day 14 in women who later experienced depressive symptoms on Day 28. These elevated inflammatory cytokine levels early in the postpartum period may serve as a measurable, identifiable biomarker of women at risk for later PPD.

Women with PPD also experience a range of physical and psychological symptoms that can lead to long-term depression and even suicide. While 47 percent to 57 percent of postpartum women return to their prepregnancy levels of function in regards to personal, infant, and household care and their participation in social and occupational activities, women with PPD were 12 times less likely to achieve many of these prepregnancy functions. However, despite their depressive symptoms, they continued to provide normal, appropriate physical infant care. At a critical time, when depressed mothers must function and adapt to their new roles, many women may find that they are unable to care for themselves, run a household, and provide nurturing interactions with their infants. Clinicians may find functional assessment a useful adjunct and a less threatening way to screen for and monitor treatment progress in women at risk for PPD.

Aging and Menopause

NINR maintains a diverse research portfolio that focuses on multiple health issues surrounding women and aging, including issues associated with menopause. NINR cosponsors, with the National Institute on Aging, the multisite SWAN. The SWAN examines women between 40 and 60 years of age in the period of the menopausal transition. In one SWAN report, NINR-supported researchers examined the association between body fat and vasomotor symptoms using a multiethnic sample of over 1,700 women transitioning through menopause. In this study, a greater percentage of total body fat was associated with an increased chance of vasomotor symptoms. Vasomotor symptoms such as hot flashes and night sweats are reported by 70–80 percent of women during the menopausal transition, and often result in impaired sleep, mood, and quality of life. The results are therefore particularly relevant given current interest in developing nonhormonal methods, including behavioral approaches, to manage symptoms of menopause such as weight loss.

In another study, SWAN participants were evaluated for bone fractures, a common problem in 40 percent of postmenopausal women. Annual bone mineral density (BMD) measurements obtained from 2,000 pre-, peri-, and postmenopausal women over the course of 3 to 4 years indicated that losses occurred at greater rates in women with low percentiles of body weight during the late peri-and postmenopausal stages. The annual rate of bone

loss during these intervals ranged from 1 to 2.5 percent. However, if this bone loss were to continue at these rates for 5 additional years, the average woman's BMD would significantly decline by 5 to 10 percent. In 2001, the National Osteoporosis Foundation estimated that the annual cost of health care and lost productivity related to osteoporosis was $17 billion. Identifying factors that are associated with rapid or slow rates of bone loss during the menopause transition could assist clinicians in making decisions to optimize the skeletal health of midlife women.

The Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study demonstrated that widely prescribed exogenous hormone products were not cardioprotective as originally hypothesized. One explanation, the "timing hypothesis," addressed in findings from these studies, suggested that hormone therapy (HT) should be initiated within 6 years of the menopause transition to extend a favorable estrogenic environment. Investigators, as part of the SWAN study, compared sex steroid and cardiovascular profiles at 5-year followup visits in premenopausal women, women using conjugated equine estrogen with or without progestin, and postmenopausal women (< 5 years) not using HT. Users of hormone therapy had 50 percent higher levels of sex hormone-binding globulin, which limits binding of sex steroids to their receptors, and higher excreted estrone metabolites (more than 60 percent) than premenopausal or postmenopausal women. These findings were, in turn, associated with higher levels of F(2a)-isoprostanes, an oxidative stress measure. HT users had a more favorable ratio of high-density to low-density lipoprotein cholesterol than did premenopausal or postmenopausal women, but higher triglyceride levels. Thus, although HT users had some more favorable lipid profiles than premenopausal and postmenopausal women, there was evidence of adverse HT effects even in women free of atherosclerosis and studied within the approximate 6-year period proposed by the timing hypothesis. From a research perspective, these results suggest thoughtful consideration in the clinical use of HT because of evidence of adverse HT effects in women free of atherosclerosis.

NINR science also addresses the impact of aging and cognition on women's health. Approximately 50 percent of the more than 1.5 million Americans residing in nursing homes have significant cognitive impairment. The majority of these residents are women. Researchers have developed simple screening tools available to nurses and other healthcare providers to detect early warning signs of cognitive decline. In a sample of elderly residents (81 percent female) in nursing homes, assisted-living facilities, and senior housing, a team approach to detect and classify early signs of cognitive impairment correctly classified the memory skills of 95 percent of elderly participants. In another NINR-supported program, the multisite Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) program looked at the risks for loss of independence in over 2,800 older adults, of which over three-quarters were women. All participants received one of three cognitive training programs: (1) memory; (2) reasoning; or (3) speed of processing. Participants with normal memory ability at baseline who received memory training showed significant improvement in memory tasks; however, those identified with memory impairments demonstrated no gains from memory training despite some gains from training in reasoning or speed of processing.

With a growing population of aging women, developing programs to maintain not only cognitive skills but also physical skills is important for functional independence. As women become elders, falls become a leading cause for injury and hospitalization. The Fall Evaluation and Prevention Program (FEPP) is an individualized, home-based intervention intended to reduce the risk of falls in elderly women. A group of over 250 women who participated in the program kept 2-year records of the falls they experienced and any followup care they received. Approximately 14 percent of the falls reported resulted in injury at an average healthcare cost of $6,600. However, about 4 percent of their fall-related injuries resulted in fracture which, in the case of a hip fracture alone, averaged over $35,000 in healthcare costs. Evaluating the healthcare use and costs related to their falls may determine cost-effective, individual-

ized prevention programs for a growing population of elderly women.

Cardiovascular Health

NINR supports a number of studies related to the cardiovascular health of women, including research that examines the prevention, early detection, and treatment of coronary heart disease (CHD). Coronary heart disease is the leading cause of death and disability for women in the United States. For these women, rapid recognition of symptoms and the expedient receipt of treatment within 1 hour of heart attack onset greatly increase their chance of survival. However, in survey data from 1,009 women who had recently suffered a heart attack, only 17 percent of all women, both Black and White, attributed their initial symptoms to a possible heart attack. The average time of delay in seeking treatment was 13 hours. White women were more likely than Blacks to correctly identify symptoms of a heart attack, with correct identification of these symptoms and the woman's eligibility for public insurance as the most significant factors associated with their active seeking of treatment.

In addition to prevention of CHD in women, NINR-supported research seeks new ways for individuals to manage their disease and comorbid symptoms. However, despite evidence for positive outcomes associated with cardiac rehabilitation (CR), little is known about rehabilitation risk factors in females with CHD. Researchers in the NINR-supported Women's-Only Cardiac Rehabilitation study found that a woman's age was a significant factor in identifying success in CHD management programs. Younger women demonstrated significantly worse psychosocial profiles than older women, were considerably more obese and inactive, and were more likely to be active smokers. In addition, younger women had almost twice the number of depressive symptoms than older women and significantly more anxiety and greater life stress specific to their families, work, finances, and health. Only 50 percent of the younger women maintained a healthy lifestyle within 6 months of completing their cardiac rehabilitation program. These results point to the need for future research that identifies alternative CR strategies for women of diverse ages and psychosocial and physiological profiles to improve successes in making healthy lifestyle changes.

Breast Cancer

Breast cancer affects older postmenopausal women at rates nearly twice that of young women. In keeping with NINR's focus on improving quality of life through symptom management, a number of NINR-supported studies have focused on the unique challenges faced by women with breast cancer. For example, fatigue, sleep disturbances, and depressive symptoms frequently occur in women with breast cancer during and following their treatment; however, these symptoms have not been well studied in older, postmenopausal women with breast cancer receiving hormonal therapy.

In one NINR-supported study, the effectiveness of a home-based walking exercise intervention was compared with a more traditional program of usual care provided to older women receiving hormone treatment for breast cancer. The team looked at the relationships among a selection of biomarkers important in regulating sleep, fatigue, and depression. Sleep quality (longer periods of sleep, less movement during sleep) significantly improved in the exercise group while no changes were noted in the usual care group. These preliminary data may contribute to the development of a better understanding of common physiologic links surrounding clusters of symptoms experienced by breast cancer patients. For the women in this study, a home-based walking exercise program provided an effective and cost-efficient intervention for reducing sleep disturbances and underscores that women of different ages diagnosed with breast cancer have different concerns and needs.

Researchers also explored the long-term effects on quality of life (QOL) of older women with early-stage breast cancer. Older women participating in a Breast Cancer Education Intervention (BCEI) program reported positive feelings about the quality of their lives within the first year of survivorship, but overall QOL as well as physical, social, and psychological well-being declined over time. Spiritual well-being, in contrast, initially declined over time, and then improved. This descriptive

study is one of the first to show the impact of spirituality in cancer treatment in relation to QOL and the effect of interventions for older breast cancer survivors.

Incontinence

For women with mild to moderate urinary incontinence (UI), simple self-management techniques may help decrease the frequency and amount of urine leakage. These techniques are generally safe, inexpensive, and easy to teach, but have not received sufficient study to recommend as a first step in UI treatment programs. Researchers conducted a clinical trial of a urinary self-monitoring intervention with 224 women with self-reported UI. The women were divided into two groups—one group participated in the self-monitoring intervention, which consisted of individualized counseling about the timing and adequacy of fluid intake, maintaining frequent voiding, limiting caffeine consumption, and doing simple pelvic floor muscle (Kegel) exercises. The control group continued in their usual care. At 3 weeks, the women who completed the intervention program had a greater average decrease in urine loss than women in the control group. In addition, women in the intervention reported a greater improvement in quality of life. The intervention was particularly effective in decreasing urine loss among women who reported 9 or more episodes of UI a day, who were over 65 years of age, and who were premenopausal or on hormone replacement therapy. These findings indicate that teaching simple self-monitoring practices can help improve urine control and quality of life, and should be considered as a treatment option for women experiencing mild to moderate UI.

Diabetes

Religion and spirituality are prominent in the lives of many African-American women with type 2 diabetes mellitus (T2D). To date, there is little research on the relationships of religion and spirituality to glycemic control (GC). A team of investigators addressed these effects through clinical assessment and related interventions facilitated by use of FICA (Faith, Importance, Community, and Address in care). In a sample of 109 Black women with T2D, religion and spirituality demonstrated significant relations with GC independent of the mediator's emotional distress and social support.

Gender Analysis

In accordance with NIH standing policy, all proposed NINR clinical studies are carefully screened for representative inclusion of both men and women, where appropriate. In addition, many NINR-supported clinical studies are specifically designed to analyze gender differences or compare the effectiveness of novel interventions in women versus men. For example, NINR supports research initiatives that explore gender as a risk factor for pain and effectiveness of pain treatments through program announcements issued under the auspices of the NIH Pain Consortium, titled Mechanisms, Models, Measurement, and Management in Pain Research (R01, R03, and R21; PA-06-544, -543, and -542, respectively). An important component of studies supported by NINR is the examination of gender differences with respect to diseases or conditions, or to the effectiveness or efficacy of clinical interventions. These include the use of animal models to examine how mechanisms of cell damage are shaped by sex steroids; the investigation of gender differences in neurobehavioral functioning following sleep deprivation and recovery; irritable bowel syndrome; premature infant sleep-wake organization; and the influence of gender on hormonal or behavioral changes in children with chronic antisocial behavior.

Perioperative stroke remains a devastating procedural complication after receipt of cardiovascular survival procedures. Because women have a greater perioperative stroke risk than men, anesthetic selection for women may be an important consideration. Gender differences in the pharmacokinetics and pharmacodynamics of inhalation anesthetics are well recognized; however, studies with preconditioning agents have only been tested in male animal models. Using IsoPC (isoflurane preconditioning anesthetic agent) as a model, a team of researchers examined whether IsoPC neuroprotection is gender specific in the young and the middle-aged ischemic mouse brain and whether IsoPC alters NIPK expression and subsequent Akt activation. Important to

this study was to evaluate if gender is a factor in modifying responses in the injured brain. Comparable to observations in previous studies with young male rodents, IsoPC mediated differences in genders through Akt activation and basal NIPK expression. IsoPC significantly reduced infarct size in young male mice when compared with a sham group. IsoPC in middle-aged females had no effect on infarction volume. A surprisingly unique response occurred in young female mice, in which the infarction volume was significantly enhanced as compared with a sham group. These results suggest that IsoPC neuroprotection is male specific in young and middle-aged mice and that in younger female mice, IsoPC can potentially exacerbate ischemic damage.

Understanding sex differences in cardiovascular disease is critical to the development of efficacious prevention and treatment strategies. Researchers have looked at the role of specific sex hormones (estrogen and testosterone) on stroke and found that the cellular and molecular pathophysiology of ischemic brain injury is strongly influenced by gender and estrogen deficiency. In order to explore how estrogen and hormone replacement therapy alter perioperative stroke risk and outcomes, researchers designed a study using groups of female mice—one group received estradiol supplementation hormone replacement therapy, or HRT, while the other group did not (non-HRT). All mice were randomly assigned to receive either a preconditioning with isoflurane or sham oxygen-only (shamPC) treatment and underwent middle cerebral artery occlusion followed by reperfusion. Infarct volumes were measured for all mice, with comparisons between IsoPC and corresponding shamPC for each treatment group. Significant decreases in infarct injury appeared in the IsoPC vs. ShamPC in the non-HRT treated mice. Further, HRT mice in the IsoPC group demonstrated significantly more cortical and caudate-putamen ischemic damage as compared with non-HRT IsoPC mice. In the genetically modified mice, treatment with ER resulted in increased post-IsoPC infarct volume as compared with the ShamPC. These results indicated that estradiol attenuated neuroprotective responses to IsoPC and increased cortical and caudate-putamen injury in the ischemic brain. When considering perioperative stroke risk, the use of isoflurane anesthesia during cardiovascular surgical procedures may provide neuroprotective benefits for men while increasing perioperative stroke risk for some women, especially in those undergoing hormone replacement therapy.

Stable sleep-wake organization in infants reflects the maturation of the central nervous system. With this maturation come increasing quiet sleep episodes with smoother and fewer transitions from sleep-wake cycles. Achieving stable organization or "state" patterns is a major developmental task for premature infants. To further understand state development of preterm infants throughout hospitalization and the effects of selected infant characteristics on state development, researchers studied medically stable hospitalized premature infants. Male premature infants demonstrated less active sleep episodes, were drowsier, and had less defined and diffuse behavioral states compared with females. The results emphasize individual variations in state organization influenced by endogenous and environmental factors with gender differences a potential source of this variation. These differences seem to continue across development. In a study of gender differences in sleep, fatigue, and daytime activity in a sample of children with acute lymphoblastic leukemia, girls napped more and had less fragmented sleep than boys. Wake time after sleep onset was sensitive to dexamethasone administration and revealed a differential direction of response for males and females.

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by abdominal pain and associated with changes in defecation. Occurring in an estimated 10–20 percent of the U.S. population, women more frequently report IBS symptoms (e.g., constipation, diarrhea) than men; however, the role of gender in IBS may involve a range of factors, including differences due to hormones, stress, and responses to inflammation and pain. A number of NINR-supported studies have examined how IBS interferes with functional activities and healthcare utilization. Special attention is given to identifying patterns within subgroups of women with IBS and underlying polymorphisms. These studies have found that women with moder-

ate to severe IBS and GI symptoms report more severe levels of depression and anxiety. Researchers have noted that women with specific IBS symptoms demonstrate significant changes in autonomic nervous system functions during sleep. Understanding these and other factors that contribute to IBS in women is important to advance new therapies to manage the complex symptoms of IBS.

Initiatives

Program Announcements

- **Advancing Novel Science in Women's Health Research**
  NINR cosponsors this ORWH-administered initiative devised to promote innovative, interdisciplinary research to advance new concepts in women's health research and the interdisciplinary study of sex/gender differences [PAS-07-381].

- **Transdisciplinary Research on Fatigue and Fatigability in Aging**
  This initiative, cosponsored by NINR in collaboration with other Institutes and Centers and ORWH, is to encourage submission of exploratory developmental research applications on fatigue and fatigability in older persons. Women are particularly affected by fatigue whether related to physical, mental, emotional, and/or social aspects of aging. Understanding the phenomenology of, and mechanisms underlying, these relationships may lead to improved methods for symptom management and intervention [PA-08-162].

- **Sarcoidosis: Research into the Cause of Multiorgan Disease and Clinical Strategies for Therapy**
  NINR participates with other ICs and ORWH in this NIH initiative focusing on the etiology and management of sarcoidosis. This work has relevance not only to health disparities among ethnic groups with sarcoidosis related to gender and age at diagnosis, but also to problematic issues involved with symptom management, and behavioral and psychosocial burdens on individuals, families, and the community [R01 portion of funding opportunity PA-07-136, PA-06-123].

- **Mechanisms, Models, Measurement, and Management in Pain Research**
  This initiative, sponsored by NINR in collaboration with the other 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, including 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 temporomandibular joint and muscle disorders [PA-06-542, PA-06-543, PA-06-544].

- **Chronic Fatigue Syndrome—Pathophysiology and Treatment**
  NINR is a cosponsor of this initiative, administered by ORWH. The initiative seeks to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS) in diverse groups across the lifespan. Of particular relevance to the strategic goals of NINR, the initiative calls for research into behavioral factors that influence CFS, and ways to manage symptoms and improve quality of life [PA-08-247, formerly PA-07-263, PA-07-264, PA-07-265].

- **Research on Causal Factors and Interventions That Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (R01)**
  NINR participates as a cosponsor with other ICs and ORWH in this funding opportunity to support research on (1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering and variation across different subgroups, and (2) the efficacy of programs designed to support the careers of women in these disciplines. NINR particularly supports underrepresented minority women and socioeconomically disadvantaged women [RFA-GM-09-012].

- **The NINR Mentored Research Scientist Development Award for Underrepresented or Disadvantaged Investigators; Research Supplements To Promote Reentry into Biomedical and Behavioral Research**

Careers
As part of NINR's focus on developing today's and tomorrow's nurse scientists, this NINR initiative encourages development of underrepresented or disadvantaged nurse scientists to become independent investigators in research settings. Through these and other awards, NINR promotes diversity among investigators in women's health and supports the training of women in scientific careers [PAR-09-074; formerly PAR-05-135; PA-08-192 and PA-08-191].

Health Disparities Among Special Populations of Women

NINR's Strategic Plan, Changing Practice, Changing Lives, highlights the elimination of health disparities as an area of research emphasis throughout the Institute's entire research portfolio, and NINR's grants related to women's health are no exception. Special populations encompassed by NINR health disparities research include adolescents, women of racial and ethnic minorities, women in poverty, immigrants, and women who reside in rural areas.

Adolescents

Despite declining birth rates over the past few decades, the United States continues to have the highest teenage pregnancy rate of all industrialized nations. Sexual activity before the age of 13 has been shown to be significantly higher in African-American adolescent girls. New research is identifying which females from low-income households may be at particular risk for sexual activity leading to increased risks for contracting HIV/sexually transmitted diseases (STDs). In one study, a review of the attitudes and practices of these young women identified that many adolescents refrain from sexual activity until after age 14 and that differences existed in the practice of sexual behaviors and self-efficacy between younger and older adolescent females. A second study found that in rural, predominantly African-American girls ages 14–19, abstinence, despite a sexually active social climate, was reinforced by self-respect, maternal impact, understanding of risks, and male-peer influences. These results suggest that education and HIV risk-reduction programs should be developmentally appropriate as well as culturally relevant and gender specific.

Minority Women

Among older Hispanic women, the prevalence of obesity is 47.9 percent compared to 21.5 percent among non-Hispanics. Despite the known benefits of physical activity (PA) in reducing obesity and other cardiovascular risks, 46 percent of older Mexican-American women report that they do not engage in PA. An NINR-supported study evaluated groups of postmenopausal, obese, and sedentary Hispanic women between 45 and 70 years of age in a PA intervention designed to reduce coronary heart disease. For 36 weeks, one group of women walked 3 days a week while a second group walked 5 days a week. The primary factor that stimulated the women to begin and sustain their walking program was the development of a "gran amiga" or special friend. These women became comrades, providing each other with consistent encouragement to care for oneself and promote better health through a planned walking program. Further research needs to focus on encouraging women to set aside time for formal walking and on examining strategies such as those that would encourage shorter and more frequent walks.

African-American women suffer disproportionately high infection rates of STDs, including HIV/AIDS. Health clinics and other primary care settings offer opportunities to teach sexually active African-American women protective behaviors to reduce their risk of STD exposure. In a study called "Sister-to-Sister: The Black Women's Health Project," researchers evaluated four separate nurse-led preventive, culturally sensitive behavioral interventions among a group of 564 sexually experienced Black women from an inner-city women's health clinic. NINR-supported researchers tested this brief, behavioral skill-building program in sessions lasting as little as 20 minutes. Less intensive, information-only interventions were also evaluated. Participants in the skill-building program reported improved protective behaviors for up to 1 year after receiving the program. Another NINR-supported investigator adapted this intervention into practice for Latino youths. Both of these programs have

been proven effective in improving HIV/AIDS awareness and protective behaviors, and have been adopted for distribution by the Centers for Disease Control and Prevention (CDC): http://www.cdc.gov/hiv/topics/research/prs/best-evidence-intervention.htm.

Rural Women

As women age, their risks for chronic illness increase, along with the likelihood that they will endure more years of disability and functional impairment than men. Rural older women, in particular, experience poorer health status and have a higher obesity prevalence than urban women. Poor diet is among the modifiable factors that affect chronic disease risk and is a suitable target for behavior change in midlife to older women. NINR has supported research that examines daily energy, food group, and nutrient intakes of late midlife to older rural women in comparison to recommended intakes for the U.S. population, physical measures, and health history. In 225 community-dwelling women aged 50 to 69 years from a rural Midwestern area of the United States, nearly half of the women had energy intakes in excess of their Estimated Energy Requirement. Mean daily servings of fruits, grains, and dairy products were below target levels identified in the 2000 Dietary Guidelines for Americans. Mean calcium and dietary fiber intakes were below recommended levels, while percentage of calories from fat (39 percent +/- 6.8 percent) were well above recommendations. Eighty percent were overweight or obese and 76 percent were prehypertensive or hypertensive, yet only 33.5 percent indicated their healthcare provider had discussed dietary factors with them in the previous year. Late midlife and older rural women need more guidance than they currently receive to learn how to make changes to meet dietary recommendations, particularly those with a focus on establishing a more healthful dietary pattern suitable for their older years.

Changing trends in HIV infection rates demonstrate it is now advancing most rapidly among women, racial and ethnic minorities, and those in rural communities. African-American women account for 67 percent of all female AIDS cases. NINR-supported researchers are providing new information on how these women access health and social services, and are identifying new strategies to design, implement, and test interventions that help women adhere to medications and cope with their conditions.

It is estimated that 6 million women in the United States misuse alcohol. Of this number, many live in rural areas and face numerous barriers to treatment. The World Wide Web has the potential to help such individuals overcome these barriers. A Web-based, self-guided alcohol treatment program for rural women included gender-specific references and decisionmaking modules, an asynchronous bulletin board, and a synchronous chat feature. At a 3-month followup, both control and Web-based treatment groups decreased their drinking with no significant differences found between the approaches. Women with substance abuse problems have traditionally been an underserved segment of society, and those in rural areas face an increased number of treatment barriers. Given the low cost and ease of accessing Web-based treatments, the development of intervention programs focused on alcohol treatment for rural women may be beneficial.

Immigrant Women

Posttraumatic stress disorder (PTSD) has been thought to be influenced by symptoms of reexperience and arousal. In fact, these two symptoms may occur at a higher frequency than avoidance symptom criterion used in the diagnosis of PTSD. A study investigated whether certain diagnostic tests may be overly conservative for Arab immigrant women at risk for PTSD due to the women's increased likelihood to have experienced war and political or ethnic/religious persecution, and gender/cultural value differences. Over a third of the Arab immigrant women studied reported experiencing multiple traumatic events, living through or witnessing a traumatic event usually related to war, a serious accident, physical trauma, political persecution, or a natural disaster. More than two-thirds reported re-experiencing PTSD symptoms when reminded of the trauma. Positive identification of women who have PTSD is particularly important in immigrant and refugee populations

where exposure to traumatic events is high and the need for intervention clear.

Women in Poverty

A high prevalence of mental health conditions are reported among predominantly poor, minority women who receive welfare. Women receiving aid through welfare programs such as Temporary Assistance for Needy Families (TANF) have more stress and poorer health than women in the general population. Studies suggest that chronic stress may contribute to their poor health via physiological mechanisms, yet little is known about these mechanisms in this population. NINR-supported research has examined psychosocial stress, salivary cortisol, 24-hour ambulatory blood pressure and heart rate, and health among single mothers before and after exiting TANF programs. As a group, perceived stress decreased after leaving a TANF program, with other measures of psychosocial and physiological stress remaining unchanged. However, within participants, changes in psychosocial stress predicted depression and general health over time. These findings indicate psychosocial stress is positively associated with depression and negatively associated with general health as women experience welfare.

Over the past 15 years, policy initiatives at the Federal and State levels have increased access to prenatal care, especially among minorities and women in poverty. Narratives about pregnancy experiences from low-income, primiparous African-American, Mexican-American, Puerto Rican, and White women participating in focus groups suggested that despite dissatisfaction with their prenatal care, these low-income new mothers demonstrated a concerted interest to enhance their health literacy through requests for information and clarification from their healthcare providers. Trust in provider relationships—as indicated by effective communication, continuity, and demonstration—creates opportunities in which women of poverty can ask and receive information about their health, their pregnancies, and postpartum issues. Developing personal relationships with a provider is critical in an increasingly diverse population and constrained healthcare system.

NATIONAL LIBRARY OF MEDICINE

The National Library of Medicine (NLM) collects, organizes, and disseminates biomedical information worldwide. The Library collects materials in all areas of biomedicine and health care, as well as works on biomedical aspects of technology, the humanities, and the physical, life, and social sciences. The collections stand at more than 9 million items, including books, journals, and images. These information resources and services are used by researchers, clinicians, health advocates, policymakers, patients, and the general public.

NLM makes many of its resources freely available through electronic means—databases and Web sites—that may be used via an Internet connection from anywhere in the world. PubMed is a database of over 17 million biomedical journal citations and abstracts that includes over 5,200 journals indexed for Medline. Millions of the citations included in this database are articles related to women's health and research involving women. MedlinePlus, a Web site intended for use by consumers, includes over 100 health topic pages (out of 750) specifically focused on women's health. Toxnet is a suite of databases in toxicology and environmental health that includes databases on the effects of chemicals and drugs on humans and specifically a database on the potential effects of drugs to which a lactating mother might be exposed.

In addition to these resources, in March 2008, the National Library of Medicine, in collaboration with the National Institutes of Health Office of Research on Women's Health (ORWH) created a new Web resource (http://womenshealthresources.nlm.nih.gov) that provides consumers with the latest information on significant topics in women's health research from scientific journals and other peer-reviewed sources.

The 2008 NIH Research Priorities for Women's Health were used to identify overarching themes, specific health topics, and research initiatives in women's health. Within each section of the Web site are topics with links to relevant and authoritative resources

and research initiatives for women's health. NLM has created specific user-friendly strategies for these topics to ease searching ClinicalTrials.gov and PubMed. Other Web resources used include AIDSinfo, American Indian Health, Arctic Health, Household Products Database, MedlinePlus, and NIH SeniorHealth. Search strategies for major studies related to women's health research have also been created and will be linked between the new Web site and the ORWH Web site. As with the topical search strategies, ClinicalTrials.gov and PubMed searches for each major report are also included.

During this time period, NLM awarded two G13 grants that are relevant to women's health. The G13 is a mechanism used only by NLM for its Grants for Scholarly Works in Biomedicine and Health. ORWH provided funding for Heather Prescott, Ph.D., Central Connecticut University, to write "The History of Emergency Contraception." This highly significant topic is of interest to women's health researchers and health policymakers. This project has the potential of increasing the understanding of how emergency contraception affects women's life and health status in their reproductive years. The project is also related to Health Disparities/Differences and Diversity in that unwanted pregnancies are more prevalent in women of lower socioeconomic status, and access to emergency contraception may be more limited for these women. The project is also relevant to the special emphasis area of Prevention and Treatment in that the study will further elucidate the issues surrounding the use of emergency contraception to prevent the health and social consequences of unwanted pregnancies.

NLM also used the G13 mechanism to fund the development of a book, *Active Bodies: Women's Physical Education in 20th-Century America,* by Martha H. Verbrugge, Bucknell University. This is the first comprehensive, analytical book about physical education for girls and women in the United States during the 20th century. The book's central figures are White and Black female physical educators who taught girls and women about their bodies, exercise, and health in various settings. Gym teachers grounded their lessons about fitness and recreation in biomechanical knowledge, but also coded physical activities by gender, race, sexuality, and class. The project addresses three important questions about this unique convergence of applied science, practical instruction, and social norms. First, how did female teachers interpret scientific theories about sex and racial difference in relation to physical activity? Against the backdrop of the nature/nurture debate, the project examines why some physical educators deployed notions of anatomical and physiological difference to stigmatize the female body and restrict women's recreation and sports, while others challenged biodeterminist beliefs and inequitable opportunities. Second, what standard of femininity did physical educators embed in their scientific concepts of active womanhood? The book analyzes White and Black teachers' diverse models of gender, inflected by race, class, and sexuality. It relates their ideas to the professionalization of physical education and changes in gender ideologies, race relations, and discourse about sexuality in 20th-century America. Third, how did physical educators put their ideas into practice in the gym? The project develops case studies of instructional programs in public schools, colleges and universities, and White and Black branches of the Young Women's Christian Association. An analysis of women's physical education will provide a historical perspective for understanding current debates about gender and health.

Fogarty International Center

Executive Summary

The Fogarty International Center (FIC) supports a range of research and research training programs focused on the needs of low- and middle-income countries. These programs cover both communicable (e.g., HIV/AIDS, malaria) and chronic, noncommunicable diseases (e.g., tobacco control, brain disorders), as well as crosscutting areas such as population health, environmental health, and research ethics. The Office of Research on Women's Health supports many of these efforts, along with several other National

Institutes of Health Institutes. Although these programs were not designed to specifically address women's health, they do support important projects related to women's health. Significant research or research training programs that are related to women's health include the following programs.

International Tobacco and Health Research and Capacity-Building Program (Tobacco)

This program supports transdisciplinary 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. This program is supporting the development of a Network for Tobacco Control Among Women in Parana, Brazil, in order to establish community and institutional capacity to promote gender-relevant tobacco control efforts among Brazilian women through community-based participatory research and training.

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 examining gender differences related to antiretroviral treatment access, AIDS-related mortality and long-term survival rates, risk for human papillomavirus infection, cultural notions of sexual reputation, and other factors that may have a differential impact on HIV-infected women. 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. Examples of research areas related to women's health include postpartum depression, psychiatric disorders/HIV interface in women, and the effects of neurotoxins/neurotoxicants in the home.

Global Research Initiative Program, Basic/Biomedical Sciences and Social Science (GRIP)

This program promotes reentry 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, and to stimulate research on a wide variety of high-priority health-related issues in such countries. Examples of GRIP-supported research topics relevant to women's health include the association between widow inheritance and HIV infections, iron supplementation in HIV-infected women, use of antenatal corticosteroids, 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 project areas supported by ITREOH that focus on women's health include pesticide exposure and reproductive function and methylene tetrahydrofolate reductase variants in women.

Significantly, FIC now incorporates strong language in all its research training announcements to encourage the recruitment and retention of women as faculty and trainees: "The International Clinical, Operational, and Health Services Research Training Award for AIDS and Tuberculosis program strongly encourages PDs

to include women and individuals from underrepresented racial, ethnic, or socially disadvantaged groups in the country as trainees and faculty at all sites. Applicants should describe strategies for recruiting and retaining women and socially and economically disadvantaged persons as trainees."

Accomplishments

The following are examples of selected projects supported by the FIC that focus on women's health.

High Rates of Death Due to HIV/AIDS Among Young Women in KwaZulu-Natal, South Africa

HIV/AIDS exacts a high toll on the population of South Africa, with estimates for AIDS-related adult deaths ranging from 40 percent in 2000 to 70 percent in 2004. The KwaZulu-Natal region of the country is one of the epicenters of the global HIV/AIDS epidemic. Although anecdotal reports have suggested high rates of AIDS-related deaths in the region, few studies have given estimates of the cause or number of deaths. This study sought to establish mortality rates and cause of death between 2003 and 2004 in a rural KwaZulu-Natal community as part of a demographic and health survey to assess the impact of HIV infection in the community. The researchers found that AIDS-related mortality was higher in rural KwaZulu-Natal than in the country as a whole. Although the overall AIDS-related mortality rates for men and women were similar, the study found that death among young women between the ages of 20 and 34 was disproportionately high. This finding underscores the importance of continued prevention efforts and access to antiretroviral treatment for young women.

HIV-Infected Rwandan Women Have a High Rate of Long-Term Survival

Despite the devastating impact of HIV in sub-Saharan Africa, few studies have evaluated long-term survival of people living with HIV/AIDS in the region. Large studies in high-income countries have been essential to understanding the natural history of HIV infection and for public health planning. Similarly, an accurate understanding of the course of infection in people living with HIV/AIDS in Africa is essential for planning and evaluation of prevention and treatment interventions. This study assessed long-term survival in nearly 600 HIV-1-infected Rwandan women recruited between 1986 and 2006. The researchers found long-term survival time in this study population to be higher than predicted by current models of HIV infection and similar to that of high-income countries. Although the reasons for the high rate of long-term survivors in this group of HIV-infected women are not clear, the researchers raise the possibility that the particular viral subtype may have an effect on disease progression.

High Distribution of High-Risk HPV Found in HIV Patients in Lusaka, Zambia

A strong association between positive HIV status and the prevalence of high-risk human papillomaviruses (HPVs) has been discovered in an existing cohort of patients at University Teaching Hospital (UTH) in Lusaka, Zambia. HPV is the primary etiological agent causing 95 percent of cervical cancers. This retrospective cross-sectional study reports on the association and effects of HIV on HPV infections in patients at the UTH. The objective of this study was to assess HPV prevalence and genotype distribution, and to identify cofactors that influence HPV infection. Forty-five percent of patients in the study group were HIV positive. This high rate of HIV infection indicated that this population was at a higher relative risk for sexually transmitted disease. The study team determined that the most common HPV genotypes detected among these Zambian patients were high-risk HPV16 and HPV18, which were found to be threefold greater and tenfold greater than the rates for HPV16 and HPV18, respectively, in the United States. The team discovered that HIV-positive patients were two times as likely to have high-risk HPV as HIV-negative individuals, while the distribution of low-risk HPVs was unaffected by HIV status. Interestingly, the team observed a ninefold increase in HPV18 infection frequency in HIV-positive individuals compared to HIV-negative

individuals. In conclusion, the study suggests a high level of interaction between HIV and HPV that is likely to de-repress the replication of high-risk HPVs. The high rates of HPV16 and HPV18 in Zambia are, at least partly, due to the prevalence of HIV infection and the immunosuppressive effects of HIV. The team suggests that this raises the question as to whether there is an increased rate of transmission of particular high-risk HPVs in couples in which one or both of the partners are HIV+.

HIV Positive Women Are Not Disadvantaged in Their Access to Antiretroviral Treatment in Most Resource-Constrained Settings

Half of the nearly 40 million people living with HIV/AIDS around the world are women, and nearly 60 percent of all HIV-infected adult women live in sub-Saharan Africa. Women, aged 15–24 years, are, on average, three times more likely to be HIV infected than men of the same age. The greater burden of HIV in women reflects gender inequalities, which are most acute in resource-constrained settings. A comprehensive international collaboration of 29 HIV treatment programs in 13 countries in Africa, Asia, and Latin America compared the gender distribution of nearly 35,000 HIV-infected adults receiving antiretroviral treatment in resource-constrained settings. This study found that the proportion of HIV-positive women who received antiretroviral treatment was similar or higher than the Joint United Nations Programme on HIV/AIDS-estimated proportion of HIV-infected adults who are women in most of the sub-Saharan African countries, Brazil, Argentina, and Thailand. However, in one program in Uganda and in the only program in India, women accounted for a lower proportion of antiretroviral treatment use than would be expected from the proportion of HIV-infected women in the population. Although women are more vulnerable than men to becoming infected with HIV, almost all the programs assessed in this study revealed that women were equally or more likely than men to start antiretroviral therapy.

Sexual Reputation and Marital HIV Risk in Rural Mexico

For a growing number of women in rural Mexico—and around the world—marital sex represents the single greatest risk for HIV infection. In rural Mexico, sexual reputation is a critical aspect of social identity, and attention to this factor provides insight into why people act in ways that are socially safer, but physically more risky. Drawing on key informant interviews, participant observation, marital case studies, and archival research, this qualitative study sought to assess the impact of cultural notions of sexual reputation and social spaces (bars, trucks, plazas) on sexual behavior. The study found that cultural notions of sexual reputation lead to behavior that minimizes the risk to a man's social status rather than risk of HIV infection, and that men's behavior may increase women's risk for HIV infection. Given the importance of public sexual reputation, community-based dialogues about marital HIV risk face the challenge of a cultural taboo against speaking publicly about infidelity. The researchers conclude that intervention development should focus on a harm reduction approach in social spaces associated with risky sexual behavior rather than risky behavior or identities.

Behavioral Intervention Improves Obstetrical Care in Argentina and Uruguay

Studies have shown that evidence-based obstetrical interventions are often underused, while ineffective or harmful practices continue to be used. Although adherence to standardized guidelines improves quality of care and health outcomes, the dissemination and implementation of strategies in accordance with evidence-based guidelines often remain suboptimal. This randomized, controlled trial assessed the impact of a multifaceted behavioral intervention (selection of opinion leaders, workshops, skills training, one-on-one visits with birth attendants) on the adoption of evidence-based practices in Argentinean and Uruguayan maternity hospitals. The primary outcomes were the rates of episiotomy and the prophylactic use of oxytocin during the third stage of labor. Evidence-based research

supports the use of oxytocin during labor, while the routine practice of episiotomy may be harmful to a woman's health. The researchers found that the rate of use of prophylactic oxytocin increased from 2 percent at baseline to 84 percent after the end of the intervention, while the rates of episiotomy decreased from 41 percent to 30 percent. These findings strongly support the use of an intense, multifaceted behavioral intervention to achieve substantial change in obstetrical practices. Moreover, this study highlights the effectiveness of active versus passive dissemination of information that could be applied to changing the behavior of healthcare workers to better align with evidence-based recommendations.

Very High Rates of Zinc Deficiency Among Pregnant Women in Subsistence Households in Ethiopia

During pregnancy, adequate zinc intake is essential for the growth and development of the fetus; zinc deficiency has been associated with pregnancy complications, reduced birthweight, and congenital anomalies. In developing countries, inadequate dietary intake of zinc has been identified as a major cause of zinc deficiency. This study aimed to quantify zinc intake in a self-selected group of pregnant women from subsistence households in the Sidama province of southern Ethiopia. Researchers found that the zinc intakes of pregnant women in this population were very low, below those reported in many developing countries, including other countries in Africa. Based on the estimated average requirement recommended by the U.S. Food and Nutrition Board, 99 percent of the women in this study had inadequate zinc intake. Indeed, the prevalence of zinc deficiency appears to be the highest reported for pregnant women in developing countries to date. This finding is important because previous studies have only emphasized the low protein content of the local diet. The authors of this study indicate that a public health intervention is urgently required to simultaneously address coexisting nutritional deficiencies.

Heightened Acute Circulatory Responses to Smoking in Women

The worldwide prevalence of smoking among women is expected to rise in the future. Despite the protective effects of female gender on cardiovascular risk, smoking-associated risk for ischemic cardiac events and stroke are as high or higher in women compared with men. Remarkably, however, the majority of women smokers perceive their lifetime risk for developing heart disease as average or below average. The mechanisms underlying differential effects of smoking on cardiovascular risk in females and males are unknown.

In a randomized control trial, researchers studied female and male habitual smokers in Gdansk, Poland, for more than 2 years to assess the effects of smoking on cardiovascular health, as indicated by electrocardiogram, blood pressure, and muscle sympathetic nerve activity (MSNA). While cigarette smoking increased systolic blood pressure and variability as well as heart rate in both female and male smokers, both cardiovascular measures increased more strikingly in females compared to males; changes in MSNA were similar in both genders. The novel and important findings of this study include (1) increases in blood pressure and heart rate during smoking are greater in female smokers than in males, (2) smoking alters cardiovascular variability to a greater extent in females than males, and (3) vasoconstrictor sympathetic tone is not suppressed in women during smoking despite the enhanced pressor response, so that sympathetic drive is inappropriately heightened in women during smoking. These differential cardiovascular responses to smoking in women compared to men might help explain the greater impact of smoking on their cardiovascular and cerebrovascular morbidity.

Decreased Susceptibility to Malaria Infection in Pregnant Women with Iron Deficiency

Malaria and iron deficiency are major contributors to severe anemia during pregnancy in malaria-endemic areas. Previous studies have suggested that iron supplementation increases mortality and morbidity among children in malaria-endemic areas of Africa,

but the effects of supplementation on pregnant women in these regions were unclear. This study examined the relationship between maternal iron status and placental malaria risk in an area of intense malaria transmission in northeastern Tanzania. The researchers found that placental malaria was less frequent among pregnant Tanzanian women with iron deficiency than among those with normal iron status and that this effect was greatest during the first pregnancy. The prevalence of placental malaria among first-time mothers was nearly three times the prevalence among mothers with multiple births, supporting the notion that women develop immunologic responses over successive pregnancies that confer resistance to malaria. This is the first study to report that iron deficiency provides protection from placental malaria.

Although malaria and anemia during pregnancy are major contributors to maternal and newborn mortality, this study shows that interactions between these conditions complicate efforts to prevent them. Iron deficiency is a common cause of anemia but appears to confer resistance to maternal malaria. Because anemia during pregnancy is commonly due to malaria acquired in tropical regions, treatment with iron may carry unrecognized risks. Further randomized trials involving pregnant women are warranted in order to guide the optimal use of iron supplementation or treatment in this vulnerable group.

Contraceptive Use Low Among Women in Kabul, Afghanistan

In low-resource countries, pregnancy-related deaths remain a major public health concern. In Afghanistan, contraceptive use remains low despite a maternal mortality ratio that is among the highest globally, with 1,600 maternal deaths per 100,000 live births. This study was conducted to assess the prevalence and correlates of prior contraceptive use among hospitalized obstetric patients in Kabul, Afghanistan. Results of this study suggest that, despite some recent improvements, the prevalence of contraception in Kabul remains low, with only one-fifth of study participants reporting any prior contraceptive use. The study further indicated several new factors associated with prior contraceptive use, including having a skilled attendant at a previous delivery and having lived outside Afghanistan in the past 5 years. That spousal or family disapproval accounted for one-third of the stated reasons why women were not planning to use a contraceptive method after delivery lends further support to the importance of contraception awareness programming targeted not only at the woman but also at her family and spouse. It is likely that contraception may not have gained sufficient social recognition as a means of preventing maternal morbidity and mortality in Afghanistan. The postpartum period affords an excellent opportunity for family planning education and counseling. Moreover, a high percentage of women stated a desire to use a contraceptive method postpartum in contrast with their limited experience in using one, which points to the need for postpartum family planning counseling and support. Because of the suboptimal contraceptive utilization in Afghanistan, further research is indicated to explore how postpartum women and their families may be effectively reached to improve contraceptive utilization.

Prevalence and Risk Factors for Carcinogenic Human Papillomavirus in Rural Rakai, Uganda

Since the introduction of the Pap test, a dramatic decline in the incidence and mortality from cervical cancer has been observed where established screening programs exist. In the developing world, where 80 percent of cervical cancers occur, differences in screening practices and low acceptability of pelvic examinations required for collecting samples for screening contribute to the high burden of cervical cancer. Information on the epidemiology of HPV in the developing world is fundamental to planning and evaluating future programs to prevent and treat cervical cancer. This study sought to assess factors associated with carcinogenic HPV prevalence from self-collected vaginal swabs in approximately 1,000 women in rural Rakai, Uganda. Carcinogenic HPV prevalence was found to be 46 percent among HIV-positive and 15 percent among HIV-negative women. Factors independently associated with carcinogenic HPV infection were HIV status, age, more than two

sex partners in the past year, and self-reported herpes zoster, candidiasis, or tuberculosis. The researchers found that carcinogenic HPV prevalence from self-collected vaginal swabs mirrored studies of HPV epidemiology based on cervical samples. Previously, the authors of this study reported a high concordance between self-collected vaginal and physician-collected cervical swabs and that self-collection was feasible in a study population based in Rakai, Uganda. Because self-collected vaginal samples were found to be similar to findings from other studies using physician-collected cervical samples, self-sampling could be a valid alternative in settings where low coverage of cervical cancer screenings and low compliance with pelvic exams may exist.

Gender Analysis

FIC has incorporated strong language in all of its research training announcements that encourages research training activities related to sex and gender differences: "Where appropriate, the design of training-related research projects should take into account potential sex and gender differences that may affect the questions asked and the analyses performed. These might include different responses to and impacts of health interventions, differences in physiology, and different behavioral bases for disease prevention strategies."

Initiatives

The Fogarty International Clinical Research Scholars Program (FICRS) (R24 mechanism)

This program responds to the acute need for future clinical investigators who can help translate basic research advances into clinical practice on a global scale. This next generation of clinical researchers will require hands-on experience in conducting clinical trials and clinical research in countries where the disease burdens are highest, typically in low- and middle-income countries (LMICs). The FICRS provides highly motivated U.S. medical and graduate students in the health sciences the opportunity to experience one year of mentored clinical research training at distinguished LMIC research institutions. Each U.S. student is paired with a foreign student, who also receives training as an equal partner. In 2008, this program was expanded to include a post-doctoral Program for medical residents and fellows, as well as scientists with Ph.D.s engaged in health-related post-doctoral programs. In 2008, the majority of Scholars and Fellows in this program were women (65 percent). In the summer of 2008, Dr. Vivian W. Pinn participated in the Scholars/Fellows orientation and ORWH contributed $150,000 to the program for FY2008.

National Center for Complementary and Alternative Medicine

Executive Summary

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, signed by the President in October 1998. NCCAM's mission is to explore complementary and alternative medical practices in the context of rigorous science, train complementary and alternative medicine (CAM) researchers, and disseminate authoritative information to the public and professionals. CAM encompasses those healthcare and medical practices that are not generally considered an integral part of conventional medicine. NCCAM conducts and supports basic and applied (clinical) research and research training within these areas. NCCAM collaborates with a number of individual Institutes and Centers (ICs) to advance research in areas of mutual interest and scientific opportunity. For example, the National Institutes of Health Botanical Centers Program is a collaboration that includes support from NCCAM, the Office of Dietary Supplements, and the Office of Research on Women's Health. Of particular relevance to women is the Center on Botanical Dietary Supplements for Women's Health at the University of Illinois, Chicago.

CAM therapies are widely used by the public, but limited rigorous research has been conducted to date regarding their safety, effi-

cacy, and effectiveness. CAM approaches are used for a broad range of health conditions affecting both men and women, including painful back and neck problems, allergies, fatigue, headaches, diabetes, and cardiovascular disease. With respect to specific women's health issues, CAM therapies are used for conditions such as menopausal symptoms, breast cancer, osteoporosis, fibromyalgia, and reproductive issues. Thus, NCCAM's research portfolio includes research on the effects and mechanisms of action of CAM interventions with respect to many diseases and health problems. Research areas encompass a spectrum of CAM modalities, including natural products such as dietary supplements; manipulative therapies such as chiropractic; and mind–body medicine such as yoga and mindful meditation. Through rigorous research, NCCAM is striving to build the evidence base regarding CAM interventions and their use in addressing chronic health problems such as pain, and in promoting and maintaining wellness. These efforts include the pursuit of translational research tools, such as biomarkers and imaging techniques, that will enable scientific assessment of CAM interventions.

IC Office or Position on Women's Health

During FY 07 and FY 08, Dr. Catherine Stoney served as the coordinator of NCCAM's women's health efforts. Currently, Dr. Sheila Caldwell serves in that capacity.

Accomplishments

Assessment of CAM Use in the United States

The importance of CAM research to women's health has been underscored by a new nationwide government survey. The survey showed that 42.8 percent of the women interviewed used CAM—compared with 33.5 percent of the men. Overall, 38 percent of adults in the United States (aged 18 years and over) and nearly 12 percent of U.S. children (aged 17 years and under) use some form of CAM. The survey revealed that adults used CAM most often to treat pain, including painful back, neck, and joint problems, and other musculoskeletal conditions. The most commonly used CAM therapies among U.S. adults were nonvitamin, nonmineral natural products (17.7 percent); deep breathing exercises (12.7 percent); meditation (9.4 percent); chiropractic or osteopathic manipulation (8.6 percent); massage (8.3 percent); and yoga (6.1 percent). Among children, CAM therapies were used most often for back or neck pain, head or chest colds, anxiety or stress, other musculoskeletal problems, and attention deficit/hyperactivity disorder (ADHD). Children are five times more likely to use CAM if a parent or other relative uses CAM. With respect to womens' health, often CAM is used in circumstances in which conventional medicine does not provide adequate care, such as addressing hot flashes during menopause.

The survey was conducted with NCCAM support as part of the 2007 National Health Interview Survey (NHIS) of the National Center for Health Statistics (NCHS), a component of the Centers for Disease Control and Prevention (CDC). The 2007 survey is considered the most current, comprehensive, and reliable source of information on Americans' use of CAM. The resulting statistics confirm that CAM practices are a frequently used component of Americans' healthcare regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and healthcare providers to openly discuss CAM use to ensure safe and coordinated care. Thus, the NCCAM's "Time to Talk" educational outreach program, which encourages individuals and their physicians to speak to each other about CAM use, is well founded. NCCAM will use the new national survey data as an important guidepost in its scientific priority setting and future program development. In addition to NCCAM funding, the development of the 2007 supplement was supported, in part, by the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, ODS, and the Office of Behavioral and Social Sciences Research (Barnes, P.M., et al. *National Health Statistics Reports; No. 12* Epub 2008 Dec 10).

Menopause

NCCAM's goals in this area include (1) to provide much-needed information on the safety and efficacy of CAM therapies used for menopausal symptoms, and (2) to gain valuable insights from basic studies about the active ingredients, mechanisms of action, doses, and bioavailability of CAM natural products. Several CAM therapies are commonly used for menopausal symptoms, including botanicals or herbs (i.e., dong quai, and ginseng), paced respiration, meditation, magnet therapy, acupuncture, and homeopathy. Many menopausal women began looking toward CAM therapies when the NIH-funded Women's Health Initiative (WHI) found an increased risk for cardiovascular disease, blood clots, and breast cancer among women receiving estrogen plus progestin to treat menopausal symptoms.

Over the past several years, NCCAM has developed a multipronged approach to improving the scientific evidence base for the use of CAM in the treatment of menopausal symptoms. One focus is to develop tools for rigorously testing treatments for menopausal symptoms—testing that depends on the quality of the outcome measures. For example, through the Small Business Innovation Research (SBIR) program, NCCAM has supported development of high-quality, noninvasive instruments to enable the collection of long-term data on hot flash frequency under ambulatory conditions. These tools are now being used in clinical studies of hypnosis for treating menopausal symptoms.

To assist women in coping with a range of menopausal symptoms—including hot flashes, osteoporosis, and cognitive/affective problems—NCCAM's clinical research on menopause targets several botanical therapies such as serotonergic botanicals and phytoestrogens, as well as nonbotanical treatments. With support from NCCAM, ODS, and ORWH, the Center on Botanical Dietary Supplements for Women's Health at the University of Illinois, Chicago, focuses on studies addressing the clinical safety and efficacy of botanicals used to treat women's health, with particular emphasis on therapies for menopause. For hot flashes, other NCCAM research includes the study of both amino acid therapy and mindfulness-based stress reduction. For the prevention of postmenopausal osteoporosis, the efficacy of turmeric extract is being explored.

NCCAM-funded researchers recently completed a systematic literature review that suggested tai chi may be a safe, effective, and practical alternative to conventional exercise for maintaining bone mineral density (BMD) in postmenopausal women. Moreover, tai chi may improve balance, reduce the frequency of falls, and increase musculoskeletal strength. The researchers noted that the findings are preliminary, but sufficient evidence of effectiveness exists to warrant further research (Wayne, P.M., et al. *Archives of Physical Medicine and Rehabilitation* 88(5):673-80, 2007).

Breast Cancer and Other Cancers

A diagnosis of cancer raises many issues for women, including the hope for successful medical treatments with limited toxicity. A variety of CAM modalities are used by cancer patients and survivors, including herbs and herbal teas, echinacea, traditional Chinese medicines, beta carotene, melatonin, hydrazine sulfate, coenzyme Q10, massage, and mind–body approaches such as yoga.

Breast cancer patients can experience debilitating fatigue while receiving radiation and/or chemotherapy, and also long after treatment ends, even in the absence of cancer recurrence. Researchers are exploring the effects of Qi gong and of Iyengar yoga for such fatigue. They are also investigating the chemopreventive properties of medicinal and food plants; the possible therapeutic efficacy of flaxseed in the prevention of ovarian cancer; and yoga for women who are attempting smoking cessation. Other lines of research include the possible chemopreventive actions of equol enantiomers, and the mechanisms of immunomodulation and the antitumor activity of polysaccharide krestin.

In one recent NCCAM-funded study, researchers investigated how a probiotic (Lactobacillus reuteri ATCC PTA 6475) might work to slow the growth of certain cancerous tumors. Their study documented the molecular mechanisms of the probiotic's effects in human myeloid leukemia-derived cells—that

is, how it regulates the proliferation of cancer cells and promotes cancer cell death. They noted that a better understanding of these effects may lead to development of probiotic-based regimens for preventing colorectal cancer (Iyer, C., et al. *Cellular Microbiology* 10(7):1442-1452, 2008).

Another study has suggested that hypnosis may reduce hot flashes in breast cancer survivors. For many survivors, vasomotor symptoms result in discomfort, disrupted sleep, anxiety, and decreased quality of life. However, survivors tend to avoid hormonal (estrogen) drugs to treat hot flashes because estrogens have been associated with an increased risk of breast cancer. Because nonhormonal treatments do not work for some women and may have adverse effects, new interventions for hot flashes are being sought. Researchers investigated the effects of hypnosis on hot flashes in a study of 60 women with a history of primary breast cancer, no current evidence of detectable disease, and at least 14 hot flashes per week over a 1-month period. The group of women who received hypnosis had a 68-percent reduction in self-reported hot flash frequency/severity. Compared with controls, they also had significant improvements in self-reported anxiety, depression, interference with daily activities, and sleep. The researchers concluded that hypnosis not only appears to reduce perceived hot flashes in breast cancer survivors, but may also have additional benefits such as improved mood and sleep. They are now conducting a randomized clinical trial with 200 participants (Elkins, G., et al. *Journal of Clinical Oncology* Epub 2008 Sep 22).

Reproductive Issues

CAM therapies are used for several reproductive issues, including premenstrual syndrome (PMS), difficulties with conception, and endometriosis that can lead to chronic pelvic pain and infertility.

CAM modalities used include natural products, probiotics, meditation, aromatherapy, guided imagery, and acupuncture. Examples of ongoing research include mechanistic studies of phytotherapy and endometriosis, and investigations of the physiologic and clinical effects of manipulative medicine in pregnancy. CAM therapies are also studied in depression that is related to reproductive issues. One study aims to determine whether eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) prevents depressive symptoms in pregnancy and postpartum. Another study is assessing maca root for the treatment of antidepressant-induced sexual dysfunction in women. Several studies focus on the effects of acupuncture on different reproductive issues: low back pain during pregnancy, reproductive hormones and ovulation, and in vitro fertilization (IVF) in infertility patients. NCCAM funds the New England School of Acupuncture, where research studies include the investigation of acupuncture's effects on chronic pelvic pain in adolescent and young women with endometriosis.

New findings indicate that acupuncture may improve rates of pregnancy—based on a review of seven clinical trials of acupuncture given with embryo transfer in women undergoing IVF. The review encompassed data on over 1,366 women. It compared acupuncture (given within 1 day of embryo transfer) with sham acupuncture, or no additional treatment. The reviewers found that acupuncture given as a complement to IVF increased the odds of achieving pregnancy. According to the researchers, the results indicate that 10 women undergoing IVF would need to be treated with acupuncture to bring about 1 additional pregnancy. Identifying a complementary approach that can improve reproductive success would be of benefit to couples who seek specialist fertility treatments, such as IVF. The study results, which are considered preliminary, point to a potential complementary treatment that may improve the success of IVF and lay the groundwork for additional clinical trials to confirm these findings (Manheimer, E., et al. *British Medical Journal* Epub 2008 Feb).

Pain

NCCAM is committed to studies of CAM therapies for alleviating pain in a wide range of conditions, including arthritis. This goal is consistent with the finding in the 2007 NHIS that various types of pain are the chief conditions for which Americans use CAM. Examples of CAM therapies related to pain management include manipulative therapies (e.g., chiro-

practic); natural products (e.g., glucosamine, chondroitin sulfate, ginger root, turmeric root, and green tea polyphenols); and mind–body approaches (e.g., mindful meditation, massage, yoga, and tai chi). For example, an NCCAM-funded pilot randomized controlled trial is examining tai chi for osteopenic women, whose low bone density makes them vulnerable to painful bone fractures.

With respect to chronic low back pain, NCCAM-funded research includes studies comparing the effect of yoga versus stretching and assessing the efficacy of acupuncture. Each year, up to one-quarter of U.S. adults experience low-back pain. Most people have significant back pain at least once in their lives. For many people, it lasts only a few weeks, no matter what treatment is used. But for others, the pain can become chronic and even debilitating. Low-back pain—such as that experienced during pregnancy—is a challenging condition to treat.

NCCAM also funds research on osteoarthritis—for example, through support for a Center for Arthritis and Traditional Chinese Medicine at the University of Maryland, where investigators are studying anti-inflammatory approaches as an adjunctive treatment for pain and functional limitation in diagnosed osteoarthritis of the knee.

To combat osteoarthritis, NCCAM seeks ways to not only treat the pain of this condition, but also to address its structural effects such as the loss of cartilage—the slippery material between joints that cushions their movement. In new findings, researchers have reported that the dietary supplements glucosamine and chondroitin sulfate—together or alone—appeared to fare no better than placebo in slowing cartilage loss in osteoarthritis of the knee, as measured by the space between joints that is seen on x-rays. However, interpreting the study results is complicated because participants taking placebo had a smaller loss of cartilage than predicted. This research was an ancillary study to the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), whose results were reported in 2006. The original study found that, overall, the combination of glucosamine plus chondroitin sulfate did not provide significant relief from osteoarthritis pain among all study participants. However, a smaller subgroup of individuals with moderate-to-severe pain showed significant relief with the combined supplements.

Although the ancillary study has limitations, it has provided important insights into osteoarthritis progression; the techniques for measuring cartilage loss; the possible effects of these dietary supplements; and the characteristics of osteoarthritis patients who may best respond to treatments. This knowledge will assist investigators in designing future studies (Sawitzke, A.D., et al. *Arthritis & Rheumatism* 58(10):3183-3191, 2008; Clegg, D., et al. *New England Journal of Medicine* 354:795-808, 2006).

Women's Cardiovascular Health

Heart disease is the leading killer of women in the United States. CAM modalities being used by the public for cardiovascular diseases include acupuncture, mind–body interventions (e.g., meditation and yoga), herbal extract treatments, dietary supplements, and several types of energy healing, such as Reiki and Qi gong.

Examples of NCCAM-funded research include investigations of phytoestrogens and progression of atherosclerosis, and studies of yoga and cardiovascular disease risk in older women. The NCCAM-funded Center for Botanical Lipids at Wake Forest University Health Sciences, North Carolina, is conducting studies to examine biological mechanisms and clinical applications of botanical sources of polyunsaturated fatty acids (PUFAs) that may have benefit in the prevention and treatment of diseases such as atherosclerosis. At the Botanical Research Center for Age-Related Diseases at Purdue University, Indiana, a multidisciplinary team of scientists is conducting research on botanicals (e.g., polyphenols) as dietary supplements for age-related diseases such as heart disease.

Women's Digestive Health

Irritable bowel syndrome (IBS) is a little-understood functional digestive disease that primarily affects women. NCCAM is pursuing research on the use of mindfulness approaches in IBS and on identification of the physiologic

characteristics of Traditional Chinese Medicine-based IBS subgroups.

NCCAM is also supporting research on inflammatory bowel disease (IBD). Conventional medical therapies for IBD are limited, and typically involve the use of anti-inflammatory drugs; however, many patients eventually require surgery. Now, researchers have found that the inflammation of IBD might be reduced by the enzyme bromelain, which is derived from pineapple stems. In the laboratory, the researchers studied the effects of bromelain on colon tissue obtained from biopsies of IBD patients. They found that bromelain reduced production of several proinflammatory substances (cytokines and chemokines) that are elevated in IBD and play a role in disease progression. Thus, bromelain treatment could potentially benefit IBD patients if similar changes also occur when colon tissues are exposed to bromelain inside the body. Additional research to understand how bromelain influences inflammation could lead to new insights into the progression of IBD and contribute to therapeutic improvements (Onken, J.E., et al. *Clinical Immunology* 126:345-352, 2008).

NCCAM is building its portfolio of research on probiotics. The most common types of these beneficial bacteria are Lactobacilli and Bifidobacteria. Previous studies indicate that probiotics may have a role in treating gastrointestinal illnesses and other health problems. In a recent study, researchers looked at whether Lactobacillus acidophilus might enhance the immune-potentiating effects of an attenuated vaccine (a vaccine prepared from a weakened live virus) against human rotavirus infection—the most common cause of severe dehydrating diarrhea in infants and children worldwide. The investigators' tests on newborn pigs found that animals given both a vaccine and the probiotic had a better immune response than the animals given the vaccine alone. The researchers concluded that probiotics may offer a safe way to increase the effectiveness of rotavirus vaccine in humans (Zhang, W., et al. *Vaccine* 26(29-30):3655-3661, 2008).

Women's Urologic Health

Urinary tract infections (UTIs) and urinary incontinence are debilitating women's health issues. NCCAM research includes several studies on the use of cranberries in UTIs, including the effect of cranberry constituents on UTI pathogenesis. In other urologic research, NCCAM is exploring the efficacy of acupuncture in treating urinary incontinence.

Alzheimer's Disease and Dementia

Research at an ODS/NCCAM-funded center, the Botanical Center for Age-Related Diseases in Indiana, includes studies to determine the efficacy of polyphenolic compounds in reducing risk of age-related diseases, including neurodegeneration. The February 2008 issue of the *American Journal of Clinical Nutrition* features articles on the NIH Botanical Research Centers Program, including this center.

Important scientific insights have been obtained from a major, long-term clinical trial, the Ginkgo Evaluation of Memory Study (GEMS). This study found that the dietary supplement Ginkgo biloba was ineffective in reducing the development of dementia and Alzheimer's disease in older people. Although gender differences do not apply to the incidence of Alzheimer's disease, there are more women than men living with the disease because women have a longer life expectancy. The GEMS findings have considerable public health relevance because, according to the 2007 National Health Interview Survey, ginkgo is one of the top 10 natural products used by Americans.

The GEMS was conducted over the course of 8 years, with study participants followed for an average of approximately 6 years. The study enrolled 3,069 participants age 75 or older with normal cognition or mild cognitive impairment. The primary objective was to determine if ginkgo would decrease the incidence of all types of dementia and, more specifically, reduce the incidence of Alzheimer's disease. Secondarily, the study evaluated ginkgo for its effects on overall cognitive decline, functional disability, incidence of cardiovascular disease and stroke, and total mortality. The primary endpoint was the diag-

nosis of dementia, as determined by an expert panel of clinicians using standard criteria for diagnosis.

Clinical investigations such as the GEMS help to build the scientific evidence base regarding botanical supplements through rigorous research. The study also provided important information about how to design and conduct large dementia-prevention trials in older Americans. Future analysis of this study may identify subgroups of these participants who may be at greater risk for developing dementia, as well as additional information on ginkgo's possible effects on cardiovascular disease, cancer, depression and other age-related conditions. In addition to funding from NCCAM, the GEMS received support from four other NIH components: NIA, NHLBI, NINDS, and ODS (DeKosky, S.T., et al. *Journal of the American Medical Association* 300(19):2253-2262, 2008).

Obesity and Energy Metabolism

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. The health benefits of weight loss are well established. NCCAM research relevant to issues of obesity includes studies of the effects of mind–body interventions on the risk of the metabolic syndrome (which includes obesity), and on the prevention of postprandial hypoglycemia.

Augmenting the scientific evidence base is a recent report from NCCAM-funded researchers that the very low carbohydrate diet known as the Atkins diet may contribute to greater weight loss in premenopausal women than higher carbohydrate plans—without negative effects such as increased cholesterol. The study was conducted in 311 premenopausal women, all of whom were overweight or obese. Each woman was randomly assigned to one of four diets (Atkins diet, Zone diet, LEARN diet, Ornish diet), each of which was selected for its different level of carbohydrate consumption. Participants in each group received books that accompanied their assigned diet plan, and attended hour-long classes with a registered dietitian once a week for the first 8 weeks. The researchers recorded body mass index (BMI); percent body fat; and waist–hip ratio—as well as metabolic measures such as levels of insulin, cholesterol, glucose, triglycerides, and blood pressure.

The Atkins diet group (consuming less than 20 grams of carbohydrates per day and increasing to 50 grams a day) reported the most weight loss at 12 months with an average loss of just over 10 pounds. They also had more favorable overall metabolic effects (Gardner, C.D., et al. *Journal of the American Medical Association* 297:969-977, 2007).

Initiatives

Several autoimmune diseases, such as systemic lupus erythematosus (SLE), have a disproportionately high prevalence among women. NCCAM issued research solicitations for both exploratory grants and regular research grants to study the mechanisms of immune modulation (RFA AT-07-004 and RFA AT-07-005). One of the grants subsequently funded is studying the treatment of SLE with N-acetylcysteine.

In addition, NCCAM cosponsored several women's health initiatives with other NIH components. These included research solicitations for studies of diet composition and energy balance; efforts for advancing novel science in women's health research (with ORWH); new interventions for menopausal symptoms (with ORWH); studies of the pathophysiology and treatment of chronic fatigue syndrome (with ORWH); and research on causal factors and interventions that promote and support the careers of women in biomedical and behavioral science and engineering (with ORWH). In FY 08, NCCAM also sponsored a grantsmanship workshop at which 43 women were among the 68 attendees who benefited from presentations regarding how to apply and be competitive for NIH research funding.

Health Disparities Among Special Populations of Women

NCCAM supports research to combat health disparities among vulnerable populations such as racial and ethnic minorities. For example, NCCAM is funding a pilot study of guided imagery intervention for obese Latino adolescents. NCCAM is also pursuing research

on diseases such as asthma and HIV/AIDS, both of which are more prevalent in minorities. For example, NCCAM funds a Center for Chinese Herbal Therapy for Asthma at the Mount Sinai School of Medicine, New York, and a Translational Research Center for CAM Therapy for Asthma at the University of North Carolina, Chapel Hill. In a very small study of mostly African-American women, researchers are studying acupuncture and relaxation response for gastrointestinal symptoms and HIV medication adherence. The goal is to assess the use of CAM as a complement to conventional medicine in terms of side effects and adherence. More generally, NCCAM is also studying why and how ethnic and racial minority populations use CAM. NCCAM is contributing to a large study of Women's Health Across the Nation that may help to shed light on these issues.

Gender Analysis

None planned.

NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES

Executive Summary

The National Center on Minority Health and Health Disparities (NCMHD) promotes minority health and leads, coordinates, and assesses the National Institutes of Health (NIH) efforts 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 (LRP), the Centers of Excellence Program (COE), and the Research Endowment Program. Additionally, the NCMHD supports the Community-Based Participatory Research (CBPR) program, the Research Infrastructure in Minority Institutions program (RIMI), the Minority Health and Health Disparities International Research Training (MHIRT) program, and the Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) program. These combined efforts position the NCMHD to lead and coordinate the NIH health disparities activities for the benefit of all affected populations, including women from the African-American, Hispanic, American Indian, Alaska Native, Asian American, Native Hawaiian, and Pacific Islander population and subpopulations, as well as women of low socioeconomic status and those residing in medically underserved communities. Additionally, the NCMHD has a long history of collaborating with other NIH Institutes and Centers and Federal agencies.

Representative accomplishments of relevance to women's health and public health and resulting from NCMHD programs and collaborations during FY 2007–2008 are summarized below. Because NCMHD-supported research is focused on the health of racial and ethnic minorities and other health disparity populations, the range of diseases and conditions under investigation by NCMHD researchers is broad. It includes, for example, cardiovascular diseases, obesity, metabolic syndrome, diabetes, cancer, HIV/AIDS, and substance abuse. Some of these projects involve research on women only. However, several of these projects include both men and women in the study population. Within the above diseases and conditions, researchers conduct research on both biological and nonbiological factors using various study types and interventions, such as prevention studies, comparative effectiveness studies, community-based participatory research studies; as well as behavioral and educational interventions. NCMHD investigators also provide training to new investigators, disseminate health information, and engage communities in innovative efforts to improve minority health and to reduce and eliminate health disparities. Central concepts found in many of the NCMHD-supported studies include cultural competency and culturally tailored interventions.

NCMHD Organizational Components

While there is no office specifically designated to address research on women's heath, women's health research is a part of the NCMHD health disparities research portfolio, which is conducted through NCMHD extramural grants, cofunding with other ICs, and other Federal agencies.

Accomplishments

The majority of the projects presented below are supported under the NCMHD COE program, the CBPR initiative, and the MHIRT program, and through cofunding with other ICs and Federal agencies. Descriptions of these NCMHD programs can be found on the NCMHD Web site, http://www.ncmhd.nih.gov. The NCMHD does not support any Phase III clinical trials.

Cardiometabolic Health (Cardiovascular Disease, Obesity, Metabolic Syndrome)

The growing epidemic of obesity and the impact of other prevalent health concerns, including diabetes, high blood pressure, high cholesterol, metabolic syndrome (MetS), and cardiovascular disease is affecting all populations, especially racial and ethnic minorities and other health disparity populations. Comparatively, in the general population, women are slightly more obese than men. However, according to Centers for Disease Control and Prevention data, American Indian or Alaska Native women (29.4 percent) were less likely than Black women (36.6 percent) and more likely than White women (20.3 percent) and Asian women (5.8 percent) to be obese. Obesity is a major risk factor contributing to cardiovascular disease and type 2 diabetes. Consequently, the NCMHD supports a range of innovative and multidisciplinary efforts focusing on women and girls and cultural/behavioral determinants and strategies for addressing obesity and associated conditions and diseases. The following are examples of research funded by the NCMHD to study some of these diseases and health conditions.

According to a recent report by the Hawaii Department of Health, cardiovascular disease (CVD) has been the leading cause of death in Hawaii since 2005 and was responsible for 2,900 deaths in the State and over $600 million in associated hospital costs. There are a number of health disparities that vary by geography, ethnicity, and socioeconomic status. Overweight and obesity are two known risk factors for cardiovascular disease. A continuing NCMHD Center for Native and Pacific Health Disparities Research at the University of Hawaii provides a regional focal point for research, research training, and community engagement aimed at cardiometabolic health and health disparities among Native Hawaiians, Alaska Native, and other Pacific Peoples including Samoans and Tongans. The Center conducts a MetS study, an epidemiological study involving Filipino, Native Hawaiians and Samoan youth. A novel CBPR project, The Partnerships for Improving Lifestyle Interventions (PILI), has been formed among five community groups, the medical school, and the State department of health to focus on reducing and eliminating obesity health disparities. It is anticipated that women will constitute 80 percent of the participants in this study. Community engagement projects in Hawaii and California will assess optimal strategies for health information dissemination and participation among Native Hawaiian, Alaska Natives, and Pacific People communities to improve cardiometabolic health and eliminate health disparities. The public health impact of the Center's activities and the CBPR studies is the potential to add new insights into the growing epidemic of obesity, Type 2 diabetes, and CVD risk and to contribute to the elimination of these health disparities in the State of Hawaii.

Researchers at the NCMHD COE established between the Charles Drew University of Medicine and University of California at Los Angeles analyzed secondary data from the Third National Health and Nutrition Examination Survey (NHANES) to examine the association between serum levels of 25-hydroxyvitamin D and select cardiovascular disease factors in U.S. adults. Findings showed lower levels of 25-hydroxyvitamin D in women, elderly persons, racial/ethnic minori-

ties, and participants with obesity, hypertension, and diabetes mellitus. Prospective serum studies are needed to assess a direct benefit of vitamin D supplementation on persons with CVD risk factors.

Uniform Services University (USU) Center for Health Disparities Research, a partnership between USU and the University of Maryland, Eastern Shore, conducts research on long-term behavioral modification aimed at reducing and preventing obesity among African-American women and applies the results of this research experience toward building a program on CVD and MetS, both of which disproportionately affect minority populations. Research includes issues related to lifestyle and health, healthcare access, health status, and health disparities. The Healthy Lifestyles among African-American Women Through Weight Loss and Exercise project is exploring ways for women within faith-based communities to sustain weight reduction and maintenance efforts using different exercise regimes and behavioral therapies. The results from the successful treatment combination could be applicable, with the appropriate cultural modification, to faith-based groups from different racial and ethnic groups. The long-term expectation for this project is a decrease in the risk and incidence of obesity and associated conditions, such as hypertension, diabetes, MetS and CVD.

The Jackson Heart Study is the largest single-site, prospective, epidemiologic investigation of cardiovascular disease among African-Americans ever undertaken. It is a population-based longitudinal cohort study located in Jackson, MS. The Jackson Heart Study exemplifies a unique collaborative model among Jackson State University, Tougaloo College, University of Mississippi Medical Center, the Jackson community, and NIH to discover and test best practices for eliminating health disparities. Since 1998, NCMHD has worked with the National Heart, Blood, and Lung Institute to initiate the study and more recently to assess success in meeting milestones, including ensuring adequate participation by key stakeholders and providing advice on scientific direction, such as the identification of genetic, biological, and environmental risk factors in African-American women. In Fiscal Years 2007 and 2008, NCMHD contributed a total of $7.55 million over the 2-year period to the Jackson Heart Study.

Researchers at San Diego State University recently published their research on MetS in Latina women. The effects of educational attainment as a measurement of socioeconomic status (SES) and psychosocial resources on MetS variables were examined. Latina women with less education reported fewer psychosocial resources and showed a higher risk profile on measures of blood pressure, waist circumference, and plasma glucose as compared with Latina women with higher education. These findings warrant further exploration of the role of resilient resources in relationships among socioeconomic positions, metabolic risk factors, and chronic disease processes.

In a study conducted at the NCMHD COE established at University of Texas, M.D. Anderson Cancer Center, researchers evaluated the relationship between the weight status of mothers and their children, 5–18 years old, at baseline in a cohort study of Mexican origin, low-SES families residing in inner-city Houston. This is highly relevant given that obesity is a risk factor for several chronic conditions later in life, including cardiovascular disease, type 2 diabetes, and some cancers. The study found obese mothers were twice as likely to have an overweight and/or at-risk-for-overweight child compared with normal-weight mothers. Women born in the United States were twice as likely to have an overweight and/or at-risk-for-overweight child compared with women born in Mexico. In addition, women with less than a high school education were twice as likely to have an overweight child compared with their more educated peers.

The Body Composition, Hormones, and Health Risk Factors in Middle-Aged Hispanic, African-American, and Caucasian Women study being conducted at the Hispanic Health Disparities Research Center at the University of Texas, El Paso, examines the obesity–disease risk relationship among racial ethnic groups in the development of healthy weight guidelines. Analyses include determination of body fat ranges related to dyslipidemia, hypertension, and elevated glucose and insulin concentrations in each group and the obesity–hormone relationship among the racial ethnic groups. This is important because of the critical role

that hormones play in metabolism and disease processes. These interrelationships are critical in developing an understanding of the etiology of diseases. Research examines the impact of fat distribution pattern on the obesity–risk factor–hormonal relationships and whether various field tests of body composition (body mass index, skin fold equations, etc.) accurately estimate body fatness in middle-aged women from these racial ethnic groups. The efficacy of these methods in African-American and Hispanic women is not well understood. Interpretation of results will focus on the relationships among body composition, hormones, and risk factors in Hispanic, African-American, and Caucasian women associated with low risk for CVD and type 2 diabetes.

The Carolina–Shaw Partnership for the Elimination of Health Disparities and the University of North Carolina published findings on NCMHD-cofunded research on cultural attitudes toward weight, diet, and physical activity among overweight African-American girls. The study examined attitudes and perceptions on these issues among African-American youth, particularly among females. This pilot study sought to qualitatively explore cultural attitudes and perceptions toward body image, food, and physical activity among a sample of overweight African-American girls. Weight and body-size preferences were found to be primarily determined by the individual and her immediate social circle and were less influenced by opinions of those outside the social circle; food choices depended on texture, taste, appearance, and context more than on nutritional value; engagement in recreational physical activity was influenced by time constraints from school and extracurricular activities and by neighborhood safety; participation in structured exercise was limited because of the cost and time related to maintenance of personal aesthetics (hair and nails); and celebrities were not perceived as role models for diet and physical activity habits. The findings imply that perceptions of weight and healthy lifestyle behaviors are largely determined by environmental and personal influences. These factors should be considered in the development of healthy-weight interventions for African-American girls.

Diabetes and Reproductive Health

The University of Oklahoma Center for American Indian Diabetes Health Disparities (OCAIDHD) has as its aim to reduce and eventually eliminate the excess mortality, morbidity, and quality of life and culture lost due to diabetes. The primary efforts of the Center focus on diabetes, maternal health, infant mortality, and obesity. The OCAIDHD confronts health disparities by focusing the expertise of a multidisciplinary, multicollege team of diabetes researchers on specific biological, physiological, behavioral, and cultural stressors of the disease. The Center also has added community strengths through partnership with the Oklahoma City Area Inter-Tribal Health Board (covering all tribes in Oklahoma, Kansas, and Texas) and its Southern Plains Center on American Indian Epidemiology. Research studies underway include (1) Early Markers of Preeclampsia in American Indians with Type 2 Diabetes, (2) Insulin Resistance and Glucocorticoid Treatment of Inflammatory Diseases of High Prevalence among AFs, and (3) American Indian Diabetes Beliefs and Practices: Maternal Care, Infant Mortality, and Adherence.

Cancer

Eliminating Racial and Ethnic Disparities in Breast Cancer Adjuvant Treatment

One model developed to account for racial and ethnic disparities is based on the greater underuse of effective healthcare services and treatments among racial and ethnic minorities compared with the majority population. Rectifying underuse may represent an effective strategy for reducing disparities. Findings published in 2007 and 2008 indicate that the use of a tracking and feedback registry that enhanced completed oncology consultations between surgeons and oncologists also appears to reduce rates of treatment underuse and to eliminate the racial and ethnic disparities in breast cancer adjuvant treatment. For this study, underuse of adjuvant treatment was defined as no radiotherapy after breast-conserving surgery, no chemotherapy for estrogen receptor (ER)-negative tumors, or no

hormonal therapy for ER-positive tumors over a certain size. The implication of these findings is that a tracking and feedback registry designed to increase patient followthrough with referrals can result in real improvement in the treatment of women with new, primary, early-stage breast cancers. Further improvements may be possible by designing interventions to address other factors contributing to underuse, such as physicians not recommending treatment or a patient's decision to not accept the recommended treatment.

Breast Cancer Prognostic Factors/ Pathobiology in Middle-Aged and Older Women

NCMHD is conducting an ongoing population-based, molecular–epidemiologic cohort study in collaboration with the National Cancer Institute (NCI). Breast cancer is the second leading cause of cancer death in women; it is the leading cause of cancer deaths among Hispanic women. In spite of improvements in stage and advances in treatment, mortality from breast cancer continues to be substantial and minimal insights exist regarding factors that influence disease progression and mortality. In particular, little is known about how patient and tumor characteristics relate to mortality in middle-aged and older women. The overall goal of the study is to evaluate patient and tumor characteristics for their relationship with the risk of breast cancer mortality. The research on patient characteristics and mortality will help to provide clinical insights on biology of breast cancer progression and determinants of prognosis.

Dietary Interventions for Breast Cancer

NCMHD supported research that will lead to a better understanding of the influence of dietary interventions on breast cancer outcomes and survivorship. In a study of Hispanic and non-Hispanic White women in the Healthy Eating and Living Study, baseline analysis of dietary intake found similarities with higher lycopene consumptions among the Hispanic patients. Further analysis will determine whether the higher lycopene consumptions will translate to greater protection against breast cancer recurrence or increased survival.

The Sister Study, a unique public–private partnership, seeks to identify some of the genetic and environmental causes of breast cancer. The Sister Study is the only long-term study in the United States and Puerto Rico of women from ages 35 to 74 whose sisters had breast cancer. Begun in 2003, the study prospectively examines the environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The Sister Study is cofunded by NCMHD and led by the National Institute of Environmental Health Sciences (NIEHS). In Fiscal Years 2007 and 2008 NCMHD contributed a total of $4.2 million over the 2 year period to the study to assist in the recruitment and retention of a diverse cohort of women—African-Americans, Asians, American Indians/Alaska Natives, Hispanics, and seniors (age 65 and older).

Researchers at the NCMHD COE established by the Center for Research on Minority Health, University of Texas M.D. Anderson Cancer Center, and Prairie View A & M University and its College of Nursing are seeking to define the biological relevance of susceptibility gene polymorphisms as risk factors for lingering genetic damage and thus, as susceptibility factors for adverse health effects and carcinogenesis. Gastric cancer can be considered an indicator of health disparity because it is more prevalent in developing countries, where the mortality is higher. In Mexico, gastric cancer is the third leading cause of mortality after CVD and lung cancer. In the United States, gastric cancer incidence is also higher in Hispanics than in White Americans. The etiologic factors for gastric cancer include *Helicobacter pylori* infection, dietary factors, and genetic susceptibility. The researchers use a molecular and environmental epidemiologic approach to assess the prevalence of the aforementioned gastric cancer risk factors among this minority population. They are developing and validating a Food Frequency Questionnaire to assess the folate and vitamin B-12 intake of Mexican-American children residing in Texas. The short-term goal is to estimate the magnitude of the prevalence of the social, environmental, and genetic factors that have been associated with gastric cancer risk among Mexican-American children, with the long-term goal of reduc-

ing the risk that can be modified through preventive interventions. The specific aims of the study are the following: (1) Generate epidemiological and dietary gastric cancer risk data from 500 Mexican-American children ages 5 to 18; (2) Genotype a key gene involved in folate-DNA methylation as an intermediate biomarker for gastric cancer risk; (3) Determine the folate, vitamin B-12, and homocysteine levels of the children; and (4) Determine the seroprevalence of antibodies against Helicobacter pylori. Findings from this study may also serve to reduce gastric cancer health disparities worldwide and in the United States. The study population will consist of 200 pesticide-exposed Mexican-American migrant seasonal farmworker women, 200 of their children, and a comparison group of 200 children (whose parents have never worked in agriculture) matched by ethnicity, age, gender, and residential status to the migrant seasonal farmworker children.

Human Papillomavirus (HPV) Vaccination: Acceptance, Delivery, and Policy Implications

This is cofunded with the NCI. This pilot project, a collaboration between the University of Maryland School of Medicine and the Maryland Regional Community Network, addresses the national priority to reduce and eventually eliminate cancer health disparities as experienced by racial/ethnic minorities. Its long-term goal is to eliminate racial/ethnic disparities in cervical cancer incidence and mortality through evidence-guided community and healthcare professional education and state-level policy initiatives, which enhance delivery and uptake of HPV immunization. The short-term goals are to determine the facilitators and barriers to HPV vaccination delivery by healthcare professionals and uptake by eligible adolescents, and to determine policy and regulatory impediments to HPV immunization.

HIV/AIDS

The impact of HIV/AIDS on women has been a growing concern, particularly among women of color who are disproportionately represented in the epidemic among the U.S. female population. NCMHD supports research efforts on culturally appropriate interventions, behavioral determinants, and the development of diagnostic and therapeutic measures for HIV/AIDS.

The University of Miami Center of Excellence is conducting a 3-year experimental study evaluating the effectiveness of a randomized HIV risk-reduction intervention led by Hispanic women and culturally tailored to the specific needs of Hispanic women who are disproportionally impacted by HIV/AIDS. The research study evaluates the effectiveness of a refined and culturally tailored specific intervention to increase HIV prevention behaviors for inner-city Hispanic women and explores the role of acculturation, family, stress, and family functioning as risk and/or protective factors in the prevention of HIV/AIDS among Hispanic women.

The Virginia Commonwealth University Center of Excellence in Health Disparities Research is conducting research on adverse pregnancy outcomes for African-American women and community health education interventions that increase safer sex skills development among pregnant women at high risk for HIV infection. Full research projects will focus on the genetics of preterm birth in African-Americans, immunological responses to periodontitis that may lead to premature birth, and increasing safer sex skills development among pregnant women at high risk for HIV infection. African-Americans have an infant mortality rate more than twice the rate for Whites. Pilot projects involve enhancing fetal exposure to antiretroviral medications and describing the geographic distribution of birth outcomes and environmental stressors. An important aspect of this research project is the Center's collaboration with community stakeholders to conduct and evaluate the impact of a community health education intervention on healthier pregnancies.

Researchers at the University of Puerto Rico published findings on the psychometric properties of the Spanish-language HIV Dementia Scale (HDS) in a group of HIV-infected women. The researchers were able to establish the value of the HDS-Spanish translation as a useful screening tool for the identification of Hispanic women at risk for developing HIV-associated symptomatic neurocognitive disturbances. They have also published their

research findings on the performance of the rapid antibody test Determine HIV-1/2 in pregnant women at Tijuana General Hospital. Findings indicated that this rapid test has a high sensitivity and specificity in pregnant women. Rapid HIV testing greatly diminishes the time to diagnosis and enables prompt intervention with antiretrovirals at delivery.

International Studies of HIV Treatments: Mother-to-Child Transmission (MTCT) Studies of Nevirapine Efficacy

This project is cofunded with the National Institute of Allergy and Infectious Diseases. Treatment of HIV-1 infection with highly active antiretroviral therapy (HAART) can markedly improve immune function and general health. Single-dose nevirapine (NVP) has been adopted by many programs to reduce MTCT of HIV-1 due to its efficacy (50 percent) at a very low cost. The studies are being conducted in Mozambique and Thailand. These studies provide insight into the selection and persistence of NVP-resistant viral reservoirs associated with single-dose NVP, and the clinical effects of these mutants. These data assist in establishing complementary MTCT prophylaxis regimens and HAART for women and children.

Sexually Transmitted Diseases and Drug Abuse

Trichomonas Vaginalis: Molecular Analysis of Adherence

This is a cofunded project with NIAID. Trichomonas vaginalis is a sexually transmitted disease causing serious health consequences for women. Trichomoniasis is a cofactor in HIV transmission and contributes to preterm labor, cervical cancer, and atypical pelvic inflammatory disease. Incidence and prevalence rates of this disease are especially high among minorities, contributing to health disparities. Despite its public health impact, fundamental aspects of trichomonad cell and molecular biology are unknown. The long-term goal of the project is to understand the molecular basis of adherence of trichomonads to vaginal epithelial cells. The rationale is that molecular dissection of this fundamental process of virulence will provide effective means for control of this infectious disease.

Drug Abuse Prevention: A Mother–Daughter Intervention

Cofunded with the National Institute on Drug Abuse (NIDA), this study is a prevention program that engages poor, minority girls and their mothers who live in New York City Housing Authority units. The study provides gender-specific drug abuse intervention (GSI) via CD-ROM to girls and their mothers on site at their housing developments. The objectives are to develop and test the efficacy of GSI compared to a no-intervention control arm in preventing girls' substance use; to test the efficacy of GSI to improve girls' mother–daughter affective quality, coping, refusal skills, mood management, conflict resolution, problem solving, self-efficacy, body esteem, normative beliefs, social supports, and mother–daughter communication, and relate these mediating factors to girls' substance use behavior. The project will determine if intervention effects differ for ethnic/racial groups and to quantify the costs of intervention development and delivery. In a recently published article based on a survey of nearly 800 adolescent girls and their mothers, the investigators found relationships between girls' use of alcohol, prescription drugs, and inhalants and girls' after-school destinations, body images, depression, best friend's substance use, maternal drinking behavior, mother–daughter interactions, and family norms surrounding substance use. These study findings have implications for the design of responsive gender-specific prevention programs.

Substance Abuse Etiology of Alcohol Use and Consequences Among Multiethnic Urban Youth

This project, cofunded with the National Institute of Alcohol Abuse and Alcoholism (NIAAA), examines trajectories, consequences, and multiple levels of influences on alcohol use among urban poor adolescents, explicitly comparing patterns of effects across ethnic and gender subgroups. The long-term outcome of this project is to improve preventive interventions with larger beneficial effects efficiently achieved across the diverse population of

U.S. youth. Study aims include (1) improve understanding of multilevel factors on trajectories of alcohol use by ethnic and gender subgroups, (2) compare effects of age of onset of alcohol use and age of initial intoxication on alcohol use at age 18 across ethnic and gender subgroups, (3) identify similarities or differences in consequences of alcohol use across ethnic and gender subgroups, and (4) assess the long-term effectiveness of the Project Northland Chicago intervention and its differential effectiveness across subgroups. Results will significantly improve the understanding of alcohol use trajectories among Black and Hispanic youth, and will guide development of theory applicable to ethnic and gender subgroups. Most importantly, results will directly guide the development of further refined interventions of increased efficacy and effectiveness.

Kidney, Ureter, and Bladder Diseases

The Boston Area Community Health (BACH) study, cofunded with the National Institute of Diabetes and Digestive and Kidney Diseases, is filling knowledge gaps in the epidemiology of urologic problems, especially variations in prevalence and risk factors by race/ethnicity, gender, age, and socioeconomic status. A random population sample of 5,506 adults (3,205 females, 2,301 males; 1,770 Black, 1,877 Hispanic, 1,859 White) was successfully recruited from 2002 to 2005. Prospective followup of well-characterized subjects provides an opportunity to address questions concerning the epidemiology of urological symptoms: natural history (progression/remission) within the same subject, longitudinal relationship with major chronic diseases, pharmacoepidemiology, the role of life experiences/events, help-seeking behavior, and formal and informal costs (bother, distress, and quality of life). It will provide much-needed incidence rates, an opportunity to test the robustness of baseline associations, and help unravel pathophysiologic pathways. This study will examine the "urologic iceberg"—the incidence of urologic symptoms in the population, risk factors, changes over time, impact on quality of life, use of health care, and the emerging burden of symptoms suggestive of urologic disease.

Bone Health

The Navajo Bone Health Study aims to begin surveillance of bone health on the Navajo Nation. These efforts will in time enable the Navajo Nation to plan screening and culturally appropriate education and intervention programs targeted to the segments of the population who are at greatest risk for fracture or osteoporosis. Specifically, the researchers hypothesize that bone density (total bone mineral density (BMD), and BMD at the hip and lumbar spine) will be distributed differently in Navajo American Indians than in Caucasians. In this study, data will be collected using dual energy x-ray absorptiometry and broadband ultrasound attenuation of the heel. BMD from a random sample of 1,296 Navajo men and women will be compared with data reported for Caucasians in the NHANES III database by age and gender. This study is an important first step in surveillance of bone health of Navajo American Indians. Gender-specific aspects of this study include the selection of 112 men and 112 women in four 10-year age groups (30–39, 40–49, 50–59, and 60 and older) to assure adequate and separate estimates of BMD in each of these gender-specific age groups. In another component, BMD will be measured on 2,500 Navajo men and women using broadband ultrasound attenuation of the heel. This study examines the association of reported adult fractures with BMD measures and will relate these measures to relevant public health outcomes.

Women in Biomedical Science Careers

In addition to the NCMHD-supported training and career development projects discussed below, the Loan Repayment Program (LRP), the NCMHD COE, the CBPR initiative, and the SBIR/STTR programs are also assisting in advancing women's careers in the biomedical and behavioral sciences. Based on a recent analysis, women constitute 47 percent of the 154 principal investigators/program directors supported by the CBPR, NCMHD COE, and SBIR/STTR programs. For the LRP, women

made up 63 and 68 percent of the award recipients in 2007 and 2008, respectively.

Training Programs for Increasing the Number of Women Scientists

The Association of Professors of Medicine (APM) intends to spearhead a concerted, long-term effort to identify, develop, and implement substantive but practical solutions that will ensure the survival and growth of the physician-scientist workforce of the next generation. The APM held a consensus conference in fall 2007 to develop recommendations specifically targeting entities such as Federal agencies and legislators, the Accreditation Council for Graduate Medical Education, foundations that support medical research, and institutions of higher education that will improve and encourage entry into and retention of the physician-scientist workforce and women in particular. The Charles R. Drew University of Medicine and Science is planning to establish a Master of Science in Clinical Research (MSCR) degree program through its College of Medicine. The specific aims of the MSCR program at Drew were to (1) implement a new curriculum for patient-oriented research that has a particular emphasis on methodologies to address health disparities; (2) increase the number of women and ethnic minority investigators well trained in health disparities research; (3) develop a cadre of well-trained clinician faculty who will pursue clinical research on diseases that disproportionately affects minority populations; and (4) continually evaluate the processes and the initial objectives of the MSCR program and utilize these assessments to make ongoing programmatic improvements in consultation with NIH program officials.

The Morgan State University Public Health Program's Complementary and Alternative Medicine Research Training Program (MSU-PHP CAMRTP) will recruit and train post- and predoctoral fellows and short-term trainees in research related to the epidemiology of CAM practices (especially among minorities), botanical content standardization, safety and efficacy of using botanicals/diet/other healing practices for prevention or treatment of diseases, integration of CAM and conventional medicine practice, as well as emerging methodologies in CAM research. This research training program is needed because more people are documented as using CAM modalities, but the evidence base for the safe and effective use of these products and practices lags behind that available for decisionmaking in conventional medicine. To date, MSU-PHP CAM Fellows have investigated the relationships of yoga to hypertension, black tea and lipid excretion, concordance of practitioner/patient beliefs on CAM treatment outcomes, herbals and memory in menopausal women, botanical content standardization, botanical extract impact on diabetes as well as providing pilot data for grant applications and publishing in peer-reviewed journals. To date, over 75 percent of the trainees in this program have been women.

Initiatives

- **NIH Pathway to Independence Award (K99/R00); PA-09-036**
  The primary purpose of the NCMHD Pathway to Independence Award program is to increase and maintain a strong cohort of new and talented, NIH-supported, independent investigators interested in conducting health disparities biomedical and behavioral research. The program is designed to facilitate a timely transition from a mentored postdoctoral research position to a stable independent research position with NCMHD support.

- **Disparities Research and Education Advancing Mission (DREAM) Career Transition Award (K22); RFA-MD-09-001**
  The purpose of the NCMHD DREAM Career Transition Award is to support former or current NCMHD LRP recipients who are highly qualified postdoctoral fellows, but have no more than 10 years of postdoctoral research training at the time of application submission, with mentored research experience.

- **NCMHD CBPR Initiative in Reducing and Eliminating Health Disparities: Intervention Research Phase (R24)**
  The CBPR 5-year competitive intervention research phase supports the development, implementation, and evaluation of effective disease intervention research studies using CBPR principles and methods to reduce and eventually eliminate health disparities in

major diseases of public health importance that disproportionately affect racial and ethnic minorities, individuals with low SES, medically underserved populations, and those living in rural areas. Diseases of major public health importance may include cancer, cardiovascular disease, HIV/AIDS, diabetes, hepatitis B, or other conditions of concern to the community.

Health Disparities and Special Populations of Women

All NCMHD-supported research is categorized as minority health or health disparities research and contributes to the promotion of minority health, the reduction and elimination of health disparities, or both. The target populations and communities include racial and ethnic populations and subpopulations and other health disparity populations.

National Center for Research Resources

Executive Summary

The National Center for Research Resources (NCRR) provides the research infrastructure for creating the necessary environments and tools for researchers to conduct biomedical and clinical research. In addition, 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. Through its support of multidisciplinary research, the NCRR is uniquely positioned to provide funds directly for research or to act in partnership with other National Institutes of Health components to address emerging clinical and basic research needs. While NCRR did not issue any specific initiatives in the area of women's health in Fiscal Years 2007 or 2008, 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.

Introduction

The NCRR provides basic scientists and clinical researchers with the resources and environment to pursue research on a wide range of diseases. This support enables discoveries that begin at a molecular and cellular level to move to animal-based in vitro 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 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 historically low NIH funding; and alterations and renovations to research animal care facilities. 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 NCRR did not specifically develop dedicated initiatives in the area of women's health in Fiscal Years 2007 or 2008. However, through its support of unique resources, NCRR contributes a significant portion of its budget to women's health and behavior research and continues to support initiatives developed by other components of NIH for such efforts. In addition, the NCRR supports research on the prevention and treatment of various diseases, disorders, or conditions that are unique to women or may have a significant impact

on women. The recent accomplishments in women's health research described below exemplify the breadth of science and technology supported by the NCRR and include research from a variety of centers committed to women's health, a mentorship program in women's health, development of 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

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, nonhuman 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.

The Institutional Development Award (IDeA) program supports Centers of Biomedical Research Excellence (COBRE) programs to build centers for research excellence in States historically underfunded by NIH. The Center of Biomedical Research Excellence for Perinatal Biology at the Women and Infants' Hospital of Rhode Island utilizes contemporary biological approaches 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. The efforts are also focused on the development of a transgenic mouse model to study the mechanisms of preeclampsia, which affects 5 to 7 percent of pregnancies.

The IDeA Program also supports a COBRE program in Women's Health at the University of Kentucky. The center focuses on advancing our understanding of the unique role of gender and female reproductive hormones in the manifestation of health and disease, and builds a cadre of junior investigators in the field of women's reproductive health. A unique strength of the COBRE in Women's Health research is the multidisciplinary approach to investigate the fundamental mechanisms and impact of hormones and gender on heart disease, brain function, HIV/AIDS, reproductive tract physiology, and behavior. Additionally, the center has catalyzed and served as the nucleus for a major expansion of women's health research at the University of Kentucky, including the creation of a new Center for the Advancement of Women's Health, which provides a clinical/translational complement to the COBRE, and a new Center for Research on Violence Against Women. COBRE leaders are also working with the deans of the College of Medicine and the College of Health Sciences to establish a new Center of Excellence in Reproductive Sciences to further promote research and education in women's health.

A COBRE program at the University of Montana studies the relationship between dietary intake, specifically Docosa Hexaenoic acid (DHA), and physical activity patterns in pregnant women who are healthy and not physically active; healthy and physically active pregnant women; and women diagnosed with gestational diabetes (GDM). A primary outcome of this project is to identify DHA status of the mothers and their babies at birth. A secondary outcome is to determine if GDM will impair the transfer of DHA to the baby.

Presently, approximately 1 percent of children born each year in the United States are conceived via assisted reproductive technologies (ARTs) and world-wide more than 1 million children have been conceived and delivered over the past two decades. Much of the morbidity that stems from ART is due to the high rate of multiple gestations associated with this treatment. To date, embryo quality assessments are based on a subjective morphological evaluation of the embryo following in vitro culture. Objective criteria for selection of high-quality embryos should increase ART

success and make single-embryo transfer a more viable therapeutic option. The COBRE program at the University of Kansas Medical Center studies for the first time early embryonic protein markers in a conditioned medium to begin to establish a signature/pattern of proteins indicative of embryo quality and pregnancy outcomes.

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 houses 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 major foci of these studies are sexual and reproductive health and sociobehavioral dimensions of HIV/AIDS. Research areas in the center have been expanded to include research on cancer, HIV/AIDS transmission, and healthcare access and quality. In addition to research facilities, the CWHR provides a locus for scientific exchange among investigators and research and training for students, residents, and faculty.

NCRR-funded Comprehensive Centers on Health Disparities (CCHDs) focus on the development of sustainable, replicable, and culturally appropriate prevention and/or intervention research programs to decrease the incidence and prevalence of disease; strengthening clinical and translational research capacity at minority medical schools committed to addressing health disparities; and enhancing opportunities for multidisciplinary research collaborations on health disparities. The Comprehensive Center for the Study of HIV/AIDS in Puerto Rico is a partnership between scientists at 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) in Puerto Rico. The research conducted in the center is focused on HIV risk behaviors, stigma, and the impact of violence and abuse in HIV/AIDS prevalence in Puerto Rican women.

NCRR has funded 38 Clinical and Translational Science Award (CTSA) programs since 2006. While the program is relatively new, the CTSA centers are already committed to supporting research in women's health. The CTSA program at University of Colorado, Denver supports a Child and Maternal Health core that is focused on lifespan issues, starting with pregnancy and birth through early childhood and extending into adolescence and adulthood. Similarly, the University of Pittsburgh and the University of Ohio have established core activities in women's health. The CTSA program at the University of Pittsburgh is undertaking a number of clinical studies and research projects related to women's health, ranging from breast cancer therapeutic trials to genetic variation studies of sickle cell anemia to pregnancy disorders.

NCRR-funded General Clinical Research Centers (GCRC) programs support a number of projects related to women's health. The GCRC at Indiana University supports a number of studies on women's health. One of the projects focuses on menopause-related gene expression in a cohort of female twins with previously established genome scans. The GCRC supports two separate studies on bone loss in women. One of the studies addresses the effect of antiepileptic medications on bone loss in women on such medications. The focus of this study is to identify early signs and develop strategies to reverse these phenomena and thereby prevent bone loss. The other study is focused on the genetics of bone loss at the hip in women. Seven hundred and sixty pairs of sisters with known bone strength, and who have had 10 centimorgans (genome screens that have identified several genes that influence bone strength), are observed in this study. The GCRC at Indiana University also supports a project on the development of an instrument that will provide objective measurements of menopausal events (hot flashes) as a better means of providing observations on menopause than subjective recording of menopausal symptoms. Another project involves studies of the pharmacokinetics and pharmacodynamics of two antibiotics (ciprofloxacin and doxycycline). These drugs might be used in the event of an exposure to anthrax as a result of bioterrorism, particularly in elderly and lactating women.

The GCRC at the University of Minnesota supports a number of projects related to women's health. A study on the effects of maternal diabetes on the neurologic development and cognitive deficits in children resulting from these pregnancies is underway. In another project, preventive strategies for sex hormone-mediated cancers in women, such as breast cancer, are explored. The specific objectives are to evaluate the effects of fat (total fat and omega-3 fatty acid) intake on plasma and urinary sex hormone levels in post menopausal women, and down-stream effects of sex-hormone related products. In a separate study, the effect of aerobic exercise on oxidative stress in women is being explored in a randomized clinical trial.

NCRR Career Development Activities and Programs

NCRR continues to promote women in biomedical research through various training programs and workshops. NCRR organized and led a workshop on "Women in Biomedical Research: Best Practices for Sustaining Career Success" in collaboration with the Office of Research on Women's Health, and the NIH Working Group on Women in Biomedical Careers, which was held March 4, 2008. The workshop attracted over 500 registrants from government, academia, industry, and other organizations. The workshop featured speakers from academia, the private sector, professional organizations, the military, and NIH, who discussed their programs aimed at sustaining career success for women in biomedical careers.

The Division of Comparative Medicine (DCM) at NCRR participates in many NIH career development programs. 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 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 DCM K99/R00 awards have female Principal Investigators (PIs). In the K01 program, 45 percent of the 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 70 percent of the trainees in these programs.

The Division of Research Infrastructure at NCRR 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 Master of Public Health degree in a clinically relevant area. The goal of the program is to promote the development of trained and independent clinical and translational 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 cofunded by the NCRR, the National Center on Minority Health and Health Disparities, the National Heart, Lung, and Blood Institute, the National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Drug Abuse, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. In the CRECD Program, approximately 70 percent of the trainees are minority women.

The NCRR supports a Roadmap K12 Multidisciplinary Clinical Research Career Development Program 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 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.

The University of Pittsburgh CTSA program fosters a multidisciplinary mentoring program that is well represented by women, who represent 43 percent of K12 scholars. Other training and degree programs recruit as much as 50 percent women.

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 Fiscal Years 2007 or 2008. However, through its support of unique resources, NCRR contributes a significant portion of its budget to women's health and behavior research and continues to support initiatives developed by other components of NIH for such efforts.

Additional NCRR Activities in Women's Health

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 primate centers are engaging in multiapproach studies. Studies involve both understanding infection at the cellular level as well as therapeutics designed to prevent transmission of the disease. Studies are underway examining the immunology of the vaginal environment and the types of cells first targeted by viral particles to better understand the mechanism and events that occur at the initial infection stages. Researchers have also tested a novel type of microbicide in rhesus monkeys using the Simian immunodeficiency virus 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 6 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. Another method of blocking transmission involves using a small interfering RNA (siRNAi} microbicide. The siRNAs block the expression of the chemokine receptor 5, which plays an important role in initial transmission of the virus into the cell. Favorable early results from animal model testing show this may be a viable approach to producing a preventative microbicide.

Researchers at the NCRR-supported Center for HIV/AIDS Disparities Research at Meharry Medical College are conducting studies on an effective yet inexpensive topical microbi-

cide, beta cyclodextrin. 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. In addition, studies carried out in collaboration with Johns Hopkins School of Medicine in Baltimore have focused on examining acute toxicity associated with applying beta cyclodextrin-containing cream to the vaginal mucosa of macaques. The results of this first toxicity study in macaques are very encouraging and confirm extensive data in the literature supporting the safety of betacyclodextrin as a mucosally applied agent. These studies are highly relevant to health disparities in AIDS given the potential of microbicides to slow down the transmission of AIDS in women.

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 cervico-vaginal secretions, suggesting that repeated use of this microbicide is safe. Investigators in the GCRC at Mount 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 characterized by chronic anovulation and hyperandrogenism and is often associated with obesity and insulin resistance. Insulin sensitizers such as the thiazolidinediones have been shown to improve ovulatory function in women with PCOS. LY mice that possess a lethal yellow mutation (Ay) at the agouti gene locus exhibit many of the same hallmarks of PCOS, including ovarian dysfunction, obesity, and altered metabolic regulation. Investigators supported by NCRR's North Dakota IDeA Network of Biomedical Excellence used LY mice to examine the effect of pioglitazone, a thiazolidinedione, on gene expression in the ovaries. Pioglitazone (0.01 mg) or another vehicle was administered daily by gavage for 8 weeks. Whole-mouse genome DNA microarrays were used to analyze differential gene expression in the ovaries. Differential expressions of 27 genes were identified. These included genes associated with cell signaling, cell proliferation and survival, adhesion, and differentiation. The data suggest that the positive effects of pioglitazone in the ovary may involve mechanisms that are not directly related to insulin sensitivity.

RU-486 To Treat Ovarian Cancer

Among women in the United States, ovarian cancer is the eighth most common cancer and the fifth leading cause of cancer death. Women diagnosed in the earliest stages have a 5-year survival rate of nearly 93 percent, according to the American Cancer Society, but only about 20 percent of ovarian cancers are found before tumor growth has spread beyond the ovaries. Consequently, the majority of patients diagnosed with ovarian cancer require surgery to remove as much of the tumor as possible ("debulking"), followed by chemotherapy that includes a platinum compound such as cisplatin or carboplatin. However, platinum-based chemotherapy is hindered by the elevated toxicity of the drug, the development of chemoresistance, and the continuing proliferation of surviving tumor cells with the capacity to regenerate the tumor ("repopulation") between rounds of chemotherapy. While wait time between doses of chemotherapy allows for the bone marrow and kidneys to recover, repopulation between rounds of lethal chemotherapy is a major obstacle that hinders ovarian cancer treatment success. One strategy to stop tumor cell repopulation is to use a selective compound between courses of chemotherapy to inhibit repopulation of tumor cells.

Investigators at the Sanford School of Medicine of The University of South Dakota demonstrated in their laboratory that the steroid compound mifepristone (commonly

known as "RU-486") displayed a potent growth inhibitory effect in ovarian cancer, and thought that it should be effective in inhibiting cell growth and preventing ovarian cancer cell repopulation if given between rounds of cisplatin therapy. These scientists developed an in vitro methodology in which a culture of ovarian cancer cells was repopulated following multiple rounds of cisplatin therapy. They then demonstrated that mifepristone was helpful in preventing the repopulation of ovarian cancer cells occurring between platinum treatment intervals. In addition, they observed that chronic exposure to mifepristone after cisplatin treatment enhanced the anticancer effects of platinum-based chemotherapy compounds by sensitization to cisplatin-mediated killing. This is the first study to document an in vitro model system of ovarian cancer cell repopulation following cisplatin treatment and a therapeutic method to prevent ovarian cancer repopulation between platinum treatment intervals. Working as an inhibitor, mifepristone may be used for chronic growth inhibition therapy following lethal platinum agents to avoid disease recurrence. Furthermore, if it holds true in vivo, the strategy of adding mifepristone to the cisplatin chemotherapeutic schedule in ovarian cancer could reduce either the number of cisplatin cycles or the dose of cisplatin without losing efficacy in inhibiting tumor growth. Consequently, scheduling mifepristone treatment between courses of platinum-based therapy for ovarian cancer has potential to improve treatment success.

Hormonal Characteristics of the Perimenopausal Transition

In an ongoing effort, NCRR supports a study that uses cynomologous monkeys (Macaca fascicularis) exposed to 4-vinylcyclohexene diepoxide (VCD), which selectively destroys ovarian primordial and primary follicles, to establish a model for menopause. Emerging evidence suggests that menopausal conditions, such as cardiovascular disease, osteoporosis, and cognitive decline, originate in the premenopausal, especially during the several years that precede menopausal transition, and which are characterized by fluctuating and declining ovarian hormone production. 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.

Role of Hormone Replacement Therapies in Breast Cancer

Over 200,000 women in the United States are diagnosed every year with invasive breast cancer. Over 10 million postmenopausal women in the United States currently take hormone therapy, which may increase the risk of breast cancer. NCRR funds several studies that examine the role of postmenopausal hormone therapies in disease development and progression. Studies involve assessing the breast cancer risk profile of different postmenopausal hormone therapies and investigate the underlying mechanisms of oncogene transforming growth factor (TGFa).

Oncostatin M (OSM) is a pleiotropic cytokine produced by many cell types, including neutrophils and tumor-associated macrophages. OSM inhibits the proliferation of breast cancer cells in vitro, and for this reason it is being examined for its potential use in cancer treatment. It is hypothesized that OSM may cause growth arrest in breast cancer cells in vitro and may lead to the induction of angiogenesis in the tumor through production of vascular endothelial growth factor (VEGF). Such an induction of angiogenesis would counter the growth arrest properties of OSM by promoting angiogenesis-dependent breast cancer progression. The COBRE program at the University of Montana is studying the role of VEGF induction in breast cancer to correctly evaluate the potential of OSM as a clinical cancer treatment.

Insight into the Genomics of Endometriosis

Endometriosis is one of the most common gynecological diseases. At least 5.5 million women in North America alone have endometriosis, causing very painful cramps or periods, affecting the quality of a woman's life. In addition, about 30 percent to 40 percent of women with endometriosis are infertile, making it one of the top three causes for female infertility. Investigators at the South Dakota Biomedical Research Infrastructure Network in the Univer-

sity of South Dakota, Vermilion, are studying the genomics of endometriosis to understand pathology of the disease, and the gene expression in eutopic (internal, or inside the uterus) and ectopic (external, or outside the uterus) endometrium. They believe that the differential expression data thus obtained open new avenues for exploration of the pathology of endometriosis (e.g., a specific subset of inflammatory genes was up-regulated).

Study and Characterization of Xenoestrogen Effects on T–Cell Mediated Immunity

Researchers at the NCRR-supported Center for Environmental Health at Jackson State University are developing and characterizing in vitro immunobiological systems for studying the nature of the dose and exposure time relationship to low-dose adverse effects on T-cell mediated immunity, focusing on molecular markers of T-cell function and survival. Endogenous estrogens, androgens, and prolactin contribute to the sexual dichotomy of immune responses and the female preponderance of autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. Several environmental, hormonally active endocrine-disrupting compounds exist, are superimposed upon the endogenous pituitary-gonadal axis, and may contribute to the incidence or development of immune disease. Investigation of xenoestrogen immunomodulation may be critical to understanding potential low-dose adverse/no adverse effects on development of immune or autoimmune disorders, resistance to infection, cancer immune surveillance, or cell cycle/cell survival abnormalities that could lead to lymphoid malignancies. The researchers hypothesize that xenoestrogens suppress lymphoproliferation and increase lymphocyte apoptosis through suppression of bcl-2 and cyclin A and stimulation of p53, and suppress IL-2 and stimulate IL-4 or IL-10 through effects on nuclear transcription. These studies will characterize the effects and delineate xenoestrogen mechanisms of action on T-lymphocyte immune responses.

Racial Disparities in Bacterial Vaginosis and Its Influence on HIV-1 Acquisition

Researchers at Meharry Medical College are examining differences in host factors expressed by vaginal epithelial cells from African-American women with bacterial vaginosis (BV) that could predispose them to an increased risk for HIV-1 infection. BV is caused by a complex milieu of bacteria and is associated with multiple gynecological diseases and dysfunctions. BV has been associated with the heterosexual transmission of HIV, though its causative activity has not been conclusively shown. BV increases the transcriptional activity of HIV, and recent research suggests that it may affect the structural integrity of vaginal tissue, which in turn allows HIV to pass between vaginal epithelial cells, which otherwise prevent the virus's ability to gain access to CD4+ cells, HIV's preferred host cell type. BV and HIV affect women of African descent in great disproportion compared to other racial groups in the United States and globally. It is possible that African-American women have a genetic predisposition to contract BV, which in turn increases their vulnerability to HIV. This study aims to discover if such a genetic connection exists, and to explore with an in vitro model the interactions between a prominent BV bacterium and HIV. Long-term results from these studies may also provide an understanding of the mechanisms involved in BV pathogenesis as well as a direction for therapeutic strategies against BV/HIV.

Genetic Factors in Common Obstetric Disorders

Researchers at the University of Hawaii, John Burns School of Medicine, with support from NCRR's Research Centers in Minority Institutions program, have undertaken a study on Genetic Factors in Common Obstetric Disorders. Their research focuses on common multigene disorders with polygenic inheritance patterns, such as preterm labor, preeclampsia, gestational diabetes, placental abruption, and thromboembolism. These conditions are characterized by multiple etiologies, chronicity, fetal involvement, adaptive clinical manifestations, and gene–environment interactions. This work will increase understanding of genetic contributions to complex diseases, and it will

ultimately lead to more specific and effective management and treatment options for clinicians and their patients.

The Mechanism of Obesity-Related Vascular Dysfunction Among African-American Women

NCRR's Research Centers in Minority Institutions program supports research at the Morehouse School of Medicine on the mechanisms of obesity-related vascular dysfunction among African-American women. The relationship between diet and vascular function is important as it could serve as the basis for broader recommendations on appropriate dietary management of obesity/insulin resistance among African-American women. The research data support a significant role for endothelial progenitor cells and adipocytokines in vascular dysfunction and subsequent progression to atherosclerosis. Results have the potential for identifying primary prevention interventions for obesity, and for secondary prevention of insulin resistance-related complications.

Office of AIDS Research

Executive Summary

The Office of AIDS Research (OAR), located within the Office of the Director of the National Institutes of Health, was established in 1988 to coordinate the scientific, budgetary, and policy elements of NIH AIDS research. No other disease so thoroughly intersects every area of clinical medicine and basic scientific investigation, and crosses the boundaries of nearly every NIH institute and center (IC) as HIV/AIDS. AIDS is a multisystem and multiorgan disease, involving malignancies; opportunistic infections; and cardiovascular, neurological, gynecological, ocular, oral, dermatological, and gastrointestinal complications. It affects people across the lifespan from infancy to old age. Behavioral and biomedical interventions are required to prevent new infections. Consequently, nearly every IC is involved in conducting or supporting AIDS research. The NIH supports a comprehensive program of basic, clinical, behavioral, and social sciences research on HIV infection, its associated coinfections, opportunistic infections, malignancies, and other complications.

The diverse HIV/AIDS research portfolio demands an unprecedented level of scientific coordination and management of research funds. Through its unique, trans-NIH planning, budgeting, and portfolio management and assessment processes, the OAR ensures that NIH HIV/AIDS research dollars are invested in the highest priority areas of science. The OAR outlines and funds the roadmap for NIH AIDS research, facilitating a united research front against the pandemic.

Accomplishments

Women and Girls

Trans-NIH Plan for HIV/AIDS Research on Women and Girls

Each year, the OAR develops the comprehensive Trans-NIH Plan for HIV-Related Research. The plan is developed in collaboration with scientists from NIH, other government agencies, and nongovernmental organizations, as well as community representatives. During the planning process, the state of the science is reviewed, newly emerged and critical public health needs assessed, and scientific opportunities identified. The strategic plan is a unique and critical document, as it serves as the framework for developing the annual AIDS research budget for each IC; for determining the use of AIDS-designated dollars; and for tracking and monitoring all NIH AIDS research expenditures. OAR requires ICs to report all AIDS-related expenditures on a quarterly basis, to an OAR trans-NIH database, coded to the corresponding objectives of the plan, permitting OAR to review and analyze the total intramural and extramural AIDS research program. The plan also is used to inform the scientific community, the public, and the HIV/AIDS-affected community about the NIH priorities for HIV research.

The overarching themes of the plan are as follows:

- A strong foundation in the basic sciences
- Research to prevent and reduce HIV transmission, which includes vaccines, microbicides, and behavioral interventions

- Research to develop better therapies for those who are already infected.

The annual process culminates with the identification of the highest strategic priorities and critical research needs in each of the following scientific areas: natural history and epidemiology; etiology and pathogenesis; microbicides; vaccines; behavioral and social science; therapeutics; training, infrastructure, and capacity building; and information dissemination. The plan also addresses research in special populations, including racial and ethnic populations; research in international settings; and women and girls. A planning exercise is conducted each year specific to the section of the strategic plan addressing research on HIV in women and girls. The planning group includes representatives from the relevant NIH ICs and nongovernment expertise. Research priorities specific to women and girls are also included in the scientific areas throughout the plan.

In the most recent versions of the plan, issues unique to the research needs of women and girls include but are not limited to—

- Understanding of the physiology, biology, immunology, microbiology, and anatomy of the female genital tract and rectum of HIV-infected and HIV-uninfected women and girls and the impact on HIV risk and prevention
- Elucidating of the wide range of host–virus interactions that impact transmission and HIV acquisition
- Understanding the risk for and course of HIV infection and across the lifecycle in women and girls
- Understanding of the social and behavioral factors that impact risk and prevention
- Developing studies to ascertain the impact of sex on the acquisition, course, and prevention of HIV infection
- Enhancing basic behavioral and social science research on sex-based stigma and discrimination
- Exploring factors that influence the use and effectiveness of women-controlled methods for HIV prevention

Microbicides

To further enhance research in the area of microbicides, the OAR reorganized its scientific staff to add a new section dedicated to microbicide research and other issues relevant to women. This new OAR section has responsibility for coordinating, planning, budgeting, and facilitating trans-NIH microbicide research. It also has the responsibility of coordinating the NIH microbicides portfolio and elevating the scientific priority and funding for this important area within the prevention research agenda.

The OAR has utilized its unique budgetary authority 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 (ARIS) to track all trans-NIH investments in and expenditures on microbicide research.

Trans-NIH Plan for HIV/AIDS Research on Microbicides

Since 2003, the OAR has utilized its unique planning process to work with the NIH ICs and outside experts to delineate the research priorities for the microbicides section of the Trans–NIH Plan for AIDS Research. The most recent versions of the annual plan outline priorities that included, but were not limited to—

- Assess endogenous factors that can prevent genital tract and anal/rectal HIV and other sexually transmitted infection acquisition
- Evaluate the impact of exogenous potential microbicide agents on the integrity of the genital and anal/rectal tract and the risk for HIV/STI acquisition
- Understand the mechanisms of HIV transmission and endogenous and exogenous factors that influence those mechanisms of transmission across genital and anal/rectal mucosa
- Identify and standardize methodologies to assess preclinical and clinical safety and activity of potential microbicide agents
- Foster the development of combination approaches to microbicides such as chemical and physical barriers, multiple

compound agents, and agents with multiple mechanisms of action

- Promote innovative methods to develop and assess acceptable formulations and modes of delivery for potential microbicides
- Utilize knowledge and applications from multiple scientific disciplines, including the behavioral and social sciences in the study of potential microbicides
- Conduct social and behavioral sciences research in concert with microbicides clinical trials, including research on product use, acceptability, sexual behaviors, and the identification and development of reliable and valid behavioral tools and measurement techniques for use in trials

OAR-Sponsored Microbicide Initiatives

OAR has sponsored or supported a number of activities to focus increased emphasis on microbicide research and enhance research and prevention efforts in women and girls. These include, but are not limited to—

- Establishing the Microbicide Research Working Group, a nongovernment panel of experts to advise NIH and the microbicides field on approaches to move the research forward
- Providing continued key planning support and funding to the biennial International Microbicides Conferences, including providing funding for scholarships that allow researchers from developing countries to attend the conference
- Providing funding and working with the Office of Research on Women's Health, the National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Institute of Mental Health to implement a new microbicide research initiative designed to facilitate innovation in the field. The Microbicides Innovation Program (MIP) provides funding to researchers with unique ideas that will further the science of microbicides research. Thus far, the MIP has funded 15 grants that address pressing scientific questions in microbicides development research
- Providing support to the Microbicides Trials Network to assess the impact of the use of ARV-based microbicides in clinical trials on the level of ARV resistance in communities
- Devoting a number of meetings of the OAR Advisory Council to issues related to women and HIV/AIDS, including microbicides and prevention in women
- Convening and chairing the Trans-NIH Microbicide Research Coordinating Committee composed of representatives from relevant NIH ICs; and convening and chairing the Trans-U.S. Government Microbicides Research Coordinating Committee, including representatives from the Centers for Disease Control and Prevention, the United States Agency for International Development, the Food and Drug Administration, and the Department of Defense to share information, and facilitate collaboration, cooperation, and the efficient use of resources.

Federal Treatment and Prevention Guidelines

The U.S. Department of Health and Human Services issues Federal guidelines documents for the medical management of HIV infection and issues surrounding HIV infection. The guidelines are written, reviewed, and updated by Working Groups of HIV experts from across the country, including physicians, pharmacists, researchers, and HIV treatment advocates convened under the auspices of the OAR. The guideline documents can be accessed on the AIDSinfo Web site: http://www.aidsinfo.nih.gov/Guidelines.

The Working Groups develop separate guidelines for Treatment of Adults and Adolescents, Treatment of Children; Treatment of Pregnant Women and Prevention of Mother-to-Child HIV Transmission, and Prevention and Treatment of Opportunistic Infections.

Through all of these activities, OAR continues to show its leadership and commitment to the study of HIV in women.

OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

Executive Summary

In response to the need for health-related behavioral and social sciences research, Congress established the Office of Behavioral and Social Sciences Research (OBSSR) at the National Institutes of Health (NIH) in 1993. NIH already had a long history of supporting health-related behavioral and social sciences research, and the results of this work have contributed significantly to our understanding of the basic underlying mechanisms and treatment of mental and physical health and illness. Establishing an office focused specifically on the behavioral and social contributions to mental and physical health and well-being enables NIH to leverage existing efforts and develop synergy across multiple Institutes and disciplines.

Situated within the Office of the Director, OBSSR furthers the mission of NIH by emphasizing the critical role that behavioral and social factors play in health, health care, and well-being. With a budget of approximately $27 million, OBSSR serves as the focal point for the coordination and development of policies, goals, and objectives in the behavioral and social sciences at NIH. OBSSR's mission is to (1) integrate a behavioral and social sciences perspective across the NIH; (2) disseminate behavioral and social sciences research findings; and (3) provide advice to and communicate with the NIH Director, Congress, other government agencies, the research community, and the general public on matters regarding behavioral and social sciences research.

OBSSR's leadership is crucial at a time when exciting scientific opportunities, persistent public health needs, and emergent public health challenges face our Nation. The vision of the office is to bring together the biomedical, behavioral, and social science communities to work more collaboratively to solve complex pressing health challenges. Notable areas of research where OBSSR has led efforts include mind–body, behavior change, adherence, social and cultural dimensions of health, community-based participatory research, health literacy, and systems science approaches to health. The four core elements of OBSSR's vision for the future are as follows:

1. *"Next-generation" basic science*: OBSSR supports and facilitates the next generation of basic behavioral and social science research informed by breakthroughs in complementary areas such as genetics, informatics, computer sciences, measurement, methods, and multilevel analyses.

2. *Interdisciplinary research*: OBSSR facilitates collaborative research across the full range of disciplines and stakeholders necessary to elucidate the complex determinants of health and health systems challenges. Such collaborations yield new conceptual frameworks, methods, measures, and technologies that speed the improvement of population health.

3. *Systems-thinking approaches to health*: OBSSR stimulates systems thinking and modeling approaches to research that integrates multiple levels of analysis—from cells to society—required to understand the ways in which individual, contextual, and organizational factors interact over time to determine health status.

4. *Population impact*: OBSSR works with its NIH partners to identify key problems in population health where scientists, practitioners, and decisionmakers can work together to accelerate the translation, implementation, dissemination, and adoption of behavioral and social sciences research findings.

Initiatives

Since opening its doors, OBSSR has worked to achieve the goals of its authorizing legislation by effectively highlighting and supporting the scientific opportunities that exist in basic and applied behavioral and social sciences research. OBSSR has been actively addressing its congressional mandate and has encouraged research in the behavioral and social sciences by developing ideas for initiatives and gaining support for them within the NIH community. Although OBSSR does not have grantmaking authority, it has been active in organizing and funding (through transfers to NIH Institutes and Centers) a variety of trans-NIH research

programs. Therefore, the majority of our contributions to women's health research are in the form of cofunding grants administered by NIH Institutes and Centers.

In 2007, OBSSR cofunded the following four grants with a Women's Health component:

- *Achieving Energy Balance in Overweight Post Partum Teens* (R01CA121534; PI: Haire-Joshu, Debra). The purpose of this research project is to test an intervention designed to reduce overweight in postpartum teens.
- *Mind/Brain/Body Interactions in Stress-Related Disorders* (R24AT002681; PI: Mayer, Emeran A.). This is an infrastructure support grant to expand the breadth of the existing University of California, Los Angeles, Center for Neurovisceral Sciences and Women's Health.
- *Genes, Prenatal Drug Exposure, and Postnatal Environment: An Adoption Study* (R01DA020585; PI: Neiderhiser, Jenae M.). This research project explores how prenatal drug exposure impacts early child development.
- *Enhancing Support for Women w/Type 2 Diabetes: Followup* (R01HL077120; PI: Toobert, Deborah J.). This study tests the impact of a lifestyle intervention designed to reduce the risk of developing coronary heart disease in postmenopausal women with type 2 diabetes.

In 2008, OBSSR cofunded the following eight grants with a women's health component:

- *Alcohol Use Trajectories Among Older Adults* (R21AA016534; PI: Bobo, Janet). Among other aims, this project aims to examine sex and gender differences in alcohol use trajectories among older adults.
- *Genes, Prenatal Drug Exposure, and Postnatal Rearing Environment: An Adoption Study* (R01DA020585; PI: Neiderhiser, Jenae M.). This research project explores how prenatal drug exposure impacts early child development.
- *Achieving Energy Balance in Overweight Post Partum Teens* (R01CA121534; PI: Haire-Joshu, Debra). The purpose of this research project is to test an intervention designed to reduce overweight in postpartum teens.
- *An Examination of the Impact of Heterogeneity and Nonrandom Mixing on Smoking Behavior—Supplement to "Modeling the Impact and Costs of Radon Policies for Lung Cancer Control"* (RO1CA120126 (supplement); PI: Mendez, David). This project modifies a simulation model of the impact of smoking prevalence and radon exposure (by gender) on cancer incidence to include policy implications.
- *Neurobiological and Behavioral Consequences of Cocaine Use in Mother/Infant Dyads* (P01DA022446; PI: Johns, Josephine). This research project seeks to elucidate neurobiological and biobehavioral consequences of cocaine use (by mothers) and prenatal exposure (in infants) that may underlie poor mother–infant interactions.
- *Work, Family, Health, and Well-being Initiative* (U01HD051218; PI: Durham, Mary). The proposed study aims to assess the effects of a workplace intervention designed to reduce work–family conflict, and thereby improve the health and well-being of employees, their families, and their workplaces.
- *Family Research Consortium V: Transdisciplinary Consortium on Mental Health Co-Occurring Disorders and Families* (R13MH082592; PI: Luthar, Suniyas). This grant supports a transdisciplinary consortium of researchers focusing on co-occurring mental health disorders, with special attention to the role of mothers in caregiving and its implications for comorbid disorders.
- *Teenagers, Families, and Well-Being* (R03HD051629; PI: Kim, Su Yeong). This study tests whether fathers' and mothers' parenting independently mediates the relationship between generational dissonance and poor developmental outcomes in children or parents immigrating to the United States from China.

OFFICE OF DISEASE PREVENTION–OFFICE OF DIETARY SUPPLEMENTS

Executive Summary

The Office of Dietary Supplements (ODS) was created in 1995 in the Office of Disease Prevention, Office of the Director, National Institutes of Health (NIH), to meet the requirements of the Dietary Supplement Health and Education Act (DSHEA) of 1994. The DSHEA defined the purposes and responsibilities of ODS as follows:

Purposes

- To explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care; and
- To promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions.

Responsibilities

- To conduct and coordinate scientific research within NIH relating to dietary supplements and the extent to which the use of dietary supplements can limit or reduce the risk of diseases;
- To collect and compile the results of scientific research relating to dietary supplements, including scientific data from foreign sources;
- To serve as the principal advisor to the Secretary and to the Assistant Secretary for Health and provide advice to the Director of NIH, the Director of the Centers for Disease Control and Prevention (CDC), and the Commissioner of the Food and Drug Administration (FDA) on issues relating to dietary supplements. These issues include dietary intake regulations, the safety of dietary supplements, the claims characterizing the relationship between the use of dietary supplements and the prevention of disease or other health conditions and the maintenance of health, and scientific issues arising in connections with the labeling and composition of dietary supplement;
- To compile a database of scientific research on dietary supplements and individual nutrients; and
- To coordinate funding relating to dietary supplements for the NIH.

Subsequent congressional mandates directed ODS to develop a botanical research center initiative (1999), conduct evidence-based reviews of the efficacy and safety of dietary supplements (2001), and accelerate the validation of analytic methods and reference materials for dietary supplements (2004).

ODS developed its mission statement as part of its first strategic planning process in 1998:

The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

Initiatives

ODS Extramural Investments

ODS's guidelines and criteria for initiating, expanding, or otherwise modifying its extramural investments have reflected DSHEA and congressional mandates. These guidelines are a response to gaps in scientific knowledge, requests for research support from investigators, requests for information, and available resources. ODS extramural investments are categorized into four broad areas: research support, research tools, communication, and science–policy interactions. The Office's key activities are grouped into 15 programs under these 4 areas (see below); these 15 programs capture most of ODS's activities.

The budget allocation for each of the four areas is included in the description of the areas. These budget figures are based on an FY 2008 extramural budget of $22.3 million for grants, contracts, interagency agreements, and workshops. Another $5.2 million covers staff

salaries and other expenses associated with ODS administration. Ninety-seven percent of the Office's extramural budget supports research grants and research tools. Communication and science-policy efforts rely heavily on investments of ODS staff time and expertise rather than direct funding.

An ODS staff member is responsible for overseeing each of the 15 ODS programs that supports extramural research, and most ODS staff members are active in more than one program. Each program interacts with one or more stakeholder communities, including research investigators; educators and teachers; health practitioners; research and educational institutions; agencies of the Federal Government; dietary supplement, food, and related industries; media; consumer and public interest groups; and members of the public. The 4 areas and 15 programs are described briefly below and in more detail in Part 3 of this report.

Area 1: Research support—73 percent of ODS FY 2008 extramural budget

- **Research Grant Portfolio**
  This portfolio consists of grants administered by NIH Institutes and Centers that receive funding from ODS for research components related to dietary supplements. This investment supports the development of new knowledge on the health effects of dietary supplements.
- **Botanical Research Centers (BRCs)**
  ODS established six centers in response to a congressional mandate. The Office administers the centers in partnership with the National Center for Complementary and Alternative Medicine (NCCAM). These centers expand the scientific base for botanicals used as dietary supplements.
- **Training and Career Development**
  These extramural investments primarily consist of cofunding for selected NIH research training and career grants. These grants enable junior scientists to develop a research program related to dietary supplements.
- **Conferences and Workshops**
  ODS funds research conferences and workshops primarily through NIH grant mechanisms, although it also supports conferences and workshops initiated by NIH. These conferences and workshops bring together key scientists to discuss and define the research needs for various dietary supplements.

Area 2: Research tools—24 percent of ODS FY 2008 extramural budget

- **Analytical Methods and Reference Materials (AMRM)**
  ODS established this program in response to a congressional mandate and administers it primarily through contracts originated by ODS. Supporting the development of analytic methods and reference materials for dietary supplements has been key to making informative studies of dietary supplements possible.
- **Surveys of Dietary Supplement Use**
  ODS provides intellectual and financial support to Federal agencies conducting national nutritional surveys that include use of dietary supplements.
- **Dietary Supplement Databases**
  ODS provides intellectual and financial support and leadership to Federal agencies that are establishing databases to enable the interpretation of survey data on public nutrition habits and use of dietary supplements. ODS and its Federal partners at the United States Department of Agriculture (USDA), CDC, National Library of Medicine, and FDA have created a dataset of dietary supplement ingredients and are developing a comprehensive database of information on supplement labels.
- **Evidence-Based Reviews**
  In response to encouragement from Congress, ODS provides intellectual and financial support, primarily to the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, to conduct reviews that are critical to determining the research needs for selected dietary supplements. These reviews are published on the AHRQ Web site and in peer-reviewed journals. Evidence-based reviews are key to identifying the status of scientifically validated knowledge about

dietary supplements and the important gaps in research.

Area 3: Communications—Less than 2 percent of ODS FY 2008 extramural budget; Communications are an integral part of ODS's ongoing outreach

- **Communications**
  ODS's communication activities include a broad spectrum of outreach activities, such as the ODS Web site, exhibits, and public information pieces related to dietary supplements.

- **Computer Access to Research on Dietary Supplements (CARDS)**
  ODS developed this consumer-friendly, Internet-based database in response to the DSHEA mandate to compile a database of scientific research on dietary supplements. CARDS contains information on federally funded research projects pertaining to dietary supplements.

- **International Bibliographic Information of Dietary Supplements (IBIDS)**
  ODS developed this consumer-friendly, Internet-based database in response to the DSHEA mandate to collect and compile the results of scientific research related to dietary supplements. IBIDS provides access to bibliographic citations and abstracts from published, international, and scientific literature on dietary supplements.

- **Federal Dietary Supplement Working Group**
  ODS established the Federal Dietary Supplement Working Group in 2005 to share information and discuss issues related to dietary supplements among Federal agencies.

Area 4: Science-Policy Interactions—About 1 percent of ODS FY 2008 extramural budget. These programs reflect the philosophy that good policy is founded on good science. ODS furnishes expertise in nutritional sciences to address public health issues related to dietary supplements.

- **Vitamin D Initiative**
  This initiative is an evolving partnership with NIH Institutes and Centers and other Federal agencies through the vitamin D Federal Working Group to address the research gaps related to vitamin D.

- **Dietary Supplement Use in the Military**
  This partnership with the DoD is evaluating the impact of dietary supplement use by military personnel.

- **Dietary Reference Intakes**
  ODS supports Federal programs to evaluate the reference standards for intakes of nutrients, including vitamins and minerals.

Evaluating ODS Investments

A comprehensive approach to the ongoing review and evaluation of ODS activities was an important component of the 2004–2009 strategic plan, and ongoing evaluations continue to be a high priority for ODS. ODS held a public meeting in 2005 to engage stakeholders in evaluating its strategic plan. During this meeting, representatives of the ODS stakeholder community and other interested parties identified emerging needs and opportunities. A synopsis of the recommendations, presentations, and comments offered at this meeting are available at: http://ods.od.nih.gov/Strategic_Planning_2004-2009/Public_Meeting_2005.aspx.

Another step in evaluating ODS activities involved analyses of needs and opportunities at ODS by external scientific panels and extramural contractors. These evaluations are described in the ODS program summaries.

To promote ongoing review and evaluation of ODS activities, ODS established the Federal Dietary Supplement Working Group and coordinated the group's first meeting in 2005. The working group enhances communications between ICs represented by the group and other Federal agencies interested in dietary supplement research. The working group meets twice yearly and serves as a forum for discussing dietary supplement-related programs, initiatives, and topics of common interest.

In preparation for the development of its strategic plan for the next 5 years, ODS is reviewing the key activities established to

achieve the five goals listed in its previous strategic plan.

Goal 1. Expand the evaluation of the role of dietary supplements in disease prevention and reduction of risk factors associated with disease.

ODS cofunded grants for research on a broad range of topics related to disease prevention or reduction of risk factors for disease. Examples include the following:

- A clinical trial to evaluate the role of supplemental folic acid in reducing vascular complications following transplantation;
- A clinical trial to evaluate the role of supplemental vitamin D in reducing the progression of knee arthritis;
- An evaluation of whether supplementation with chromium picolinate can reduce insulin resistance in obese individuals at risk of type 2 diabetes;
- A study of the role of supplemental vitamin K in preventing fractures in children with cerebral palsy or other physical disabilities;
- A study of the mechanisms by which Saint John's wort affects the way that people respond to many prescription drugs;
- A study of the efficacy of nighttime melatonin supplementation as a countermeasure to the side effects of beta-blockers; and
- A clinical trial to evaluate the long-term effects of supplemental soy protein on the progression of atherosclerosis in postmenopausal women.

ODS collaborated with other ICs in supporting funding opportunities for research on the roles of dietary supplements in ameliorating various disease states, such as the Request for Applications for studies on "Mechanisms of Alcoholic and Nonalcoholic Fatty Liver."

ODS cofunded the training and career development of junior scientists with research interests relevant to dietary supplements. Some of these awards enabled selected NIH intramural scientists to expand their research into dietary supplements.

Goal 2. Foster research that evaluates the role of dietary supplements in maintaining and improving optimal physical and mental health and performance.

ODS staff have performed the following:

- Initiated the Vitamin D Federal Working Group to develop a vitamin D initiative that addresses research gaps related to the role of vitamin D in maintaining optimal health; an evidence-based review and ODS-cosponsored workshops identified these gaps;
- Collaborated with the U.S. Army Research Institute of Environmental Medicine in evaluating the use and safety of dietary supplements among soldiers;
- Partnered with National Health and Nutrition Examination Survey (NHANES) staff to evaluate the use of dietary supplements by Americans; and
- Partnered with the CDC's National Health Interview Survey to study motivations for using dietary supplements.

In addition, ODS and its Federal partners have provided funds to the Institute of Medicine to evaluate the new Dietary Reference Intakes for key vitamins and minerals.

Examples of research cofunded by ODS include the following:

- The role of dietary supplements in promoting health, such as the role of specific dietary supplements in infant development and promoting a healthy pregnancy;
- The safety and efficacy of dietary supplements, such as a comparison of the efficacy of calcium phosphate to that of calcium carbonate in promoting bone health and a study of the role of calcium supplements in regulating body weight;
- Potential risks of dietary supplements in certain populations, such as an evaluation of the adverse effects of iron supplementation in HIV-infected pregnant women; and
- The role of dietary supplements in maintaining health through a clinical trial

in partnership with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to examine the role of saw palmetto (Serenoa repens) and pygeum (Pygeum africanum) in alleviating lower urinary tract symptoms in men with benign prostatic hyperplasia.

Goal 3. Stimulate and support research to further understanding of the biochemical and cellular effects of dietary supplements on biological systems and their physiological impact across the lifecycle.

Studies on the mechanisms and impact of dietary supplements cofunded by ODS include the following:

- A study of how bitter melon juice improves the hepatic insulin signaling cascade and activates the mammalian longevity gene sirtuin (Sirt1) to prevent or treat diabetes;
- A study of whether selected gene–environment interactions are risk factors for obesity in the Yup'ik people by assessing the role of polyunsaturated fatty acids in regulating gene expression;
- A study of how trans-10, cis-12 conjugated linoleic acid reduces the triglyceride content of human adipocytes and the potential metabolic consequences of this activity, especially on the reduction of obesity; and
- An NIH intramural project on the ability of polyphenols to improve metabolic and cardiovascular health.

Goal 4. Promote and support the development and improvement of methodologies appropriate to the scientific study of dietary supplement ingredients.

- ODS's AMRM program greatly expanded the development of approximately 18 validated analytical techniques and approximately 30 reference materials for identifying specific dietary supplement ingredients to meet the needs of investigators.
- The BRCs disseminated the results of new research on the chemical and biological characterization of botanicals as dietary supplements through a workshop at the 2007 Experimental Biology meeting as well as through peer-reviewed publications.
- ODS has partnered with AHRQ and its Evidence-Based Practice Centers to award contracts for evidence-based reviews of six key dietary supplements: omega-3 fatty acids, ephedra, vitamin D, soy, B vitamins and berries, and multivitamin/mineral products.
- ODS has fostered the improved measurement of dietary supplement and nutrient intakes in population surveys through partnerships with the USDA and CDC's NHANES to support the development of ingredient and label-based databases for dietary supplements.

Goal 5. Expand and conduct outreach efforts that inform and educate the public, healthcare providers, and scientists about the benefits and risks of dietary supplements.

- ODS serves as a key information resource for DHHS and other Federal agencies through its comprehensive Web site and the Federal Dietary Supplement Working Group.
- ODS promotes the transfer and translation of information about dietary supplements in several ways, including providing extensive information on dietary supplements on the ODS Web site (http://ods.od.nih.gov) and in peer-reviewed journal articles, offering collaborative workshops on dietary supplements and publishing the reports on the ODS Web site, and supporting evidence-based reviews and publishing the results on the Office's Web site.
- ODS has enhanced access to ODS information and databases by improving its Web site design. ODS has enhanced and expanded the two databases mandated by the DSHEA, IBIDS and CARDS, for Web accessibility.
- ODS has expanded its communication activities by, for example, adding media resources to the ODS Web site, improving exhibition displays for national meetings, and posting resources on its Web site from

the AMRM program. To "teach the teachers" about dietary supplements, ODS staff designed and offered an annual weeklong practicum on dietary supplements for academic, Federal, and industry researchers.

Office of Disease Prevention–Office of Medical Applications of Research

Executive Summary

The Office of Medical Applications of Research (OMAR) works closely with the National Institutes of Health Institutes, Centers, and Offices to assess, translate, and disseminate the results of biomedical research that can be used in the delivery of important health services to the public. A major responsibility of OMAR is the coordination of the NIH Consensus Development Program. Under this program, OMAR organizes major conferences on complex issues of medical importance to healthcare providers, patients, and the general public. These conferences are open to the public, broadcast on the Internet, and offered free of charge to participants. The NIH Consensus Statements and State-of-the-Science Statements produced by these conferences are disseminated widely to healthcare practitioners, policymakers, patients, the media, and the general public. The diseases, conditions, and treatment issues addressed by Consensus Development and State-of-the-Science Conferences often disproportionately affect women or minority groups.

An evidence-based assessment is prepared for each conference topic. The assessment involves a systematic review of the medical literature to define the state of medical practice or science by using rigorous criteria for categorizing the strength of the available evidence. OMAR routinely meets with scientists, clinicians, representatives from other Federal health agencies, and public representatives to discuss methods to further enhance the mission of the Office.

In addition, through the Medicine in the Media program, OMAR seeks to enhance the ability of journalists to critically assess scientific reports and medical findings using an evidence-based approach, and to add context to make reports on research in the popular media more useful to readers. A majority of participants in each year's course are women, many of whom report for predominantly female audiences.

Initiatives

NIH State-of-the-Science Conference: Prevention of Fecal and Urinary Incontinence in Adults, December 10–12, 2007

Although fecal incontinence affects individuals of all ages, it is more common in women and older persons. Urinary incontinence can affect persons of all ages and is most common in childbearing women and older men and women. An independent panel examined the available evidence on the prevention of fecal and urinary incontinence in adults. The resulting conference statement will help inform both the research community and general public, and shape the research agenda for this embarrassing and undertreated condition. The panel's findings pertinent to women include the following:

- It has been difficult to identify persons at risk for or affected by incontinence because the condition is often not reported or diagnosed. Prevention of fecal and urinary incontinence has been hindered by limited research and incomplete knowledge about the biological causes and interacting social and environmental factors.
- Routine episiotomy is the most easily preventable risk factor for fecal incontinence. Risk factors for both fecal and urinary incontinence include female sex, older age, and neurologic disease (including stroke). Increased body mass, decreased physical activity, depression, and diabetes may also increase risk.
- Pelvic floor muscle training and biofeedback are effective in preventing and reversing fecal and urinary incontinence in women

for the first year after giving birth, and these approaches may also prevent or reduce urinary incontinence in older women and in men undergoing prostate surgery. Fecal and urinary incontinence may be prevented by lifestyle changes, such as weight loss and exercise.

- Efforts to raise public awareness of incontinence and the benefits of prevention and management should aim to eliminate stigma, promote disclosure and care seeking, and reduce suffering. Organized approaches to improving clinical detection of fecal and urinary incontinence are needed and require rigorous evaluation.

The Office of Research on Women's Health was a nonfunding cosponsor of this conference:

NIH Medicine in the Media courses: April 12–14, 2007—Bethesda, MD; May 5–7, 2008—Hanover, NH

The NIH Medicine in the Media course is a free annual training opportunity to help develop journalists' and editors' ability to evaluate and report on medical research. The course examines the challenges and opportunities inherent in the process of communicating the results of medical research to the public. Stressing an evidence-based approach and reexamining intuitive beliefs about medicine, the course prepares participants for the crucial task of interpreting and evaluating research findings, including understanding statistics, selecting stories that hold meaningful messages for the public, and placing them in appropriate context. The course faculty includes experts in medical research and medical journalism. Sessions are interactive, with hands-on opportunities to apply lessons learned, and incorporate journalists' special perspectives on the public's need for useful medical knowledge.

Participants in the 2007 and 2008 courses included writers and editors from *Prevention*, *Ladies' Home Journal*, *Woman's Day*, *Health*, *Real Simple*, and *Good Housekeeping* magazines, and the *Harvard Women's Health Watch* newsletter—all of whose audiences are predominantly female. Moreover, women make up a disproportionate share of the audience for health news across all media.

OFFICE OF DISEASE PREVENTION– OFFICE OF RARE DISEASES

Executive Summary

A rare disease is a disease or condition affecting fewer than 200,000 people in the United States. Although the prevalence of each of the approximately 7,000 known rare diseases may be quite small, as many as 25 million to 30 million people in the United States have a rare disease. About 80 percent of rare diseases are genetic. The mission of the Office of Rare Diseases Research (ORDR) is to coordinate, stimulate, and support research on rare diseases and respond to the needs of patients and their families. The major activities of the ORDR include the following:

- Collaboration with the National Institutes of Health Institutes and Centers (ICs) to fund the Rare Diseases Clinical Research Network (RDCRN) with approximately 50 rare diseases at 70 sites across the Nation and in other countries;
- Support for the Collaboration, Education and Genetic Test Translation for Rare Genetic Diseases Program that moves tests from the research laboratories to Clinical Laboratory Improvement Amendments-certified clinical settings, thereby making the genetic tests available to the public;
- Collaboration with NIH ICs and other entities nationally and internationally to stimulate rare diseases research by supporting scientific conferences to identify where research scientific opportunities exist and to stimulate research;
- Support for an intramural research collaboration with the National Human Genome Research Institute (NHGRI) that includes a focus with the NIH Clinical Center Hospital on studying undiagnosed rare diseases;
- Support with NHGRI of the Genetic and Rare Diseases Information Center (GARD)

that provides needed information to patients and their families, health professionals, researchers, and the public; and

- The Undiagnosed Diseases Program at the NIH Clinical Center is trans-NIH in scope. It is organized by the NHGRI, the NIH ORDR, and the NIH Clinical Center. Many medical specialties from other NIH research centers and institutes contribute expertise needed to conduct the program, including endocrinology, immunology, oncology, dermatology, dentistry, cardiology, and genetics, which are represented among more than 35 senior attending physicians who may participate in the initiative.

Accomplishments

The Rare Diseases Clinical Research Network

Since FY 2003, the ORDR has collaborated with NIH ICs, including the National Center for Research Resources, National Heart, Lung, and Blood Institute (NHLBI), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Disorders, and the National Institute of Neurological Disorders and Stroke, to support the Rare Diseases Clinical Research Network (http://rarediseasesnetwork.epi.usf.edu/).

On April 19, 2007, NIH published a Notice of Intent to announce a forthcoming Request for Applications (RFA). The RFA was open to current consortia as well as to new applicants (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-062.html). On February 8, 2008, NIH released the RFA Rare Diseases Clinical Research Consortia for the RDCRN (U54) (http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08-001.html). Grant awards will be made in the summer of 2009.

In the RDCRN, for FY 2007 and FY 2008, studies of rare diseases of particular interest to women's health included those described next.

Rett Syndrome

The course of Rett syndrome, including the age of onset and the severity of symptoms, varies from child to child. Before the symptoms begin, however, the child appears to grow and develop normally. Then, gradually, mental and physical symptoms appear. Hypotonia (loss of muscle tone) is usually the first symptom. As the syndrome progresses, the child loses purposeful use of her hands and the ability to speak. Other early symptoms may include problems crawling or walking and diminished eye contact. The loss of functional use of the hands is followed by compulsive hand movements such as wringing and washing. The onset of this period of regression is sometimes sudden. The consortium is studying individuals fulfilling consensus clinical criteria for Classic or Variant Rett Syndrome or individuals with MeCP2 mutations who do not meet the clinical criteria in a natural history study.

Congenital Adrenal Hyperplasia (CAH)

The most common form of CAH results from a deficiency of the enzyme 21-hydroxylase. There are two forms of 21-hydroxylase congenital adrenal hyperplasia, a severe form, termed "classical CAH," with profound 21-hydroxylase deficiency, and a mild form, called "nonclassical CAH," which has a lesser deficiency of 21-hydroxylase. The classical form of CAH may be life threatening if untreated. 21-hydroxylase deficiency in the classical forms, both salt wasting and simple virilizing, results not only in reduced secretion of cortisol, but also increased secretion of male-like hormones from the adrenal gland. These male-like hormones masculinize the female fetus in utero so that the genitalia are ambiguous. CAH can be diagnosed prenatally following amniocentesis or chorionic villus sampling. Classical CAH can be treated prenatally to prevent masculinization of the genitalia of affected females.

11b-Hydroxylase deficiency is the second most common form of CAH. Like 21-hydroxylase deficiency, it causes masculinization in the female fetus, but it also causes high blood pressure. It is diagnosed by hormone testing and DNA analysis and is treated by steroid

hormone replacement. Like 21-hydroxylase deficiency, it can be prenatally diagnosed and treated, and has severe and mild forms. Consortia studies include a natural history study; a study to determine whether differences in other genes can modify the clinical course of adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency; and long-term outcome in offspring and mothers of dexamethasone-treated pregnancies to determine whether prenatal treatment with dexamethasone has any long-term effects on those who were treated as fetuses and who are now 12 years and older.

Lymphangioleiomyomatosis (LAM)

LAM affects almost exclusively women of childbearing age. LAM is typically slowly progressive. There are currently no proven therapies for LAM. The current protocol 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.

Progressive Familial Intrahepatic Cholestasis (PFIC)

PFIC is passed from parents to children through genes. For a child to get PFIC he/she must receive two changed copies of a gene, one each from the mother and the father. These changes in genes are called mutations. Carrying one changed copy of a gene and one normal copy of a gene does not usually cause disease, and is relatively common. Thus parents of children with PFIC usually have no liver or other medical problems. One exception to this may be that women with one changed PFIC gene may develop liver disease during pregnancy. The purpose of the current longitudinal study of genetic causes of intrahepatic cholestasis is to learn about the natural history and progression of PFIC and three other cholestatic liver diseases.

Takayasu's Arteritis

One of the vasculitides, Takayasu's Arteritis (TAK), is a rare form of vasculitis affecting medium- and large-sized blood vessels, primarily of the aorta and its large branches. Inflammation of the large blood vessels may cause segments of vessels to weaken and stretch, resulting in an aneurysm (weakening of the vessel wall) or, more commonly, the inflammation of the vessel wall leads to thickening and subsequent partial blockage or complete blockage of the artery. These blockages can result in the surrounding tissues being deprived of an adequate blood supply, which causes mild to very severe problems, including cramping in the arms and legs, kidney damage with severe hypertension, strokes, or heart attacks. Many other symptoms and problems can be seen in TAK, including joint pains, fevers, fatigue, and others. Takayasu's arteritis generally first strikes people when they are young (in teens and people in their 20s or 30s), and is much more common in women than men. It is also more common in Asia. The cause of Takayasu's Arteritis is unknown.

Currently, there are three studies underway: a longitudinal protocol for TAK; an imaging protocol for magnetic resonance and positron emission tomography in TAK to compare x-ray-like tests that would not be a part of regular medical care (PET/CT) with x-ray-like tests that are a part of a regular care (MRI). The third study determines if the medication abatacept is safe and effective in giant cell arteritis as well as Takayasu's Arteritis.

Antiphospholipid Antibody Syndrome (APS)

APS is an autoimmune disease. In this disorder, antibodies, which are found in the blood and normally fight off infections, are instead turning against the body's own normal clotting mechanisms. These antibodies make people more prone to certain problems, such as clots in the deep veins in the arms and legs, known as deep vein thrombosis or in the lung, known as pulmonary embolism. People with APS can also develop clots in their arteries, known as heart attacks or strokes. In certain women, these antibodies can cause recurrent pregnancy loss. The treatment of choice for patients with APS who have had a blood clot is anticoagulant therapy (blood thinner). For women with APS and recurrent miscarriages

who have not had a prior blood clot, the use of anticoagulant therapy during the pregnancy may increase the likelihood of a successful outcome. Some individuals may have elevated antiphospholipid antibodies, but have no clinical manifestations of the syndrome. These individuals do not need anticoagulant therapy, but studies are ongoing to evaluate whether an aspirin a day might be beneficial for these individuals. The purpose of the current study genetics of APS is to find the genes that cause APS. While part of the RDCRN, this project is fully funded by NHLBI.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is a rare blood condition characterized by a low platelet count and the widespread formation of small blood clots throughout the circulation. Platelets are the smallest of the cells in the blood, and they function as tiny corks that form a plug to stop bleeding. In general, a very low platelet count, referred to as thrombocytopenia, is associated with bleeding problems, and these patients may present with large bruises. These patients also develop clotting complications, involving the brain, kidneys, and virtually any organ in the body.

TTP appears to occur more frequently in women than in men. The primary treatment for TTP is a process called plasma exchange, during which a patient's plasma (the liquid part of the blood) is removed and replaced with plasma from blood donors. This treatment is very effective and life saving in the majority of patients. Other treatments that have been used include steroids, aspirin, and certain chemotherapy agents. In a subset of patients, the TTP may recur after stopping treatment. These patients may require treatment to be restarted, or a different type of therapy may become necessary. The study incidence of thromboembolic events in patients with antibodies to heparin-PF4 after cardiac bypass will determine how often heart surgery patients who receive heparin develop an immune response (heparin-induced thrombocytopenia) that leads to clots forming in different parts of the body. While part of the RDCRN, this project is fully funded by NHLBI.

Conferences and Workshops

In 2007, conferences cofunded by ORDR with a focus on women's health included—

- "Profiling of Immune Response to Guide Cancer Diagnosis, Prognosis, and Prediction of Therapy," which included sessions on T regulatory T cells as predictors of survival in ovarian cancer and Interleukin-6 polymorphism as predictor of outcome in high-risk breast cancer. The meeting highlighted the clinical significance of immunologically regulated molecules as markers and validation approaches for basic and clinical researchers interested in marker development.
- "The Status and Future of Acupuncture Research: 10 Years Post-NIH Consensus Conference," which synthesized the current status of the research evidence base for the efficacy of acupuncture for a number of diseases, including rare diseases, through plenary sessions, breakout sessions, and workshops. Overall, the goal was to strengthen the evidence base for acupuncture therapy. Sessions included Acupuncture in Female Infertility–Basic and Clinical Studies, and Functional Neuroimaging of Acupuncture in Fibromyalgia: Insights into Mechanisms and Clinical Trial Design.
- "Stillbirth Definition and Classification System: Developing an International Consensus" gathered international experts and researchers to address the definition of stillbirth, the goals of a stillbirth classification system, and the necessary criteria for assigning cause of death. The development of an agreed-upon classification system should facilitate analyses of larger amounts of stillbirth information with greater sample sizes, allowing for more robust conclusions from the international research currently conducted on stillbirth.
- The 2007 LAM Foundation Lymphangioleiomyomatosis International Research Conference brought together basic scientists working in different disciplines pertinent to LAM with pharmaceutical experts from industry, clinical investigators, patients, and other advocates to advance research

on understanding and treating LAM. The ultimate goal was to identify new targets for therapeutic interventions.

In 2008, conferences with a focus on women's health included—

- "Mental Health Promotion and Injury Prevention in the Context of a Diverse, Transforming China" addressed issues including (1) risk factors for suicide and injury mortality in Chinese women, (2) the implications of rapid economic and technological development for risk of suicide and injury in men and women, and (3) ethnic differences.
- "Orphan Mechanisms of Primary Ovarian Insufficiency: Passion for Participatory Research." Galactosemia is a rare metabolic disorder that is associated with the development of primary ovarian insufficiency. Despite appropriate dietary restriction of galactose, many girls and young women develop primary ovarian insufficiency. Participants addressed the following: mechanisms of ovarian toxicity related to galactosemia; induction of puberty in girls with galactosemia who have primary ovarian insufficiency; hormone replacement in women with galactosemia who have primary ovarian insufficiency; mental health aspects of primary ovarian insufficiency as it relates to galactosemia; and pregnancy in women with galactosemia.
- "Cognitive and Neuroplastic Changes Following Surgical Hemispherectomy and In Utero Strokes Affecting an Entire Hemisphere." The main goal of this conference was to ascertain the state-of-the-art in hemispherectomy outcome as a precursor to preparing a protocol to test four assumptions. To that end, leading neurologists, neurosurgeons, and cognitive neuroscientists were invited to discuss their experience with patients receiving hemispherectomies.
- "Preconception Care Research: Improving Birth Outcomes and Reproductive Health Conference" brought together a broad spectrum of experts, including clinicians and basic and behavioral scientists, to define a multidisciplinary framework for developing a research agenda in preconception care research.
- "The Fifth Scientific Meeting of The TMJ Association: Can Studies of Co-Morbidities with TMJDs Reveal Common Mechanisms of Disease?" The specific aims of this meeting were to identify similarities across these diseases, finding common pathways that could elucidate the underlying pathophysiology of temporomandibular joint and muscle disorders and point to novel targets for diagnosis and treatment.

Genetic and Rare Diseases Information Center

The ORDR supports, with the NHGRI, the Genetic and Rare Diseases Information Center. GARD provides information to patients and their families, health professionals, researchers, and the public. By the end of FY 2008, GARD had responded to a total of approximately 23,000 inquiries since its inception in September 2001. A customer service satisfaction survey showed that typically, information center customers are White, non-Hispanic, English-speaking females between the ages of 31 and 40 with a postgraduate education. Information center customers requested information for themselves and for family members or friends who could be male or female.

To reach an even wider audience, GARD now focuses on making available questions and answers on the ORDR Web site in addition to services by e-mail, telephone, or letter. The GARD section of the ORDR Web site has received an average of 30,000 visits per month in addition to continued inquiries by e-mail, telephone, and letter.

OFFICE OF STRATEGIC COORDINATION

Executive Summary

The National Institutes of Health (NIH) Reform Act of 2006 established the Common Fund to "identify research that represents important areas of emerging scientific opportunities, rising public health challenges, or

knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between 2 or more national research institutes or national centers, or would otherwise benefit from strategic coordination and planning." Programs funded by the Common Fund to date are known collectively as the NIH Roadmap. In addition to the parameters established by the Reform Act, all Roadmap programs are expected to address fundamental roadblocks to a wide spectrum of health research and are therefore not disease specific. In addition, Roadmap programs are expected to be stimulatory and therefore short term (5–10 years) in nature; followup funding for research in any of the Roadmap areas is expected to come under the purview of the Institutes and Centers.

All Roadmap programs have the potential to contribute to research on women's health. In 2007 and 2008, three programs had significant Women's Health components: the Interdisciplinary Research Program; the Human Microbiome Program; and the Metabolomics Initiative of the Building Blocks, Biological Pathways, and Networks Program.

The Roadmap Interdisciplinary Research Program promotes interdisciplinary research and training efforts through several initiatives, including the Interdisciplinary Research Consortia initiative funded in September 2007. There are nine interdisciplinary research consortia, each with a unique scientific challenge requiring an interdisciplinary approach. One of these consortia is focused on oncofertility, a topic of high relevance to women's health because it deals with the preservation of fertility in women with a cancer diagnosis.

The Human Microbiome Program develops resources to facilitate research into the microbes, including bacteria and viruses that inhabit our bodies. Although it has been appreciated for years that microbes cause disease, it has become clear only recently that microbes can help us maintain health. The genetic composition of the multitude of microbes that inhabit us is termed "the microbiome." To determine whether healthy people have a common microbiome, and to decide whether changes in one's microbiome correlate with changes in one's health status, a reference set of several hundred microbial genomes is needed. The program will isolate and characterize microbes from the vagina, as well as four other body sites.

The Roadmap Building Blocks, Biological Pathways, and Networks Program consists of two initiatives designed to develop new technologies to allow molecular events in cells to be studied in high resolution in real time, one of which has contributed to research on women's health in 2007 and 2008. The Metabolomics Initiative is developing and applying technologies to detect comprehensive profiles of metabolites, including carbohydrates, lipids, and amino acids within a single cell or even a specific part of a single cell. These improved methods can detect metabolic differences between normal and diseased cells, helping to predict the human body's response to disease, injury, or infection. The Metabolomics Initiative supports a research project focused on identifying the metabolic changes that make certain breast and ovarian cancer cells more able to spread.

Accomplishments

The Roadmap Interdisciplinary Research Program

As part of the Roadmap Interdisciplinary Research Program, the mission of the Oncofertility Research Consortium is to preserve fertility in women with a cancer diagnosis. Progress has been made toward growing and maturing nonhuman primate follicles in vitro. Less mature (preantral) nonhuman primate follicles have been cultured to the more mature (antral) follicle stage in a three-dimensional structure (Zelinski, et al. Society for the Study of Reproduction 41st Annual Meeting 633, 2008). This advance in a nonhuman primate model is significant because it provides the groundwork for preserving fertility in prepubescent girls who cannot undergo ovarian hormone stimulation protocols and for women with estrogen-responsive breast cancer for which these protocols are dangerous.

The Roadmap Human Microbiome Program

The Human Microbiome Program was approved in 2007 to sequence 600 microbial genomes of microbes that inhabit five body sites, including the vagina. The Common Fund provided "jumpstart funds" in 2007 to supplement four NIH-supported sequencing centers to begin sequencing the genomes of these microbes. In 2008, dozens of microbial genomes were sequenced, including several from microbes that inhabit the vagina. The reference sequences will be used by many researchers, including those that will be funded by the Human Microbiome Program to examine whether changes in the human microbiome correlate with changes in health and disease.

The Roadmap Building Blocks, Biological Pathways, and Networks Program

The general aim of metabolomics is to identify, measure, and interpret the concentration, activity, or flux of metabolites in cells, tissues, and other biosamples such as blood, urine, and saliva. This mechanistic understanding of pathways and networks should eventually lead to better diagnoses and disease treatments. In RO1CA132630, Dr. Benjamin Cravatt proposed a highly innovative plan to identify both new metabolites and new metabolic pathways altered in aggressive breast and ovarian cancers. In 2007 and 2008, he succeeded in discovering new metabolic pathways that contribute to the aggressive properties of cancer cells, including migration, an attribute necessary for metastasis. Because most cancer patients die from metastases, it is hoped that Dr. Cravatt's discoveries will contribute to novel biomarkers and drug treatments for cancer.

Gender Analysis

The Oncofertility Consortium of the Interdisciplinary Research Program is developing a project to provide insight into the choices that cancer patients make regarding fertility preservation as a function of key social characteristics, particularly gender. For example, in one of the five studies, a longitudinal survey will evaluate the fertility concerns and treatment choices of patients throughout their cancer treatment, and will compare these concerns and decisions by gender, as well as age, racial/ethnic background, religious affiliation, family status, and socioeconomic status. Patients will complete a questionnaire during their first cancer center visit and complete the same questionnaire 3 months later, and annually thereafter for a period of up to 5 years to reveal potential health disparities (http://oncofertility.northwestern.edu/research/social-science-and-oncofertility/project-5).

A second study looks at the ethics of fertility preservation and considers how the issues differ when parents must subject a daughter to a highly invasive procedure compared to a noninvasive or less invasive procedure for a son.

In 2008, the Human Microbiome Program developed a protocol for collecting samples of microbes from several body sites from healthy male and female donors so that gender-specific differences in the microbiomes can be identified. These samples will be sequenced and contribute to the public reference collection of microbial genomes.

Initiatives

The objective of the Roadmap "Interdisciplinary Research Consortium" initiative (RFA-RM-06-008) is to support interdisciplinary approaches to solving significant and complex biomedical problems, particularly those that have been resistant to traditional approaches. One of nine funded consortia is the Oncofertility Consortium. The consortium application was submitted as a single U54 grant consisting of multiple-component grants that were disaggregated at the time of funding into the following:

"The Oncofertility Consortium: Fertility Preservation for Women" (U54), "Novel Methods for Cryopreservation and Recovery of Female Follicles" (R01), "Bioengineering Primate Follicles: From Immature Eggs to Live Births" (R01), "Preservation and Growth of Human Follicles" (R01), "An Interdisciplinary Perspective: A Social Science Examination of Oncofertility" (R01), a "Biomaterials Core" (P30), the "National Physicians Cooperative to

Preserve Fertility for Female Cancer Patients" (P30), "Learning Modules in Oncofertility" (R25), "Training the Globally Ready Scholar" (T90/R90), and the "Pediatric Program" (K01).

The Human Microbiome Program began the microbial sequencing effort through supplements to four NIH-funded sequencing centers. In 2009, additional funding will be provided to centers that compete well in response to a funding opportunity announcement.

The Metabolomics initiative was RFA-RM06-010, "Using Metabolomics to Investigate Biological Pathways and Networks" (RO1). This initiative sought to encourage the use of innovative metabolomics technologies to establish methods and model systems for advancing the understanding of biological pathways and networks, their temporal and spatial resolution, and their regulation in health and disease states.

Health Disparities Among Special Populations of Women

The Oncofertility Consortium of the Interdisciplinary Research Program is developing a project to provide insight into the choices that cancer patients make regarding fertility preservation as a function of key social characteristics. The project, involving a longitudinal survey, will include data on race, ethnicity, and socioeconomic status to reveal potential sources of health disparities in cancer survivorship and fertility preservation decisions in a subset of the enrolled patient population (http://oncofertility.northwestern.edu/research/social-science-and-oncofertility/project-5).

Appendix A

Ad Hoc Research Subcommittee of the NIH Coordinating Committee on Research on Women's Health, FY 2007 and FY 2008

FY 2007

Representative	*Title*	*Institute, Center, or Office*
Elaine Collier, M.D., FACP *Chair*	Assistant Director for Clinical Research	NCRR
Mary Blehar, Ph.D.	Program Director	NIMH
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.	Science Policy Analyst	NIDDK
Karen A. Johnson, M.D., Ph.D., M.P.H.	Program Director	NCI
Sooja Kim, Ph.D.	Chief, EMNR IRG	CSR
Cheryl Kitt, Ph.D.	Program Director	NIGMS
Anna Levy, M.S.	Director, Office of 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 Programs	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., RN	Director of Research Programs	ORWH
Madeline Turkeltaub, Ph.D., RN, CRNP	Deputy Director, NIAMS Extramural Program	NIAMS

Ad Hoc Research Subcommittee of the NIH Coordinating Committee on Research on Women's Health, FY 2008

FY 2008

Representative	*Title*	*Institute, Center, or Office*
Elaine Collier, M.D., FACP *Chair*	Assistant Director for Clinical Research	NCRR
Mary Blehar, Ph.D.	Program Officer	NIMH
Maria Teresa Canto, D.D.S., M.P.H.	Director, Epidemiology Research Program	NIDCR
Carolyn Deal, Ph.D.	Chief, STD Branch	NIAID
Patrice Desvigne-Nickens, M.D.	Medical Officer	NHLBI
Eleanor F. Hoff, Ph.D.	Science Policy Analyst	NIDDK
Karen A. Johnson, M.D., Ph.D., M.P.H.	Program Director	NCI
Sooja Kim, Ph.D.	Chief, EMNR IRG	CSR
Anna Levy, M.S.	Director, Office of Women's Health	NCI
Patty Mabry, Ph.D.	Health Scientist Administrator/ Behavioral Scientist	OBSSR
Pamela Marino, Ph.D.	Program Director	NIGMS
Mary Frances Picciano, Ph.D.	Senior Nutrition Research Scientist	ODS
Catherine Roca, M.D.	Chief, Women's Programs	NIMH
Cora Lee Wetherington, Ph.D.	Women and Gender Research Coordinator	NIDA
ORWH Liaisons		
Lisa Begg, Dr.P.H., RN	Director of Research Programs	ORWH
Madeline Turkeltaub,* Ph.D., RN, CRNP	Deputy Director, NIAMS Extramural Program	NIAMS

** (deceased, June 2008)*

Appendix B

ORWH-Cofunded Research Summaries, FY 2007

Adolescent Health

Title: National Longitudinal Study of Adolescent Health
P.I.: Kathleen Mullan Harris
Institution: University of North Carolina - Chapel Hill
Grant No.: 5 P01 HD031921-12
Award: $200,000

The National Longitudinal Study of Adolescent Health (Add Health) is a longitudinal study of a nationally representative sample of more than 20,000 adolescents in grades 7–12 in the United States in 1994–1995 who have been followed through adolescence and the transition to adulthood with three in-home interviews. In this application for a continuation of the Add Health Program Project, we propose to conduct a fourth followup interview with the Add Health cohort in 2007–2008 when survey respondents will be aged 24–32, and propose a set of analysis subprojects that represents an interdisciplinary research program entitled, Add Health Wave IV: Social, Behavioral, and Biological Linkages. The scientific purpose of our Research Program is to study developmental and health trajectories across the life course of adolescence into young adulthood using an integrative approach that combines social, behavioral, and biomedical sciences in its research objectives, design, data collection, and analysis. In Wave IV, we will collect longitudinal survey data on the social, economic, psychological, and health circumstances of our respondents; longitudinal geographic data; and new biological data to capture the prevailing health concerns of our Add Health cohort as well as biological markers of future chronic health conditions. We employ innovations in the collection of biological measures in a field setting on a large national sample that are both practical and ground-breaking. The combination of longitudinal social, behavioral, and environmental data with new biological data will expand the breadth of research questions that can be addressed in Add Health. Using an integrative life course theoretical framework, Program Project investigators have proposed significant new research on predisease pathways, gene–environment interactions, the relationship between personal ties and health, factors that contribute to resilience and wellness, the development of healthy relationships, and environmental sources of health disparities. With Wave IV, Add Health will provide the research community with a broad new set of opportunities to pursue interdisciplinary science, influence social and health policy, and improve the health and well-being of young people.

Aging

Title: Phytoestrogens and Aging: Dose, Timing and Tissue
P.I.: William G. Helferich
Institution: University of Illinois Urbana–Champaign, IL
Grant No.: 5 P01 AG024387-04
Award: $97,100

The overall research objective of this Program Project 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 differ-

ent 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. In summary, the overall goal of the P01 is to conduct highly interactive investigations of the effects of phytoestrogen dietary exposure using well-established animal models, each having specific advantages for the study of breast cancer progression to hormone independence, obesity and risk of diabetes, and cognitive function. This goal will be achieved through four complementary, synergistic projects: (1) Genistein and Endocrine Resistance in Breast Tumors, (2) Dietary Phytoestrogens and Adipocyte Development, (3) Dietary Estrogens and Cognitive Function During Aging, and (4) Phytoestrogen Action Through Estrogen Receptors alpha and beta. Investigators will be aided by an Administrative Core that oversees interproject meetings and provides budgetary, reporting, and external advisory needs; an Analytical and Bioavailability Core that will provide analysis and standardization of blood and tissue isoflavone levels for projects 1–3; and a Dietary, Genomics, and Chemistry Synthesis Core that will provide uniform diets, gene expression profiling analysis by microarray and quantitative PCR methods, and chemical synthesis of phytoestrogens and phytoestrogen metabolites.

Title: **National Social Life, Health, and Aging Project**
P.I.: **Linda J. Waite**
Institution: **National Opinion Research Center – Chicago, IL**
Grant No.: **5 R01 AG021487-05**
Award: **$237,045**

This study will explore health and well-being in American men and women age 57–84. We propose a nationally representative in-home survey of 3,000 noninstitutionalized people to describe, for the first time, distributions of physical and psychocognitive health, illness, medication use, intimacy, and sexuality among older adults and to evaluate the relationships among these components of health in different sociocultural contexts. Specifically, we aim to (1) Describe the health of older community-residing Americans: (A) Describe distributions of physical and psychocognitive health, social networks and capital, illness, medication use, and sexuality among older adults. (B) Evaluate the relationships among these components of health in different sociocultural contexts. (C) Evaluate the relationship between quality of life and health behaviors among older adults, including sexuality; physical activity; nutrition; sleep; and alcohol, tobacco, and other substance use. (2) Evaluate the relationship between health and older adult sexuality, focusing on (A) Physical illness and disability: arthritis; Alzheimer's disease; cancer; cardiovascular disease; diabetes; obesity; urinary incontinence; and sexually transmitted diseases, including HIV/AIDS; (B) Mental illness: depression, dementia, stress, anxiety, low self-esteem, poor bodyimage. (C) Medication use: prescription, self-medication, and alternative remedies. (3) Examine sexuality within social networks and the encompassing sociocultural context (A) Evaluate the relationship of older adult sexuality to important life stages (retirement; divorce; widowhood; and formation of new partnerships, including remarriage). (B) Evaluate the relationship between sexuality and social embeddedness including sociability; independence; loneliness; and physical, emotional, and sexual abuse. (C) Ascertain older adults' perceptions about the relationship of sexuality to health and their needs for physician–patient communication and healthcare services in this domain.

Title: **Biological Mechanisms of Arterial Stiffening With Age and Estrogen Deficiency**
P.I.: **Kerrie Moreau**
Institution: **University of Colorado Denver – Denver**
Grant No.: **5 R01 AG027678-02**
Award: **$48,550**

The purpose of this R01 proposal is to determine the key functional mechanisms by which the loss of female sex hormones, particularly estradiol (E2), contribute to the age-related decrease in large artery compliance. The overall hypothesis is that basal large artery compliance will decrease in response to acute sex hormone suppression in pre- and perimenopausal women due in part to a decrease in vascular endothelial-dependent vasodilatory tone mediated, in part, to the development of vascular oxidative stress. However, E2 administration during sex hormone suppression will decrease vascular oxidative stress, improve endothelial vasodilatory tone, and restore arterial compliance to basal levels. Secondary and tertiary hypotheses are that the changes in arterial compliance and vasodilatory function with sex hormone suppression and E2 will be related to unfavorable, and favorable, respectively, changes in vascular endothelial cell protein expression, including oxidant (e.g., NADPH) and antioxidant (e.g., glutathione peroxidase) enzymes, vasoconstrictors (endothelin-1), and estrogen receptor alpha (ERalpha). To test these hypotheses, healthy pre-, peri-, and postmenopausal women will be studied at, before, and following acute sex hormone suppression (gonadotropin releasing hormone antagonist [GnRHant]) with or without E2 add-back therapy. The GnRHant intervention will enable us to study the direct mechanisms associated with sex hormone deficiency and the E2 add-back intervention will enable us to isolate the independent effects of E2. Insight into the molecular mechanisms mediating the decrease in large artery compliance will be obtained using a novel translational research technique to determine changes in vascular endothelial cell protein expression of genes involved in the regulation of cellular and systemic adaptations to aging and sex hormone deficiency, including oxidative stress, nitric oxide bioavailability, and the potent transcription factor ERalpha proteins. The results should provide new insight into the integrative biological mechanisms by which sex hormone deficiency modulates the age-related reduction in large-artery compliance in women as they transition through menopause.

Title: **Impact of Endocrine Aging on Brain and Immune Responses**
P.I.: **Farida Sohrabji**
Institution: **Texas A&M University Health Science Center – College Station, TX**
Grant No.: **5 R01 AG027684-02**
Award: **$48,550**

The goal of this application is to determine the mechanisms by which reproductive aging and estrogen replacement alter the inflammatory response and consequently the neuronal environment. In a series of studies, we have established that estrogen replacement to young adult animals increases trophic support in the forebrain and attenuates inflammation following neural injury. However, estrogen replacement at reproductive senescence, which is physiologically akin to menopause, fails to increase trophic factors and paradoxically, increases inflammatory mediators following neural injury. Collectively, these data suggest that the timing of estrogen replacement in relation to reproductive aging may critically determine whether estrogen has a benign or deleterious outcome. Our central hypothesis is that the age-related decline in endogenous hormones triggers compensatory changes in estrogen receptor systems in specific immune cells, thus increasing the central and peripheral inflammatory response. This hypothesis will be tested in three Specific Aims, using animal and human tissue models that span the reproductive spectrum, namely, normally cycling (premenopause), irregularly cycling (perimenopause), and reproductive senescent (postmenopause). In Specific Aim 1, we will test the hypothesis that permissive changes in the blood–brain barrier will cause a more rapid and robust neural inflammation in reproductive senescent animals as compared to normally cycling or irregularly cycling animals. Animals will be injected systemically with the bacterial pathogen lipopolysaccharide (LPS) and inflammatory mediators will be measured in

peripheral organs and the brain. Additionally, we will examine endothelial cells of the blood–brain barrier for reproductive age-related changes in this barrier. In Specific Aim 2, we will determine if the inflammatory response of peripheral blood mononuclear cells (PBMCs) is affected by clinically relevant variables, namely, the route of hormone administration (oral versus transdermal) and diet (regular versus high cholesterol). The Response Quotient, derived from an ex vivo LPS challenge assay, will be measured in rat and human blood samples to determine if salient lifestyle variables increase the risks associated with reproductive aging. Finally, in Specific Aim 3, we will test the hypothesis that compensatory alterations of the estrogen receptor system, resulting from ovarian decline, is a principal mechanism underlying estrogen's deleterious effects in reproductive senescence. Changes in the pattern and levels of estrogen receptor-alpha will be evaluated by immunohistochemistry and Western blots, while functional changes will be evaluated using signaling arrays. Human and rodent PBMCs and rodent cerebral endothelial cells from each reproductive stage will be studied. Collectively, these studies will test the hypothesis that in order for estrogen replacement to be beneficial, therapy must be initiated before compensatory responses to ovarian decline.

Title: **Study/Women/Health Across Nation III/Coordinating Center**
P.I.: **Kim Sutton Tyrrell**
Institution: **University of Pittsburgh – Pittsburgh, PA**
Grant No.: **5 U01 AG012553-13**
Award: **$237,045**

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 followup examinations during which 895 (48%) women will have transitioned to postmenopause. This application requests funding to complete four additional followup 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 followup visits will continue to contribute to the SWAN biological specimen repository (annual blood and urine samples as well as DNA and immortalized cells). This is a separately funded component that broadens the opportunities to address future hypotheses about health and disease in aging women. As women reach the end of early postmenopause (2 years following the final menstrual period), we will shift from an annual to a biannual followup examination schedule with mail and telephone contact in the alternating years. This will permit cost-effective and less intensive followup. SWAN's organization and operations have been modified to enhance productivity and we are poised to publish important biological, symptom, and behavioral results pertaining to the menopause transition. With SWAN III, many of the original goals of SWAN will be brought to fruition. We will build upon the rich foundation developed during SWAN I and II and link these data to important menopause-related and health outcomes in SWAN III.

Alcohol and Substance Abuse

Title: Reducing Alcohol & Risks Among Young Females
P.I.: Lydia N. O'Donnell
Institution: Education Development Center, Inc. – Newton, MA
Grant No.: 5 R01 AA014515-05
Award: $142,227

Education Development Center, Inc., will conduct an intervention study to characterize and address the combined effect of early alcohol use and risky behavior within a population of urban African-American and Latina adolescent females who are at high risk for HIV, AIDS, and other infections. Past research by the investigative team has documented that nearly 10 percent of females in our target population are at risk in 7th grade and more than half by spring of 10th grade. Although alcohol use is more comparable with national figures, the combination of early alcohol and risky behavior is troubling, yet underaddressed by existing interventions. This randomized experiment will test a theoretically derived and empirically grounded selective intervention that specifically targets high-risk young adolescent females. The intervention builds upon a promising strategy for influencing adolescents: parent education. Three parenting mechanisms (PM) shown to influence adolescent risk behavior are targeted: parental monitoring (P-PM), household rule setting (HR-PM), and communication (C-PM). In continuing collaboration with New York City public schools and a community advisory board, the aims are to (1) Develop a set of three audio CDs to be delivered at intervals over a 6-month period to parents of young adolescent daughters that address alcohol prevention and the link between early alcohol use and risk taking. (2) Enroll 500 parents and their 8th grade daughters and randomly assign families to one of three conditions: an audio CD intervention focused on prevention of alcohol use, an attention-controlled condition, or a nonattention controlled condition. (3) Conduct a baseline telephone survey of parents to assess parental monitoring (P-PM), household rules (HR-PM), parent–child communication (C-PM) and perceptions of daughters' alcohol and other behaviors. (4) Conduct a baseline survey of adolescent daughters to assess their attitudes and behaviors about alcohol, P-PM, HR-PM, and C-PM. (5) Conduct a 3-month postintervention telephone survey of parents and test the efficacy of the audio CD intervention in improving P-PM, HR-PM, and C-PM. (6) Conduct a 3-month postintervention survey of daughters and test the efficacy of the audio-CD intervention in fostering attitudes and behaviors related to reduced alcohol and risk taking. (7) Examine whether changes from baseline to 3-month followup in daughters' attitudes and behaviors are explained by changes in P-PM, HR-PM, and C-PM, and whether these three parenting mechanisms mediate the relationship between experimental condition and daughters' outcomes. The study has the potential to improve understanding of the link between early alcohol and risky behavior and to provide a proven, selective, female-focused intervention for addressing these risks. The goal is to set young women on a course that protects their health and reduces the burden that problem drinking and HIV disease is taking on African-American and Latino communities.

Title: Affect Regulation Training for Pregnant Smokers
P.I.: Clara M. Bradizza
Institution: State University of New York at Buffalo – Amherst, NY
Grant No.: 1 R01 DA021802-01A1
Award: $352,622

Recent data indicate that approximately one-third of women of childbearing age smoke cigarettes, and 25–50 percent of women smoke during pregnancy. Cigarette smoking during pregnancy is a significant public health issue that can have profound effects on women's health and the health of their developing fetus. Smoking among pregnant women is associated with high levels of negative affect, which play a key role in the maintenance of smoking behavior and in difficulty quitting smoking during pregnancy. Despite the clear role of negative affect in the maintenance of smoking among pregnant women, and while this issue has received increased attention by clinicians and researchers, we know of no smoking cessation intervention that combines coping skills and emotion

regulation approaches to address the role of negative affect in smoking cessation. Smoking cessation treatment strategies that have demonstrated effectiveness in regular smokers have not translated into effective treatment strategies for pregnant women, particularly low-income pregnant women. The goal of this project is to develop and test an affect regulation smoking cessation intervention for low-income pregnant smokers. The major aims of this project will be addressed in two sequential phases. In Phase 1, we will develop two eight-session smoking cessation treatment manuals, including Affect Regulation Training and Cognitive Behavioral Treatment (ART+CBT) and Cognitive-Behavioral Treatment (CBT). In Phase 2, we will conduct a randomized clinical trial pilot study (total n=60) to compare the ART+CBT and CBT conditions on (1) the feasibility and acceptability of the interventions, (2) the impact of these interventions on smoking cessation rates at post treatment and at 6 months post-quit date, (3) affect regulation skills, and (4) negative affect among pregnant smokers. The long-term goal of this proposed research is to increase smoking cessation rates among pregnant smokers, which would provide significant long-term health benefits for both mothers and their infants. This Stage 1 application will be used to generate feasibility and preliminary efficacy data, setting the stage for a Stage II efficacy trial.

Cancer

Title: **Social Cognitive Theory and PA after Endometrial Cancer**
P.I.: **Karen M. Basen-Engquist**
Institution: **University of Texas M.D. Anderson Cancer Center – Houston, TX**
Grant No.: **5 R01 CA109919-04**
Award: **$106,582**

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 survivor populations. The goal of the project is to study predictors of adherence to physical activity in sedentary endometrial cancer survivors who receive an intervention to increase their physical activity. The specific aims of the study are (1) to test a social cognitive theory-based model of physical activity adoption among sedentary endometrial cancer survivors who receive an intervention to increase physical activity, (2) to elucidate the role of cardiorespiratory fitness and somatic sensations during physical activity on self-efficacy, (3) to determine whether intervention dose is related to physical activity adherence, and (4) to test the effects of adherence to physical activity on endometrial cancer survivors' quality of life. Two hundred sixty-seven sedentary Stage I–IIIa endometrial cancer survivors will be recruited to participate in this 6-month study. Participants will complete fitness tests, questionnaires, and cognitive tests every 2 months to assess functional capacity and efficiency, physical activity, and social cognitive theory-related variables. All participants will receive an intervention to increase their physical activity, consisting of a customized exercise prescription, telephone counseling, and written materials. Results of the study will provide a rigorous test of social cognitive theory as it is applied to physical activity, and will inform the development of effective interventions for cancer survivors.

Title: **Caregivers' Strengths-Skills: Managing Older CA Patients**
P.I.: **Victoria H. Raveis**
Institution: **Columbia University Health Sciences – New York, NY**
Grant No.: **5 R01 CA115315-03**
Award: **$47,409**

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+) posttreatment 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 experiencing during the cancer survivorship period. By focusing attention on families' potential

role in palliative care efforts during the posttreatment 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 10 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 posttreatment 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), and (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.

Title: **A Topical Treatment for Genital Papillomavirus Infections**
P.I.: **Richard Schlegel**
Institution: **Georgetown University – Washington, DC**
Grant No.: **5 R21 A1071977-02**
Award: **$179,897**

HIV-positive individuals have a higher prevalence of human papillomavirus infection and its preneoplastic sequelae than age-adjusted populations. While prophylactic vaccines will soon be available commercially for the prevention of HPV infection and cervical cancer, these vaccines will have little or no benefit for HIV-positive women who are already HPV infected. In addition, these vaccines do not prevent infection with several HPV types that account for 20–30 percent of cervical cancers. Therapeutic and preventative strategies to combat these HPV lesions are desperately needed. In this application, we will examine two compounds that show dramatic potential for preventing and treating this sexually transmitted disease. The first compound is carrageenan, which was recently shown by Dr. John Schiller's laboratory to be a potent inhibitor of papillomavirus infection in vitro by blocking cellular attachment. This is a nontoxic compound used in food preparations and, in consultation with Dr. Schiller, we will evaluate carrageenan's ability to inhibit vaginal papillomavirus infections. The second compound is dihydroartemisinin (derived from the Chinese herb, Artemisia annua). Dihydroartemisinin strongly induces apoptosis in HPV-expressing cervical cells and prevents tumor formation in vivo (using a canine oral papillomavirus or COPV model). In this application, we propose to develop the first in vivo assay for papillomavirus infection of the female genital tract. Our first 2 years (the R21 phase) will focus on adapting the COPV, which normally infects the oral mucosa, to infect and induce tumors in vaginal mucosa. In humans, the oral and genital mucosae are infected by the same HPV types. In the dog, COPV prefers the oral mucosa but it can also spread to the genital tract if the animals are mildly immunosuppressed. We plan to use documented methods of immunosuppression to develop a simple and reproducible assay for papillomavirus infection of vaginal epithelium. In the R33 phase of the application, we will formulate dihydroartemisinin derivatives and carrageenan and test them for their ability to inhibit papillomavirus infection, replication, and tumor formation. We will also determine if viral persistence and latency are altered by these compounds. The combined use of this new animal model, along with the newly identified inhibitors of papillomavirus infection, offer exciting possibilities for extending these trials into humans.

Title: Pharmacogenetics Research Network and Knowledge Base
P.I.: David Alastair Flockhart
Institution: Indiana/Purdue University at Indianapolis – Indianapolis, IN
Grant No.: 5 U01 GB061373-08
Award: $237,045

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 Aims 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.

Cardiovascular Disease

Title: Estrogen Dual Effects on Coronary Arteries
P.I.: Richard E. White
Institution: Medical College of Georgia – Augusta, GA
Grant No.: 5 R01 HL073890-03
Award: $19,420

Clinical and experimental studies have demonstrated beneficial effects of estrogens on the human cardiovascular system. Recently, however, the Women's Health Initiative study has indicated that combinational postmenopausal hormone replacement therapy may actually increase the risk of coronary artery disease (CAD), whereas studies with unopposed estrogen therapy are still ongoing. Clearly, there is much confusion concerning the physiological and/or therapeutic effects of estrogen. Because CAD is the most common cause of death for both women and men in the United States, a major challenge facing biomedical research is to identify and characterize the molecular basis of estrogen action on coronary circulation. Helping to meet this challenge is the direct focus of the present proposal. We propose an integrated, comprehensive investigation of how estrogen effects coronary artery smooth muscle cells, and thereby influences coronary blood flow. Our preliminary data indicate dual and opposite effects of estrogen on porcine coronary arteries: both relaxation and contraction. Therefore, we believe these data can shed some significant light upon one of the most important controversies in cardiovascular medicine. The hypothesis of the proposal is that estrogen can both contract and relax coronary smooth muscle by targeting a single enzyme: Type 1 or neuronal NOS, in coronary myocytes to release either a vasodilator (NO) or a vasoconstrictor (superoxide) substance to modulate Ca2+ or K+ channel activity. Aim 1 will determine the effects of

estrogen on isolated coronary arteries in vitro. Pharmacological studies will identify the signal transduction and ionic mechanisms underlying estrogen-induced contraction of coronary arteries. Aim 2 will investigate the cellular/molecular basis of estrogen's dual effects by employing both whole-cell and single-channel patch-clamp studies to examine the effects of estrogen on calcium and potassium channels directly in single coronary myocytes. Aim 3 will employ molecular, biochemical, and cellular fluorescence studies to identify the NOS isoform involved in the response to estrogen, and determine the role of superoxide in estrogen-induced contraction. Aim 4 will identify and characterize signaling molecules that link estrogen receptor activation to NOS activity (e.g., HSP90, PI3 kinase, Akt). Coimmunoprecipitation will determine estrogen-stimulated bimolecular interaction of these molecules, and we will employ molecular expression techniques to overexpress and/or knock out critical signaling molecules. The function of these molecules will be characterized by employing cellular (NO fluorescence) and molecular (patch-clamp) functional studies, and findings will be related back to function of intact coronary arteries. The long-term goal is to understand how estrogen can either contract or relax coronary arteries, and thereby help to reconcile the apparent controversy between basic research into estrogen action and clinical trials. It is hoped that these findings will contribute to the development of new therapeutic measures that will make the potential health benefits of estrogen therapy available to both men and women of all ages.

Title: **Angiogenesis and Mechanisms of Exercise Training in PAD**
P.I.: **Brian H. Annex**
Institution: **Duke University – Durham, NC**
Grant No.: **5 R01 HL 075752-05**
Award: **$237,045**

Peripheral arterial disease (PAD) impairs arterial blood flow to the legs and is a major indicator of systemic atherosclerosis. PAD affects 5 percent of the U.S. population over 50. Approximately one-third of patients with PAD have typical claudication, defined as pain in one or both legs on walking that is relieved by rest. Patients with claudication have a marked impairment in exercise performance similar to patients with NYHA class III heart failure. Goals of treatment for PAD patients include risk-factor modification and antiplatelet drug therapy to address increased cardiovascular mortality risk. Supervised exercise training is the most efficacious treatment to improve walking capacity, demonstrated in many (small) randomized trials. Neither the pathophysiology of claudication nor the mechanism(s) by which exercise training improves walking times in persons with IC are completely understood. It is unknown how long-term exercise training affects 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 toward 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 regimens 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. In this RFA (HL-03-003) (AMNESTI in PAD), men and women (n=160), over 40 years, with IC and an ankle/brachial systolic blood pressure ratio < 0.8 at rest, will be recruited from Duke University Medical Center and the University of Colorado Health Science Center. Patients will be randomized to a supervised or home-based exercise program. Evaluations will be at baseline, 3 weeks (supervised exercise), and 3 months. Age-gender matched healthy controls (n=66) will be tested at baseline. The central hypothesis is that the beneficial effects of exercise training are primarily mediated through an angiogenic effect. Specific Aim 1 will establish the baseline vascular abnormalities present in patients. Specific Aim 2 will establish the ability of the selected vascular abnormalities in Specific Aim 1 to predict peak oxygen consumption in PAD using a prediction model. Specific Aim 3 will establish the ability of exercise training to modify the vascular abnormalities in PAD. Specific Aim 4 will examine the gender specificity of the results obtained in Specific Aims 1–3.

Title: Genetics of Early-Onset Stroke
P.I.: Steven J. Kittner
Institution: University of Maryland, Baltimore – Baltimore, MD
Grant No.: 5 R01 NS045012-05
Award: $291,300

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. We 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 association studies of older stroke patients and will be a continuing resource for understanding the genetic basis of stroke risk.

Title: Heart Failure Evaluation in Postmenopausal Women: The Women's Health Initiative
P.I.: Liviu Klein
Institution: Northwestern University – Evanston, IL
Grant No.: 1 R21 AG 027471-01A2
Award: $266,811

Chronic heart failure (CHF) is the only cardiovascular disease in the United States for which the prevalence and morbidity are increasing. Despite treatment advances, 5-year mortality for patients with CHF remains around 50 percent, with over 1 million hospital admissions for CHF in 2005. Older women represent 50 percent of those with CHF in the general population, but limited epidemiologic and treatment data exist in this population because older women account for less than 20 percent of those enrolled in CHF clinical trials. Hormone replacement therapy (HRT) has a potential role in reducing CHF incidence in women, based on limited data from small, retrospective studies and beneficial effects on endothelial function, neurohormonal activation, and myocardial remodeling. However, estrogen-progestin HRT is associated with increased risk of myocardial infarction (MI), an important risk factor for CHF. In addition, there are no data examining HRT in primary prevention of CHF among postmenopausal women, or its effects on survival in women who develop CHF. Given the main results of the Women's Health Initiative (WHI), which showed increased risk for MI, stroke, and venous thromboembolic events with HRT, testing our hypothesis in a prospective randomized trial would be difficult. Our objective is to evaluate the association between HRT and risk of incident CHF and subsequent mortality in 27,347 postmenopausal women in WHI. The central hypothesis is that HRT will reduce CHF incidence and improve survival among those who develop CHF. Our specific aims include (1) To investigate the association between HRT and CHF incidence

among participants free of CHF at baseline; (2) To examine the association between HRT and all-cause mortality among participants who develop CHF; and (3) To explore the association between HRT and CHF incidence and mortality, based on CHF etiology (ischemic versus nonischemic) and systolic function (impaired versus preserved). The proposed research is innovative because it uses a new approach to identifying CHF cases, using the largest existing database to study the relationship between HRT and CHF in postmenopausal women. The results will further the knowledge on the role of HRT in CHF prevention and/or treatment, and will contribute to the better understanding of CHF epidemiology in older women, who represent a large proportion of the population at risk for CHF. Our study is cost effective, using data previously collected, but never analyzed for this specific purpose. It is unlikely that other cohort studies will be able to provide similar data in the foreseeable future. Despite the fact that women represent up to 50 percent of the heart failure patients, few epidemiological and clinical studies to date have addressed the gender-specific risk factors and treatments for heart failure. Based on limited retrospective data, hormone replacement therapy has a potential role in reducing heart failure incidence and associated mortality in women. We will be using the largest existing database to study the relationship between hormone replacement therapy and heart failure in postmenopausal women. The results will further the knowledge on the role of hormone replacement therapy in heart failure prevention and/or treatment, and will contribute to the better understanding of heart failure epidemiology in older women, who represent a large proportion of the population at risk for heart failure.

Title: **Phytoestrogens and Progression of Atherosclerosis**
P.I.: **Howard N. Hodis**
Institution: **University of Southern California – Los Angeles, CA**
Grant No.: **5 U01 AT001653-05**
Award: **$94,818**

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 nonhuman 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 our knowledge have been published or proposed to determine the long-term effects of soy protein on the progression of atherosclerosis in postmenopausal women. We 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. We 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 cardioprotection afforded by endogenous estrogen into menopause without the increased risk of thromboembolic events and certain cancers associated with traditional HRT. Because 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 the progression of atherosclerosis in postmenopausal women is not only timely, but also of immense medical and financial importance because atherosclerosis remains the number one killer of postmenopausal women.

Chronic Fatigue Syndrome

Title: Risk Factors Associated With CFS and CF Prognosis
P.I.: Leonard A. Jason
Institution: DePaul University – Chicago, IL
Grant No.: 5 R01 AI055735-03
Award: $94,818

Chronic fatigue syndrome (CFS) and chronic fatigue (CF) are severe, disabling conditions. Few studies have examined the natural history course of CFS and CF over time, particularly in random, community-based, multiethnic populations. In the past, almost all studies with samples of CFS and CF patients have relied on referrals from physicians or health facilities, which biased the sample by illness, help-seeking behaviors, or differential access to health care. In contrast, a recent community-based study found the prevalence rate of CFS to be 4 percent among adults, and the prevalence of CFS among adults was higher among Latino and African-American samples than among the White sample (Jason et al., 1999). These findings might be due to the fact that this sample was collected from an urban area, and a community-based approach was used, thus minimizing the influence of biased data collection procedures. The proposed study will rigorously evaluate the natural history of CFS and chronic fatigue in an ethnically and socioeconomically diverse sample unbiased by illness and help-seeking behaviors, or by differential access to the healthcare system. Increasingly, the studies suggest that a variety of socioenvironmental and psychological risk factors are associated with CFS and chronic fatigue maintenance over time. We will perform followup on Wave 1 subjects with CFS and chronic fatigue to determine if the associations identified in Wave 1 between CFS and a variety of risk factors will be associated with poorer prognosis in Wave 2. Similar comparisons will be conducted for those with chronic fatigue. Major benefits of this grant application are the diversity of the population, identification of cases from the community rather than the healthcare system, and the use of a medical exam to confirm CFS and CF diagnoses.

Title: HERV-K18 as a Risk Factor for CFIDS
P.I.: Brigitte T. Tufts
Institution: University of Boston – Boston, MA
Grant No.: 1 R01 AR053821-01A2
Award: $164,058

The etiology of Chronic Fatigue Syndrome (CFS) is far from understood and is likely due to multiple genetic components. Infection with EBV and treatment with IFN-a have been implicated in the pathogenesis. Our laboratory has shown that EBV infection, and exogenous IFN-a, activate transcription of the env gene of a Human Endogenous Retrovirus, HERV-K18. This provirus is normally silent, but when induced, it encodes a superantigen (SAg), which is a class of proteins that is capable of deregulating the immune system. Three alleles of HERV-K18 env have been documented, K18.1, K18.2, K18.3, whose gene products have SAg activity, but are predicted to differ biochemically and functionally. Our working hypothesis is that HERV-K18 is a risk factor for CFS. In a pilot study, the allele and genotype distributions of the HERV-K18 env gene were compared between various groups of CFS patients and healthy controls. Although only a limited number of samples were available in the various cohorts, the odds ratios that were obtained were statistically significant. The most intriguing interpretation of these data are that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the coinvestigator, Dr. Renee Taylor. Dr. Ben Katz, board certified in both pediatrics and pediatric infectious diseases, will clinically evaluate the patient cohort, and Dr. Inga Peter, a genetic epidemiologist and biostatistician, will oversee the statistical analyses. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during

the course of the disease, will be tested ex vivo, using a T cell hybridoma reporter assay that has been developed in our lab. Because SAg-activated T cells produce massive quantities of chemokines, lymphokines, and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs, as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of this chronic disease. CFS is a disease that affects a significant number of people worldwide, yet the underlying mechanism(s) of pathogenesis remains unclear. The herpesvirus EBV and IFN-a have been suggested to be associated with CFS, although these concepts are far from accepted. We propose a novel genetic aspect in the EBV/CFS association, namely the presence of certain HERV-K18 alleles that differ in their superantigen activity.

Title: **Chronic Fatigue Syndrome in Adolescents**
P.I.: **Renee Taylor**
Institution: **University of Illinois at Chicago – Chicago, IL**
Grant No.: **5 R01 HD043301-05**
Award: **$284,454**

In the Senate Labor, Health, and Human Services Appropriations Report, it was recommended that researchers explore issues related to the etiology and natural course of chronic fatigue syndrome (CFS) using longitudinal, repeated-measures designs, with particular attention to pediatric samples. Researchers have documented the development of a fatigue syndrome following mononucleosis in prospective studies of adults. One objective of the proposed investigation is to prospectively study the relationship between infection with mononucleosis and the onset and course of chronic fatigue syndrome over time in adolescents. The following hypotheses will be tested using a prospective, case-control design: (1) Baseline predictors of postinfectious CFS and fatigue severity at 6 months will include greater levels of baseline psychological distress, having a psychiatric diagnosis at baseline, a greater degree of stressful life events at baseline, and higher levels of activity prior to initial infection; (2) Adolescents with CFS, compared with matched controls, will report higher levels of psychological distress, higher rates of psychiatric diagnoses, a greater degree of stressful life events, and lower levels of physical activity following infection at the 6-, 12-, 24-month time points; and (3) Compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol (peak and trough), reduced natural killer cell function and count, and elevated proinflammatory cytokines at the 6-, 12-, and 24-month time points. At the 6-month time point (clinic visit), adolescents with CFS will also demonstrate higher rates of orthostatic intolerance; and (4) In response to an exercise challenge test at the 6-month time point, compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol and plasma ACTH, and elevated cytokines, illustrating impaired communication between neuroendocrine and immune systems with physical stress. An exploration of the nature and timing of these relationships would provide a preliminary model of etiology and natural course of illness for adolescents with postviral chronic fatigue syndrome. Results from this investigation may assist physicians in identifying adolescents at high risk for CFS and allow them to initiate preventative measures.

Title: **Autonomic Nervous System in Chronic Fatigue Syndrome**
P.I.: **Italo Biaggioni**
Institution: **Vanderbilt University – Nashville, TN**
Grant No.: **5 R01 NS055670-02**
Award: **$372,621**

The overall goal of this application is to determine the role of the autonomic nervous system in the abnormalities associated with chronic fatigue syndrome (CFS). We propose to test the hypothesis that the sympathetic nervous system contributes to the cardiovascular and inflammatory abnormalities present in CFS and, in particular, in the subset of patients characterized by postural tachycardia (POTS). CFS and POTS are seen mostly in otherwise normal young women, and are the cause of significant disability. Our preliminary evidence indicates a decrease in plasma volume in patients with POTS, which can contribute to, and be the consequence of, sympathetic activation. Our preliminary studies also indicate an interaction between the sympathetic nervous system and nitric oxide mechanisms; this may also create a negative feedback mechanism whereby a decrease in nitric oxide results in sympathetic activation, and increased sympathetic activity results in impaired nitric oxide mechanisms. We have developed a paradigm that will allow us to define selectively the contribution of endothelial nitric oxide to blood pressure regulation and will apply this approach to patients with CFS and POTS. In addition, our preliminary studies indicate that sympathetic activity is associated with inflammatory processes. In particular, C-reactive proteins are increased in patients with POTS and, conversely, decreased in patients with low sympathetic tone due to pure autonomic unsuccessful undertaking. We propose to measure validated indices of sympathetic activity, inflammation, and oxidative stress in patients with CFS and POTS, and compare them to appropriate control groups, including patients with CFS without POTS, POTS without CFS, and normal controls. If our hypothesis is correct, and sympathetic activity contributes to the pathophysiology of CFS, then chronic inhibition of sympathetic tone will result in improvement of symptoms, cardiovascular alterations, volume defects, and inflammatory abnormalities present in CFS.

Title: **Cognitive Behavioral Stress Management for Chronic Fatigue**
P.I.: **Michael Howard Antoni**
Institution: **University of Miami – Coral Gables, FL**
Grant No.: **5 R01 NS055672-02**
Award: **$334,267**

This is a 4-year study that uses a 10-week telephone-based cognitive behavioral stress management intervention (T-CBSM) to illuminate neuroimmune mechanisms underlying the effects of stress and stress management on physical health status and immune regulation in individuals with chronic fatigue syndrome (CFS) relative to participants receiving a health promotion telephone (T-HP) intervention. CFS is characterized by physical symptoms that bring about severe limitations in lifestyle behaviors and vocational activities. Associated symptoms include debilitating fatigue, low-grade fever, lymph node pain and tenderness, cognitive difficulties, and mood changes. There is growing evidence that CFS patients may also show abnormalities in HPA axis functioning and on several indices of immune functioning. Chronic stress is also associated with a flattened diurnal secretion pattern for cortisol. An inability to maintain regulation in the HPA axis may contribute to the pathophysiology of CFS via diminished control of proinflammatory cytokines and associated physical symptoms related to chronic immune activation and inflammation. Given the debilitating nature of CFS, we propose to deliver the T-CBSM intervention through a telecommunications system (i.e., Telecare) designed to enhance access to formal and informal care for a population that may have difficulty accessing traditional psychotherapeutic settings. In our prior work with individuals with CFS, we have shown that individuals in a structured group CBSM intervention report significantly improved quality of life, perceived stress, fatigue, memory, muscle pain, and postexertional malaise compared to individuals in the control condition. The Telecare system has been successful in delivering a supportive intervention for older caregivers of dementia patients. This study is novel in expanding our

prior work to individuals with CFS who have reported difficulty participating in structured groups due to physical burden. The study design is a 2 X 3 randomized experimental design with group (T-CBSM, n=60 vs. T-HP, n=60) as the between-group factor, and time (Preintervention, Postintervention, and 6-month followup) as the within-group factor. Our primary objective is to evaluate the extent to which a T-CBSM intervention aimed at building skills in anxiety reduction, distress tolerance, stressor appraisals, and adaptive coping strategies may improve physical health status and immune regulation in CFS by modulating neuroimmune interactions.

Title: **Neuropeptide Y and Dipeptidyl-Peptidase IV (CD26) in Chronic Fatigue Syndrome**
P.I.: **Mary A. Fletcher**
Institution: **University of Miami School Medicine – Coral Gables, FL**
Grant No.: **5 R21 AA016636-02**
Award: **$147,653**

According to the Centers for Disease Control and Prevention case definition, chronic fatigue syndrome (CFS) is an illness of severe fatigue with defined associated symptoms that cannot be ascribed to any other pathologic condition. Although studies on CFS have increased in recent years, no unanimity of opinion regarding etiology has emerged. Several etiologies have been proposed, immunological, neuroendocrine, and autonomic, and yet no physiological mechanism has been consistently and uniquely related to CFS. It is probable that CFS encompasses subpopulations that share a common symptom profile, yet are mediated by different factors. Neuropeptides such as neuropeptide Y (NPY) have long been proposed to play a role in the pathogenesis of inflammatory diseases. NPY is a 36 amino acid neuropeptide, which participates in the regulation of a large number of physiological and pathophysiological processes in the cardiorespiratory system, immune system, nervous system, and endocrine system. In the periphery, NPY is concentrated in the sympathetic nerve endings and is released alone or with catecholamines. NPY receptors are present in most cells of the immune system, including NK cells. NPY suppresses natural killer cell function (NKCC). Given the potential for adverse effects with a constant stimulus, down-regulation mechanisms are essential for neuropeptides, including NPY. One regulator of NPY is dipeptidyl peptidase IV (CD26). Preliminary data from our lab indicate that CD26 concentrations on lymphocytes are abnormally low. The role of NPY in CFS is undefined. Our goal is to improve the understanding of CFS pathophysiology and to develop biomarkers useful in diagnosis, in defining subsets, and in therapeutic trials. In this study, we will study one aspect of the neuroimmune relationship in CFS. Specific Aim 1 is to determine the extent to which patients, or a subset of patients who meet the CFS case definition, have elevated NPY as compared to healthy, sedentary controls. Specific Aim 2 is to determine the relationship of NPY to the cell surface concentration of CD26 in patients with CFS as compared to controls. Specific Aim 3 is to define the relationship of NPY and CD26 to NKCC in CFS. Specific Aim 4 is to determine the relationship of NPY and CD26 to clinical severity in CFS patients.

Title: **Mast Cells, Antidepressants, and Chronic Fatigue Syndrome**
P.I.: **Theoharis C. Theoharides**
Institution: **Tufts University Boston – Boston, MA**
Grant No.: **5 R21 AA016701-02**
Award: **$104,140**

Chronic fatigue syndrome (CFS) is characterized by fatigue, malaise, and sleep and autonomic disturbances; it is considered a neuroimmune disorder with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, precipitated by stress and associated with high disability. CFS often occurs with comorbid diseases such as fibromyalgia, irritable bowel syndrome, interstitial cystitis, and migraines, all of which also worsen by stress. There are no reliable animal models for CFS. Mast cells have emerged as a major regulator of neuroimmune endocrine processes affected by stress and have been implicated in all comorbid diseases associated with CFS. We have shown that (a) mast

cells have functional associations with nerve endings; (b) acute stress activates mast cells, an action blocked by pretreatment with corticotropin-releasing hormone (CRH) neutralizing antiserum; (c) stress increases blood–brain barrier permeability, which is inhibited by the CRH-receptor-1 (CRH-R1) antagonist Antalarmin and does not develop in mast cell–deficient W/W mice; (d) human mast cells express CRH receptors, activation of which leads to selective release of vascular endothelial growth factor (VEGF); (e) some of the stimulatory effects of CRH on mast cells are mediated by neurotensin (NT), which has been shown to regulate the HPA axis. Tricyclic antidepressants are helpful in CFS and in the other comorbid diseases, but this mechanism of action is unknown. Our preliminary results show that the tricyclic antidepressant amitriptyline can inhibit rat mast cell secretion and intracellular calcium ion levels. Hypothesis: CRH, or the structurally related urocortin (Ucn), secreted by stress activates diencephalic mast cells, either alone or together with other neuropeptides such as NT, leading to release of molecules that contribute to the central pathogenesis of CFS, and secretion of which can be inhibited by tricyclic antidepressants. We will investigate Aim 1—The dose-response (0.1-100 uM) and time-course (0.5,1,6, 24 h) effects of three different classes of antidepressants, (a) the tricyclic (amitriptyline, imipramine); (b) the selective serotonin reuptake inhibitors (fluoxetine, sertraline); and (c) bupropion on secretion of histamine, IL-1, IL-6, IL-8, IL-13, TNF, tryptase, and VEGF from normal human umbilical cord-derived cultured mast cells (hCBMCs) derived from CD34+ progenitors triggered by IL-1, CRH, or Ucn (100 nM). Aim 2—The effect of those antidepressants shown to be effective in Aim 1 for their ability to inhibit brain mast cells developed by culturing human umbilical cord matrix stem cells that are CD34- in the presence of 10 nM IL-4 and nerve growth factor, stimulated as in Aim 1 +/- NT (0.1-100 mM). Results from these studies will further our understanding of molecules released in response to stress hormones and which antidepressants may be useful in inhibiting these effects. Future studies will build on these findings to develop in vitro and in vivo models of CFS and lead to clinical trials with select antidepressants or other molecules that inhibit brain mast cells.

Diabetes

Title: **Validity of Diabetes Self-Reports in the Women's Health Initiative**
P.I.: **Karen L. Margolis**
Institution: **Health Partners Research Foundation – Minneapolis, MN**
Grant No.: **1 R21 DK074646-01A2**
Award: **$244,409**

Patient-oriented and epidemiologic research projects, particularly multicenter projects, typically generate data with potential utility beyond the specific hypotheses and questions for which they were designed. The Women's Health Initiative (WHI) Clinical Trials enrolled 68,133 female participants aged 50–79 in dietary and hormone therapy trials. Self-reports of the primary and secondary outcomes (e.g., breast cancer, coronary heart disease) were confirmed by reviews of medical records. In contrast, self-reported incident type 2 diabetes mellitus was not independently confirmed by review of medical records, nor was routine diagnostic testing performed. Confirming that participant self-report of diabetes in WHI is accurate would greatly enhance the value of the WHI data as an unparalleled resource for further investigation of the effects of dietary, hormonal, and other influences on diabetes in older women. Approximately 7% of WHI clinical trial participants reported diabetes at baseline, and the self-reported incidence of new-onset medication-treated diabetes in WHI has been close to 1% per year. In previous epidemiologic studies, self-reports of diabetes were confirmed at widely ranging rates, from 64% to 98%. Preliminary data from medical record reviews at the Minneapolis WHI Field Center showed that the positive predictive value of self-reported incident diabetes during followup was 85% (74%–94%) and the negative predictive value of never self-reporting diabetes was 99% (92%–100%). The principal aim of the proposed study is to obtain more precise estimates of the positive and negative predictive values of WHI self-reports of incident diabetes in the WHI clinical trials by expanding the study to three other WHI Field Centers. These additional Field centers collectively represent WHI closely with regard to diabetes risk factors, demographics,

prevalence, and incidence of self-reported diabetes. We will use existing data in the WHI database, supplemented by newly collected data from a questionnaire and medical record reviews in a subset of participants, to carry out the study's aims. The new data collection employs similar methods to those already in place for adjudication of other self-reported WHI primary outcomes, and will be used to establish a gold standard to which the self-reports of diabetes in WHI can be compared. Secondary aims are to compare the confirmation rates of self-reported diabetes between intervention and control arms within the trials, and develop a prediction model for incident diabetes that incorporates clinical characteristics (e.g., age, race/ethnicity, education, body mass index) along with self-reported diabetes status. This is the first study to examine the negative predictive value of self-reports of diabetes. The availability of serial fasting serum glucose data from a large cohort of postmenopausal women provides a unique opportunity to estimate the rate of underreported incident diabetes in this population. This study will examine whether postmenopausal women who self-reported diabetes in the Women's Health Initiative study really had diabetes according to standard diagnostic criteria. The results of the study will help determine whether self-reported diabetes can be used for other analyses of the WHI data and for post menopausal women in other studies.

Title: **University of Medicine**
P.I.: **Xinhua Chen**
Institution: **University of Medicine and Dentistry of New Jersey – Stratford, NJ**
Grant No.: **1 R21 DK078865-01**
Award: **$233,250**

Approximately 9–19% of pregnant women have a positive glucose challenge test when screened for diabetes but a normal diagnostic oral glucose tolerance test (OGTT). Women with a positive glucose challenge test and normal OGTT do not obtain usual diabetes care, diet counseling, and plasma glucose monitoring. The proposed study determines the impact of a positive glucose challenge test and normal OGTT on maternal–fetal outcomes in young, low-income minority pregnant women in Camden. Potential links with abnormal metabolism will be examined, as well. Based on the information collected from prior prospective cohort studies (n=2789) and using blood specimens collected and stored at entry to prenatal care (< 20 weeks) and in the 3rd trimester (24–28 weeks), we propose to (1) determine the influence of a positive glucose challenge test and normal OGTT on adverse pregnancy outcome, using data from the whole cohort, and (2) determine if fundamental metabolic abnormalities are present comparing cases from the cohort (n=200) to controls (n=600) who are randomly selected from among women with a negative glucose challenge test. Metabolic abnormalities include (i) Insulin resistance and secretion; (ii) Fasting plasma free fatty acid (FFA) level , FFA composition, and dietary fat and fatty acid intake; (iii) Circulating levels of adiponectin, TNF-a, C-reactive protein. This study will be the first to examine in detail the effects of a positive glucose challenge test and normal OGTT on maternal–fetal outcomes along with potential mechanisms in a young, low-income minority women. Prenatal care during pregnancy is critical and one of the few times when these women obtain preventive health care. Should this application demonstrate that women with positive glucose challenge test and normal OGTT have increased adverse maternal–fetal outcomes or detectable abnormalities in metabolism, fuel substrates, and inflammatory biomarkers comparing with negative glucose challenge test women, it would have important public health implications for reducing adverse maternal–fetal outcomes in vulnerable women. Low-income ethnic minorities usually receive only intermittent medical care apart from pregnancy. If such women are at risk for type 2 diabetes, preventive intervention that takes place in the context of prenatal care would provide an opportunity to prevent or delay the development of type 2 diabetes and its precursor, gestational diabetes mellitus.

Title: Post DPP Followup Study: Data Coordinating Center
P.I.: Sarah E. Fowler
Institution: George Washington University – Washington, DC
Grant No.: 5 U01 DK04848914
Award: $284,454

The Diabetes Prevention Program is a multicenter controlled clinical trial examining the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease (CVD) and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the lifestyle intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo-treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, 1 year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n approximately 700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include (1) Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular disease, atherosclerosis, CVD risk factors, quality of life, and cost-benefit; (2) Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; (3) Determine the incidence of CVD, CVD risk factors, and atherosclerosis in new onset type 2 diabetes and IGT; and (4) Examine topics 1–3 in minority populations, men vs. women, and in older subjects in the DPP. The current application is for 5 years of funding, although some goals of the projects described will require a 10-year study.

Title: Look AHEAD: Action for Health in Diabetes
P.I.: Mark Andrew Espeland
Institution: Wake Forest University Health Sciences – Winston-Salem, NC
Grant No.: 5 U01 DK057136-09
Award: $94,818

Look AHEAD is a randomized clinical trial examining the long-term health effects of an intensive weight loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity, or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and non-fatal Ml and stroke and cardiovascular deaths) over a planed followup of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well—the sample of 5,145 was recruited on time, retention has been excellent, and the intervention has been effective in producing initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific Aims

are to retain the cohort over time, continue to complete annual in-person visits and semi-annual telephone interviews for outcome assessments, and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular-related factors and complications, and cost-effectiveness of the intervention.

Complementary and Alternative Medicine

Title: **Botanical Dietary Supplements for Women's Health**
P.I.: **Norman R. Farnsworth**
Institution: **University of Illinois at Chicago (UIC) – Chicago, IL**
Grant No.: **5 P50 AT000155-08**
Award: **$94,100**

The UIC/National Institutes of Health Center for Botanical Dietary Supplements Research was established in the fall of 1999 to address the issues of standardization, quality, safety, and efficacy of botanical dietary supplements. The Center then adopted and will continue to implement a multidisciplinary strategy to achieve its basic and clinical research objectives. Participating faculty Co-investigators and collaborators are drawn from the Departments of Medicinal Chemistry and Pharmacognosy and Biopharmaceutical Sciences in the College of Pharmacy; the Department of Medicine (Section of Endocrinology and Metabolism) in the College of Medicine; and the Department of Math, Statistics, and Computer Science in the College of Liberal Arts. The Center studies botanicals with potential benefits for women's health, focusing on plants that are reported to alleviate the symptoms of menopause and premenstrual syndrome. Botanical extracts are subjected to rigorous chemical evaluation followed by both in vitro and in vivo biological testing. Standardized botanical extracts that appear efficacious and demonstrate adequate safety profiles in in vitro and animal models will be candidates for clinical Phase I trials. Hops (Humulus lupulus L.) will undergo Phase I evaluation in this grant cycle. In order to achieve this comprehensive agenda for the development of chemically and biologically standardized botanical dietary supplements, the renewed BRC research program will be organized around three Projects, supported by two Cores: Project by Farnsworth, Standardization of Botanicals; Project by Bolton, Mechanism of Action of Botanicals (Menopause); Project by van Breemen, Studies of Metabolism, Bioavailability, and Toxicity; and Administration and Development Core and Analytical Core. The Administration and Development Core will administer two additional programs: a Pilot Project Program and a Training and Career Development Program. The experiments proposed in this application will greatly enhance our understanding of the mechanism of action of botanicals and whether they are safe and efficacious for women's health.

Title: **Alpha-Tocopherol Modulation of Xenobiotic Metabolism**
P.I.: **Maret G. Traber**
Institution: **Oregon State University – Corvallis, OR**
Grant No.: **5 R01 DK067930-02**
Award: **$204,117**

Drug-nutrient interactions are of increasing concern as it has been estimated that 15 million Americans consume dietary supplements concurrently with prescription medications. Vitamin E has antioxidant benefits and is generally considered to be nontoxic even in relatively high doses (>1,000 IU). Of potential importance are recently published intervention studies that have reported adverse effects of vitamin E, which may be directly related to its hepatic metabolism. Although vitamin E itself may not have adverse effects, our data suggest that a-tocopherol up-regulates xenobiotic metabolism, specifically cytochrome P450 3A (CYP 3A), the major CYP in human liver and intestine that is also the predominant enzyme involved in the metabolism of >50% of therapeutic drugs. Our long-term goal is to further elucidate the pathways involved in vitamin E regulation in order that vitamin E supplements may be used with optimal benefits in maintaining human health. The objective of

this research is to define hepatic pathways for a-tocopherol catabolism and its disposition, as well as to specifically address a-tocopherol interactions with pharmacologic agents and their metabolizing systems. The central hypothesis of these studies is that pharmacologic amounts of a-tocopherol alter hepatic xenobiotic catabolism and excretion pathways that simultaneously prevent excess hepatic vitamin E accumulation. Our rationale for these studies is that their successful completion will allow formulation of public health recommendations using evidence-based knowledge of vitamin E interactions and potential interference with other pharmacologic agents and xenobiotics. We propose to: Aim 1. Define the intracellular pathway for a-tocopherol metabolism. Aim 2. Define how a-tocopherol modulates hepatic cytochrome P450 enzymes (CYPs) involved in the metabolism of therapeutic drugs. Aim 3. Determine the ability of a-tocopherol to modulate hepatic transport proteins known to be involved in the biliary excretion of a-tocopherol and/or therapeutic drugs. Aim 4. Determine alterations by a-tocopherol on other vitamin E's metabolism. The proposed research is innovative because it will challenge the current paradigm that a-tocopherol acts solely as an antioxidant. Our studies will demonstrate how a-tocopherol alters hepatic xenobiotic metabolism. We believe these studies are critical to our understanding of a-tocopherol actions, particularly in light of recent reports of adverse drug–vitamin E interactions. We believe that our findings may well have a significant impact on current self-medication practices of the millions of Americans currently taking prescription drugs and vitamin E supplements.

Title: **The Status and Future of Acupuncture Research: 10 Years Post-NIH Consensus Conference**
P.I.: **Lixing Lao**
Institution: **University of Maryland, Baltimore – Baltimore, MD**
Grant No.: **1 R13 AT004143-01**
Award: **$14,200**

Lixing Lao, Ph.D., Principal Investigator SAR Conference 2007 Abstract. This R-13 application requests support for a conference entitled The Status and Future of Acupuncture Research: 10 years Post-NIH Consensus Conference. The three specific aims of the conference are to (1) Critically evaluate, synthesize, and disseminate the state of the evidence regarding efficacy, safety, and mechanisms of acupuncture for specific indications as defined in the 1997 NIH Consensus Statement as well as new indications that have been documented in systematic reviews during the past 10 years, placing major emphasis on evaluation of study designs and research methodologies. (2) Provide an international forum for Acupuncture and Oriental Medicine (AOM) researchers, practitioners, and policymakers to rigorously assess and strengthen the acupuncture evidence base and stimulate collaborations that will drive future research. (3) Provide unique learning opportunities for those new to acupuncture research, e.g., biomedical researchers and providers, AOM college faculty, administrators, and students. The proposed conference will be held November 8–11, 2007, on the campus of the University of Maryland School of Medicine, Baltimore, MD. The conference's primary sponsors include the Society for Acupuncture Research, Center for Integrative Medicine at the University of Maryland School of Medicine, Harvard Medical School's Osher Institute, Georgetown University School of Medicine, New England School of Acupuncture, and Oregon College of Oriental Medicine. Leading researchers in the field from the United States and abroad will be invited to give keynote and overview presentations assessing progress in the past decade, and challenges and opportunities for future research. Acupuncture researchers will be solicited for original presentations in three main areas: clinical trials, basic science, and research methodology. Key issues in each of these domains will also be addressed in panel discussions, break-out sessions, and poster sessions. Abstracts of all keynote talks and invited oral and poster presentations will be published in the Medline-indexed Journal of Alternative and Complementary Medicine. Preconference workshops will address fundamentals of AOM research for those new to this field. A Scientific Review Committee will employ a rigorous peer review process to assure quality and relevance of original research. Marketing efforts will target a broad range of audiences, including researchers, students, healthcare administrators, and health policy analysts. Special recruiting efforts will be employed to encourage

the participation of national and international acupuncture and AOM professional organizations and OM colleges, as well as minorities and junior researchers. The proposed conference will mark the 10th anniversary of the 1997 NIH Consensus Development Conference on Acupuncture, a landmark event in the growth and acceptance of acupuncture in the United States. The highly cited consensus statement that emerged from the 1997 NIH conference summarized the state of acupuncture research and sketched a roadmap for future work. To date, however, no attempt has been made to convene members of the acupuncture and biomedical research communities to comprehensively update, reevaluate, and propose means to strengthen the evidence base for acupuncture. The proposed conference will do so.

Endocrinology

Title: **Control of IGF-1 Gene Transcription by Growth Hormone**
P.I.: **Peter S. Rotwein**
Institution: **Oregon Health and Science University – Portland, OR**
Grant No.: **5 R01 DK069703-02**
Award: **$20,000**

Insulin-like growth factor-1 (IGF-1), a conserved 70-residue secreted protein, plays a fundamental role in somatic growth in mammals and other vertebrate species. Although much evidence has accumulated supporting IGF-1 as a major postnatal growth factor, regulated by growth hormone (GH), many studies have suggested a broader range of functions for this peptide, including actions on local tissue growth, maintenance, and repair throughout the lifespan, as well as deleterious effects in cancer and aging. These observations in turn imply not only that control of IGF-1 synthesis may be multifactorial, but also that each regulatory pathway may exert key critical actions on different aspects of growth, development, and disease. As part of a long-term effort to understand the mechanisms by which IGF-1 synthesis and action are controlled under different physiological conditions, the focus of the application will be on regulation of IGF-1 gene transcription by GH. Key goals will be to define the molecular mechanisms by which GH controls IGF-1 expression via the transcription factor, StatSb. Toward this end, the following 4 Specific Aims are proposed: (1) To define the initial steps in activation of IGF-1 gene transcription by GH through StatSb. (2) To characterize mechanisms of termination of GH-stimulated IGF-1 transcription. (3) To determine if the HS7 region of the IGF-1 locus is both necessary and sufficient to mediate GH-regulated IGF-1 gene activation. (4) To characterize mechanisms of dysfunction of a natural amino acid substitution in human StatSb that is associated with profound growth failure.

Title: **Amygdala: Sex Differences in Behavior, Cognition, and Neuroendocrine Development**
P.I.: **Kim Wallen**
Institution: **Emory University – Atlanta, GA**
Grant No.: **2 R01 MH050268-11A1**
Award: **$550,926**

The amygdala, a sexually differentiated brain structure intimately involved in emotions, cognition, social behavior, and sexuality, is particularly important in monkeys for recognizing and responding to social context and danger. This structure continues to develop postnatally and is sexually differentiated prior to puberty, yet nothing is known about its contribution to sex differences in behavior and cognition, its impact on neuroendocrine function, or its role in modulating social signals influencing puberty. Puberty in monkeys and humans is affected by social context and the amygdala may be one of the modulators of the interaction between social context and neuroendocrine function. We will investigate social, emotional, cognitive, and neuroendocrine consequences of neonatal and postpubertal amygdalectomy in male and female rhesus monkeys. Subjects will live in seminatural complex social groups. A team with expertise in emotional regulation, cognition, neuroendocrine

function, and social behavior, will track the development of these systems and relate changes in juvenile function to the pubertal transition and adult social behavior. Forty-eight monkeys, distributed between 8 male and 8 female controls, 8 neonatally amygdalectomized of each sex, and 8 postpubertally lesioned subjects of each sex, will be created in 2 annual cohorts of 24. Neonatal gonadal function, anxiety, fear, and maternal attachment will be assessed along with extensive observations of social interactions in the subjects' natal group during the first year of life. Social observations, assessment of emotionality, and stress physiology will continue for the 2nd through 4th years of life. At 2 years of age, cognitive tasks, using continuously available computer kiosks, will assess object and spatial memory span and object discrimination. Sex differences in social interactions and social integration will be investigated through detailed observations of social behavior. At 2 years of age, females will start intense endocrine sampling to assess pubertal timing as well as pubertal changes in social and sexual behavior. Three-year-old males will be removed from their natal group to simulate male migration and formed into bachelor groups for investigation of the pubertal transition. It is hypothesized that the different male and female natal social environments, combined with the sexually differentiated nature of amygdala function, will result in different magnitudes of effect of amygdala damage, with males likely more severely affected than females. We hypothesize that amygdalectomized females will uniformly show early puberty. Altered amygdala function is found in a number of neurodevelopmental disorders and while amygdalectomy does not serve as a model for any single human mental disorder, understanding its functional effects on a range of behavioral, cognitive, and neuroendocrine endpoints will be invaluable for understanding the developmental trajectory of alterations produced by early amygdala dysfunction in human neurodevelopmental disorders.

Title: **The Biologic Effects of Androgens in Men and Women**
P.I.: **Theodore C. Friedman**
Institution: **Charles R. Drew University of Medicine and Science – Los Angeles, CA**
Grant No.: **5 U54 HD41748-05**
Award: **$194,000**

With a longstanding history of collaborations in education, health services research, and community service, Drew University, the only historically Black medical school west of the Mississippi River, and University of California–Los Angeles (UCLA), one of this Nation's premier universities, are strategically positioned to establish a multidisciplinary, collaborative, thematically focused and integrated reproductive science research program aimed at studying the biologic effects of androgens in men and women. The Drew–UCLA Reproductive Science Research Center will augment and strengthen the research infrastructure and research capabilities of faculty and trainees at Drew University by supporting the development of several new translational and clinical research projects deemed to be of high priority and significance because of their relevance to reproductive health of men and women. The objectives of this grant proposal—to develop an integrated research program that serves as the foundation for future expansion in reproductive biology, reproductive endocrinology, and reproductive medicine at Drew—are reflected in the following Specific Aims: (1) Support the implementation of two reproductive science research projects that effectively use the scientific strengths of our institutions, and promote multidisciplinary approaches to the specific research topics in the priority areas identified by this RFA; (2) Provide support for two pilot projects to generate data to facilitate the development of innovative hypotheses and studies, and support the efforts of our investigators to generate preliminary data and publications that can help assure their transition to independent funding; (3) Facilitate and formalize new collaborative networks in reproductive science between scientists at Drew University and UCLA; (4) Develop an Administrative and Planning Core to support the scientific projects. These Specific Aims will be accomplished by implementing two core research projects and two pilot projects, each having interrelated Specific Aims consistent with the Center's long-term objectives. The research projects will be supported by an Administrative and Planning Core. The proposed core and pilot projects are interlinked by a common theme, namely, Biologic Effects of Androgens in Men and Women. Energetic program leadership, cross-disciplinary research projects that are thematically linked and that evolve logically from our current strengths;

enthusiastic commitment of bi-institutional support; a large pool of talented, participating faculty; deep historical roots of our institution in the minority communities; and strong infrastructural support from preexisting Hormone Assay, Body Composition, Research Center for Minority Institution Molecular Medicine Core, and Exercise Physiology Core laboratories, along with university administration, make our institution particularly suitable to benefit from this *Eunice Kennedy Shriver* National Institute of Child Health and Human Development initiative.

Genitourinary

Title: **Role of Gene Expression in Interstitial Cystitis**
P.I.: **Charles Anthony Buffington**
Institution: **Ohio State University – Columbus, OH**
Grant No.: **1 R21 DK076745-01A1**
Award: **$225,000**

The long-term goal of our research is to use a naturally occurring feline model to gain a sufficient understanding of the causes of interstitial cystitis (IC), an idiopathic chronic pain syndrome affecting humans and domestic cats, to permit development of effective therapies. Converging lines of research have found that adverse experience during the prenatal and early postnatal periods can result in a reprogramming of the stress response system that is hypothesized to predispose susceptible individuals to a variety of diseases in later life. Such events have occurred in many patients with disorders comorbid with IC. Moreover, an adrenocortical abnormality in cats with IC likely results from early adverse experience, making these cats an important naturally occurring model of IC. The hypothesis to be tested in this proposal is that adverse experience leads to alterations in DNA methylation, an epigenetic change that results in altered gene expression and increases susceptibility for the development of the bladder and neuroendocrine abnormalities observed in cats with FIC and humans with IC. The specific objectives of this proposal are to (1) investigate the differential expression of genes in urothelium and adrenal cortex between normal cats and cats with FIC using a general screening strategy called rapid subtraction hybridization, and to use RT-PCR to examine differential expression of three candidate genes: glucocorticoid receptor (GR), ACTH receptor (ACTHR) and corticotropin releasing factor (CRF); and (2) to explore the role of DNA methylation as a mechanism of altered gene expression by comparing global methylation patterns using DNA methyl-acceptance capacity, and DNA methylation patterns in the 5′ regulatory regions of genes identified using subtraction hybridization, and of the GR, ACTHR, and CRF genes. Identifying altered patterns of gene expression in a naturally occurring model of IC could significantly affect our understanding of the causes of IC, which naturally will lead to novel approaches to treatment of this condition, including tests of drugs not heretofore considered for use in these patients. More importantly, identification of the presence of this disease mechanism could lead to significant changes in public health recommendations for pregnant women and children to avoid environmental circumstances that could lead to such detrimental changes in gene expression patterns. Given the common occurrence of co-morbid disorders in patients with IC, these recommendations may be pertinent to the entire category of disorders currently lumped together as medically unexplained syndromes.

Title: **Autoantibody Signatures as Biomarkers of Interstitial Cystitis**
P.I.: **Brian C.-S. Liu**
Institution: **Brigham and Women's Hospital – Boston, MA**
Grant No.: **1 R21 DK078566-01**
Award: **$262,500**

Interstitial cystitis (IC) is a debilitating, chronic bladder syndrome. Currently, there are no validated biomarkers for IC. It is well established, however, that inflammation is associated with IC. Although autoimmunity is debated as a potential cause, certain aspects of IC suggest that it may play a role in initiating or sustaining the chronic inflammatory response evident in this disease. For example,

autoantibodies have been detected in the sera of IC patients to a greater extent than in controls, and the variety of antigens recognized by autoantibodies in IC suggests that the degeneration of bladder epithelial cells that occurs may stimulate the production of autoantibodies. Thus, the presence of inflammation/autoimmunity in IC may allow the use of the body's own immune response as a means of identifying biomarkers of IC. Clearly, knowledge of these potential autoantigens might better enable a greater understanding of the pathobiology of IC, and facilitate the development or use of autoantibody signatures as potential diagnostic biomarkers. With all of the potential advantages, the Achilles heel of autoantibodies is their sensitivity. Lessons from autoimmune diseases show that typically only 15–20% of patients demonstrate a response to any given antigen. However, proteomics may hold the key to success because of its ability to provide the means to multiplex. By linking the responses to several antigens together, the sensitivity and specificity of the test increases considerably. Recently, we described the development and use of a reverse capture autoantibody microarray, a platform that immobilizes 500 specific antigens using a high-density monoclonal antibody capture array. These antigen targets are proteins that are involved in signal transduction, cell-cycle regulation, gene transcription, apoptosis, cell growth, receptors, membrane proteins, as well as adhesion and migration molecules. Using the immobilized antigens as baits, we can determine the autoantibody reactivity between test and controls to the immobilized antigens. We believe this platform may be well suited for the study of IC. Thus, the objectives of our research for this application are (1) to test the hypothesis that the serum autoantibody repertoire from patients with IC can be exploited for autoantibody profiling, and (2) to determine the feasibility, robustness, and reproducibility of the reverse capture autoantibody microarray to identify autoantibody signatures as biomarkers of IC. Interstitial Cystitis (IC) is a debilitating, chronic bladder syndrome characterized by urinary urgency, frequency, and pelvic/bladder pain. A current need in IC research is the identification of IC biomarkers, as there are presently no validated biomarkers for IC. The identification of IC biomarkers is important because they could potentially be used to create clinical tools for the diagnosis of IC and for the development of targeted treatments for IC patients. While the cause of IC is currently unknown, one possible contributor to this condition is worth noting: inflammation. Although autoimmunity is debated as a potential cause of IC, there is published evidence that suggests it may play a role in initiating or sustaining the chronic inflammatory response seen in this disease. In this application, our goal is to identify biomarkers of IC by using antibodies from individual patients with IC.

Title: **Epidemiology of Interstitial Cystitis/Painful Bladder System**
P.I.: **Sandra Berry**
Institution: **RAND Corporation – Santa Monica, CA**
Grant No.: **5 U01 DK070234-04**
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 it difficult to meet patients' needs for medical and nonmedical care. In the proposed research, therefore, we 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: **Seroprevalence and Incidence of Genital Herpes in Uganda**
P.I.: **Edith Nakku-Joloba**
Institution: **New Mulago Hospital – Kampala, Uganda**
Grant No.: **5 R01 TW006672-05**
Award: **$49,813**

Prevalence of herpes simplex virus types 1 and 2 (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 (1) To estimate the age and sex-specific prevalence of Herpes simplex type 1 and 2, (2) 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 (3) 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, 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 of genital herpes, gaining new knowledge about genital herpes in urban Uganda and highlighting the modifiable risk factors that can be targeted for effective interventions.

Title: **PRIDE: Program To Reduce Incontinence by Diet and Exercise**
P.I.: **Deborah G. Grady**
Institution: **University of California, San Francisco – San Francisco, CA**
Grant No.: **5 U01 DK67860-05**
Award: **$97,000**

Network evaluating how weight loss and weight control affects urinary incontinence.

HIV/AIDS

Title: AIDS International Training and Research Program
P.I.: Arthur L. Reingold
Institution: University of California, Berkeley – Berkeley, CA
Grant No.: 5 D43 TW000003-20
Award: $50,000

We will provide multidisciplinary training to physicians, dentists, pharmacists, scientists, and support personnel from selected developing countries in research methods relevant to epidemiological and behavioral studies related to AIDS, HIV transmission, interventions designed to prevent AIDS/HIV transmission, and treatment to prevent or delay morbidity and mortality in HIV-infected persons. Highest priority will be given to training individuals involved in collaborative research projects designed to prevent sexual transmission of HIV via treatment of other sexually transmitted diseases and behavioral or structural interventions; projects testing the efficacy of new HIV vaccines; projects examining how best to use antiretroviral drug regimens to treat HIV-infected persons and monitor outcomes in resource-constrained settings; and projects aimed at improving the prevention and the treatment of tuberculosis and other opportunistic conditions in HIV-infected individuals. Training will be available in planning, managing, and analyzing data from AIDS-related clinical trials and HIV vaccine trials; epidemiological and behavioral research relevant to AIDS, HIV transmission, sexually transmitted diseases and tuberculosis virology, immunology, serology, and other diagnostic methods related to AIDS/HIV; clinical microbiology related to sexually transmitted diseases, tuberculosis, and other opportunistic infections; and the ethical issues involved in human research in general and AIDS-related research in other countries in particular. In all instances in which U.S. faculty are assigned to be in-country for training and supervision of trainees, they will be situated in host institutions conducting high-quality, ongoing collaborative AIDS research, particularly research dealing with behavioral and structural interventions designed to prevent transmission of HIV; HIV vaccine trials; and clinical trials of drugs given to treat HIV infection and AIDS, including antiretroviral drug regimens.

Title: AIDS International Training and Research Program
P.I.: Carey Farquhar
Institution: University of Washington – Seattle, WA
Grant No.: 5 D43 TW000007-20
Award: $50,000

The University of Washington's International AIDS Research and Training Program (IARTP) has trained 150 foreign and 44 U.S. investigators since the program was initiated in 1988 by Dr. Joan Kreiss. Areas of research training may include perinatal transmission, pediatric AIDS, infant mortality, sexually transmitted diseases, HIV-associated diseases (cancer, hepatitis, tuberculosis), infectious diseases, pelvic inflammatory disease, and women's health. Overall, 93% of foreign trainees have returned to their home country following training, with a return rate of 98% for trainees who completed their training within the past 5 years. IARTP training has focused on four target countries: Kenya, Peru, Mozambique, and Thailand. Former IARTP trainees in the two most established sites, Kenya and Peru, have emerged as successful and highly motivated investigators capable of securing funding for expanding research groups and developing proposals for long-term capacity building through CIPRA and ICOHRTA mechanisms. The primary goals of the University of Washington's IARTP will be to promote international collaborative HIV/AIDS research and develop research and public health infrastructure in these countries. Nine members of the International Advisory Board and three track directors in epidemiology, laboratory sciences, and biostatistics will work with the director, codirector, and core faculty to nominate, select, and mentor trainees. The 31 core and more than 50 resource faculty represent multiple disciplines and offer trainees opportunities to collaborate with established HIV/AIDS programs (CFAR, HVTN, HPTN, SCHARP, ACTG, other FIC programs). New additions to the IARTP infrastructure include the following (1) a Biostatistics Track

has been created to meet the need for biostatistics training in our target countries, (2) two faculty members with expertise in therapeutic and prevention trials have been selected to coordinate training for candidates interested in clinical research, and (3) an external review committee, the Training Advisory Group, will review the program annually and conduct peer review of thesis/dissertation research proposals. The training program will continue to emphasize long-term training in epidemiology and health services through the School of Public Health's MPH program, especially in Mozambique, Thailand, and India, a new University of Washington training site that is being proposed in a competing supplement. In Peru and Kenya, more emphasis will be placed on providing opportunities for long-term training in biostatistics and basic science disciplines. Capacity building through short-term training in biomedical ethics and administration will be a major focus in all four countries. During the next 5 years, the IARTP will select three to four foreign postdoctoral trainees each year for MPH training and one to two predoctoral candidates for master's or doctoral degrees in other disciplines. Two University of Washington postdoctoral fellows or predoctoral students will also receive long-term training at a collaborative site. Medium- and short-term training for approximately 14 foreign candidates will be available in epidemiology, biostatistics, laboratory science, biomedical ethics, and administration. Training will involve a wide variety of health professionals and include Kenyan and Peruvian medical students as part of a new UW student bilateral exchange. The IARTP will complement training at the University of Washington with development of in-country training programs for HIV/STD research methods, the responsible conduct of research, grant writing, and grants management. Regional collaborations with other AITRPs and University of Washington Fogarty programs will be strengthened to maximize the benefits of these courses/workshops and south–south collaborations between IARTP sites (e.g., Kenya and Mozambique) will be promoted.

Title: **AIDS International Training and Research Program**
P.I.: **Warren D. Johnson**
Institution: **Weill Medical College of Cornell University – New York, NY**
Grant No.: **5 D43 TW000018-20**
Award: **$50,000**

This proposal requests support for Weill Medical College of Cornell University (WMC or Cornell) to continue training Haitian scientists in the performance of biomedical, epidemiological, interventional, and behavioral research on HIV and related opportunistic infections. The program is based in the Division of International Medicine and Infectious Diseases at Cornell, with an interdisciplinary group of investigators who have extensive collaborations with Haiti. New and strengthened collaborations with Vanderbilt, Harvard, University of California (Berkeley), Meharry Medical College, the New York City Department of Health, the Hastings Center, and the Aaron Diamond AIDS Research Center offer diverse training opportunities. The program will continue to emphasize long-term training and advanced research training in Haiti. Since its inception, the AITRP program has provided medium- and long-term training to 67 Haitian biomedical personnel, with 96% currently conducting HIV/AIDS work in Haiti. The training offered will be related to six general HIV/AIDS research categories: (1) HIV vaccine trials; (2) antiretroviral clinical trials; (3) pediatrics and maternal-infant transmission research; (4) HIV-associated opportunistic infections and tuberculosis; (5) ethics and behavioral research; and (6) pathogenesis, immunology, and virology. The proposed training will be conducted largely in Haiti, with much of the training done by the former Fogarty trainees. The training program is embedded in the ongoing collaborative Cornell-Vanderbilt GHESKIO HIV research activities, including the HIV vaccine trials unit (HVTN), international clinical trials unit (ICTU), WHO/TDR tuberculosis and syphilis research, United Nations Global Fund, and proposed CIPRA and ICOHRTA grants. The highest priority will be given to training that will facilitate the conduct of HIV vaccine and clinical trials and to other intervention programs in Haiti. In addition to research training in Haiti, trainees will have the opportunity for advanced training with outstanding U.S. mentors. The program's U.S. core and collaborating training faculty are funded scientists committed to AIDS research. The faculty constitutes a cohesive unit, with diverse but focused interests. Five competing supplements to this AITRP renewal are also submitted. Four of the supplements are

for expansion of research training either geographically (Brazil, Nigeria, and Dominican Republic) or in our emphasis country (Haiti). The fifth supplement is for in-country reentry support for a Fogarty trainee (Francine Noel, M.D.). The titles of the supplements are Tuberculosis/AIDS Training and Research Program – Brazil/Cornell University, Scale-Up of Community-Based HIV Prevention and Care – Haiti/Harvard University, AIDS International Training and Research Program – Dominican Republic/Columbia University, Creating Sustainable HIV/AIDS Research – Nigeria/Cornell University, and Models of HIV Pediatric Care – Haiti/GHESKIO/Vanderbilt University.

Title: **Recombinant CCR5 Inhibitors for Topical Microbicides**
P.I.: **Donald E. Mosier**
Institution: **Scripps Research Institute – La Jolla, CA**
Grant No.: **5 R21 AI071935-02**
Award: **$13,000**

This R21/R33 Phased Innovation Award application proposes to develop novel RANTES derivatives capable of recombinant expression as candidate topical microbicides. These molecules target the CCR5 coreceptor used by HIV-1 isolates responsible for primary transmission. Two lead candidates with antiviral activity against CCR5-using HIV-1 isolates equivalent to the fully synthetic PSC-RANTES have been identified using an innovative phage display selection process that allows screening of millions of CCR5-binding molecules. One of these molecules shares the inhibitory mechanism of PSC-RANTES, CCR5 internalization and sequestration, and also shares signaling activity via CCR5. The second molecule, although equally potent at inhibiting virus infection, does not cause CCR5 internalization or signaling via CCR5. These properties could improve the safety profile of this molecule. The objectives of the R21 phase of the proposal are to determine the mechanism of activity of the two molecules, the duration of activity after compound removal, and the activity against clade A, C, and D primary transmission isolates from sub-Saharan Africa. We will also attempt to generate resistant variants to both molecules in vitro and compare the stability of the molecules to low pH, high temperature, and exposure to cervicovaginal lavage fluid. The molecule with the best combination of properties in these experiments will be selected for preclinical evaluation in the R33 phase using the SHIV162P3 vaginal challenge model in female rhesus macaques. These experiments will establish the effective dose for preventing transmission, determine if that dose protects against delayed virus challenge, and evaluate local inflammation and induction of proinflammatory cytokines as indicators of safety. Virus recovered from treated animals with delayed viremia will be evaluated for development of resistance to the lead RANTES derivative. These studies are designed to lead to a safe, effective, and inexpensive protein CCR5 inhibitor for incorporation into a topical microbicide for use in areas most impacted by the global HIV/AIDS pandemic.

Title: **Improved Macaque Safety Model for Topical Microbicides: Postcoital Assessments**
P.I.: **Dorothy L. Patton**
Institution: **University of Washington – Seattle, WA**
Grant No.: **1 R21 AI071939-01A1**
Award: **$13,000**

Topical microbicides represent an emerging strategy for the prevention of transmission of HIV and other sexually transmitted infections (STIs). A successful topical microbicide product will be applied prior to intercourse, without necessitating partner consent, and will be active against a variety of STIs, including HIV. It will be acceptable to potential users in terms of physical characteristics, availability, ease of use, and safety and efficacy properties. We have utilized the macaque vaginal safety model (currently contracted by the NIH, N01-AI-95388) to provide standardized preclinical safety data for numerous topical microbicide products in development. In this model, measures of product safety include cervicovaginal colposcopy, vaginal microbiologic evaluation, and vaginal pH monitoring. This model characterizes the vaginal environment's response to repeated topical prod-

uct applications in the absence of the exogenous factors of intercourse and potentially infectious ejaculate. While our preclinical evaluations of topical microbicide products have been well rounded in many aspects, we have yet to investigate the effects of sexual intercourse on the cervicovaginal environment. Mucosal perturbation and potential microtrauma in the form of epithelial abrasions are likely to result from sexual activity. Additionally, the effects that seminal fluid may induce on the cervicovaginal environment, as well as its effects vis-a-vis topical microbicide product safety and efficacy, have not yet received their due attention. We propose to enhance our standardized vaginal safety evaluations conducted in the pigtailed macaque model to include evaluations after sexual activity and with the presence of seminal fluid. With continued R33 funding, we will collect baseline data from 24 female macaques, assessing the cervicovaginal environment before and after mating. In addition, we will collect parallel assessments, when mating has occurred, with a placebo gel (HEC universal placebo) in place. These studies will provide urgently needed data regarding topical microbicide use with coital activity.

Title: **Implementation of a Vaginal/Rectal HIV Transmission to Model to Evaluate Microbicides**
P.I.: **Victor J. Garcia-Martinez**
Institution: **University of Texas Southwestern Medical Center at Dallas – Dallas, TX**
Grant No.: **5 R21 AI071940-02**
Award: **$13,000**

The long-term goal of our laboratory is to investigate novel approaches to prevent HIV transmission by the use of microbicides. For this purpose, we have developed and implemented a novel small-animal model where human stem cells are used to reconstitute the hematopoietic system of immunodeficient mice. In these humanized mice (designated BLT to represent the fact that they are generated from a bone marrow transplant of mice previously implanted with a piece of autologous human fetal liver and thymic tissue), there is systemic reconstitution with human hematopoietic cells in all hematopoietic and nonhematopoietic tissues tested. As shown in the Preliminary Results section, these humanized mice are susceptible to intrarectal infection with HIV-1. Infection results in plasma antigenemia and progressive depletion of human CD4+ cells from the peripheral blood. We show that human CD4 T cell depletion is systemic and most dramatic in the human thymic organoid, where double-positive thymocytes are depleted. Using in situ hybridization, we show the presence of infected cells in the large and small intestine, mesenteric lymph nodes, spleen, and thymic organoid. We also demonstrate that infectious virus can be isolated from these tissues. In this grant, we propose to expand on these remarkable results and to establish the suitability of the BLT system to evaluate HIV transmission and its prevention by microbicides. With this in mind, we propose the following aims for the R21 portion of this grant: Specific Aim 1: To characterize the systemic replication of R5 HIV-1 after intrarectal inoculation of BLT mice. Specific Aim 2: To evaluate the efficacy of a topical or systemic microbicide to prevent intrarectal transmission of HIV-1 in BLT mice. After completion of these two Aims, we propose to determine the susceptibility of BLT mice to intravaginal infection, as indicated below in the Specific Aims for the R33 portion of this grant. Specific Aim 3: To evaluate the susceptibility of BLT mice to intravaginal infection with cell-free X4 and R5 HIV-1. Specific Aim 4: To determine the efficiency of topical microbicides to prevent intravaginal HIV infection in the BLT model. Once we have established these basic parameters and, at the same time, determined the BLT's limitations, we will be able to move forward with this novel system to contribute to the development and implementation of novel microbicides to prevent HIV transmission.

Title: Topical Immune Modulatory Strategies To Prevent HIV Transmission
P.I.: Michael Lederman
Institution: Case Western Reserve University – Cleveland, OH
Grant No.: 5 R21 AI071944-02
Award: $13,000

Recent years have witnessed a welcome explosion in the study and development of topical microbicides to prevent HIV transmission. Among the important recent developments are contributions of members of this team. Developing an amino-terminus–modified RANTES analogue, PSC-RANTES, which is several logs more potent than the native RANTES and is so far the only agent shown to afford high-level protection (10/10 animals) from SHIV in the rhesus vaginal challenge model, we have demonstrated that CCR5 blockade alone is sufficient to block SHIV transmission in this system. Nonetheless, current costs of synthesis may render this reagent too expensive for use at the highest, most effective concentrations. At the same time, one member of our team has demonstrated that combinations of microbicide candidates can synergize to provide high-level protection in the rhesus challenge model. We therefore propose in this application a series of high-risk, exploratory studies to test the rationale for combination microbicide strategies by testing the following hypotheses: (1) Cellular activation at mucosal sites of HIV entry promotes HIV dissemination and a topical immune modulator can antagonize activation and provide synergistic activity with lower doses of PSC-RANTES. This is plausible since there is increasing evidence that cellular activation is a critical underpinning of HIV pathogenesis, of viral dissemination from mucosal sites during early infection, and possibly also in susceptibility to HIV infection. (2) Topical application of type 1 interferons will block HIV replication without the topical inflammation induced by TLR stimulation, and this activity will synergize with CCR5 blockade as induced by PSC-RANTES. This is a plausible strategy as interferons comprise a major arm of innate host defenses against viral infection, are suppressive of HIV replication, and also play a role in the arming of other innate and adaptive defense mechanisms. (3) Topical application of immune modulators will provide synergistic antiviral activity when coadministered with a type I interferon, as the latter will block HIV infection of target cells and arm both innate and adaptive immune defenses, while the former will block dissemination of infection that is dependent upon immune activation. These hypotheses will be tested in PBMC, in epidermal Langerhans cells, and in ectocervical explants. If warranted by results in these systems, a promising combination strategy will be selected for further testing in the rhesus vaginal challenge model with concurrent studies of protective activity, safety, and effects on immunologic indices and microbiologic indices of topical immune suppression. We expect that the results of these studies will provide insights into mechanisms of HIV acquisition across mucosal surfaces that will guide the further development of topical strategies to prevent HIV transmission.

Title: Lactobacilli as a Source of Natural Microbicides Against HIV-1
P.I.: Ruth Ingrid Connor
Institution: Dartmouth College – Hanover, NH
Grant No.: 1R21 AI071948-01A1
Award: $10,000

Topical microbicides formulated for vaginal use may help stem further spread of HIV-1 by reducing the number of new infections in women. One microbicide strategy under consideration is to strengthen the natural defenses in the vaginal mucosa where HIV-1 transmission takes place. Lactobacillus species are the predominant commensal bacteria found in genital tract secretions of healthy women. Under anaerobic conditions, these bacteria produce lactic acid and certain strains also produce hydrogen peroxide, a potent antimicrobial that has been shown to inactivate HIV-1 in vitro. Lactic acid bacteria also produce an array of antimicrobial molecules, termed bacteriocins, that are effective against competing organisms in the local milieu. Whether these natural antimicrobial factors can inhibit transmission and replication of HIV-1 in vaginal tissues is unknown. In preliminary studies, we have shown that conditioned media from cultures of *Lactobacillus rhamnosus* GG (LGG) inhibits

replication of HIV-1 by 2 to 4 logs10 in primary CD4+ T lymphocytes, and this antiviral activity is distinct from both lactic acid and hydrogen peroxide. We hypothesize that natural bacteriocin-like molecule(s) produced by commensal lactic acid bacteria can enhance innate immunity in the vaginal mucosa and can inhibit infection and/or replication of HIV-1 in these target tissues. The goal of studies proposed in the exploratory (R21) phase is to purify and identify the low-molecular-weight active factor(s) produced by LGG bacteria and determine the extent to which the LGG-purified factors (LGG-PF) (1) inhibit replication of HIV-1 in vitro; (2) modulate cell activation, proliferation, and transcriptional regulation; and (3) affect the secretion of innate immune factors from primary epithelial cells from the human female reproductive tract. In the developmental (R33) phase, we will evaluate the effect of LGG-PF on HIV-1 infection and secretion of innate immune factors in primary explant cultures of human cervical and vaginal tissues and will further evaluate cervicovaginal toxicity and inflammation in a mouse model developed for preclinical evaluation of topical vaginal microbicides. If the purified factor(s) secreted by LGG bacteria are shown to inhibit HIV-1 replication in relevant target cells in vitro, and modulate expression of innate immune factors in female genital tract tissue explants, this would provide evidence of a novel and beneficial effect that extends well beyond the established antimicrobial function of these bacteria. Moreover, these results would lay the foundation for application of *lactobacilli*-derived products as HIV microbicides, either alone or in combination with targeted compounds that block HIV-1 infection and replication.

Title: **Proteolytic Antibody HIVcides**
P.I.: **Paul Sudhir**
Institution: **University of Texas Health Science Center Houston – Houston, TX**
Grant No.: **5 R21 AI071951-02**
Award: **$10,000**

A specific, irreversible, and cost-effective topical microbicide for HIV prophylaxis will help slow sexual transmission of the pandemic. Here, we propose the development of catalytic antibodies capable of degrading the HIV envelope protein gp120 as candidate HIVcides. The promising features of the antibodies are the permanent destruction of the envelope protein; reuse of a single catalyst molecule to degrade thousands of gp120 molecules; and the recognition of a conserved gp120 region, the superantigen region, permitting neutralization of diverse HIV strains. Polyclonal antibody studies from uninfected and HIV-infected subjects indicated that high-level proteolytic and HIV-neutralizing activities are a noteworthy property of IgA-class antibodies. In the R21 project phase, characterization of our existing antibodies and their single-chain Fv (scFv), IgA, and IgG variants is proposed. The existing antibodies were obtained as IgGs by immunization with an electrophilic gp120 analog that induces antibodies with enhanced nucleophilic reactivity, a prerequisite for the catalytic reaction. Using an electrophilic probe to the gp120 superantigen site, additional proteolytic antibodies were obtained as scFv constructs cloned from the immune repertoire of lupus patients, who tend to produce antibodies with proteolytic activity directed to the gp120 superantigen site. The antibodies will be characterized with respect to HIV degrading efficiency; specificity, potency, and breadth of HIV neutralization; and the ability to perform these functions in the vaginal milieu. To isolate novel, improved antibodies, we will screen the proteolytic and HIV-neutralizing activity of salivary and serum IgAs from HIV-negative and HIV-positive subjects in the R21 project phase. In the R33 phase, monoclonal IgAs with the desired properties will be cloned from lymphocytes by cell fractionation based on covalent binding of an electrophilic gp120 peptide analog, a property associated with proteolytic antibody-producing cells. Proof of principle for in vivo antibody efficacy will be obtained in the R33 phase using the SHIV–macaque model of infection. The Abs will also be examined for activity in vitro as microbicide excipient formulations under conditions simulating the vaginal environment following sexual intercourse. These studies may identify proteolytic antibodies suitable for further development as a topical HIVcide.

Title: **Syndecan Agonists and Antagonists as Microbicides**
P.I.: **Philippe Gallay**
Institution: **Scripps Research Institute – La Jolla, CA**
Grant No.: **5 R21 AI071952-02**
Award: **$10,000**

The development of a safe, effective, and acceptable topical microbicide to prevent the sexual transmission of HIV-1 could play a major role in worldwide reduction of the over 14,000 new HIV-1 infections per day and potentially save millions of lives. We obtained several lines of evidence suggesting that HIV-1 exploits syndecan-1 and -2 to successfully cross the genital epithelium. Thus, syndecans represent new targets for the development of topical microbicides. We propose to develop compounds that prevent HIV-1-syndecan interactions, both in vitro (R21 phase) and in vivo (the R33 phase). Specifically, we propose to develop and test compounds that neutralize either the mucosal syndecans (syndecan antagonists) or the syndecan binding of HIV-1, gp120 (syndecan agonists). Importantly, we have already generated a couple of syndecan antagonists and agonists, which efficiently prevent the passage of HIV-1 through primary human genital epithelial cells, further emphasizing that syndecans represent attractive targets for the development of microbicides. Since compounds that interrupt gp120–syndecan interactions have never been exploited as microbicides, they represent a novel class of microbicides and thus differ from existing tools. One advantage of using compounds, which target gp120-syndecan interactions as microbicides, is that all primary R5, X4, and R5X4 HIV-1 as well as HIV-2 isolates bind syndecans. Thus, these compounds will have a broader impact than, for example, RANTES derivatives, which neutralize R5 viruses only. Since we found that compounds that block gp120-syndecan interactions also block gp120-CCR5 interactions, their dual inhibitory effects represent another advantage of using them as microbicides. Moreover, another advantage of using microbicides that target syndecans is that many sexually transmitted pathogens also exploit syndecans for host colonization, such as *Herpes simplex* virus and *Neisseria gonorrhoeae*. Thus, microbicides targeting gp120–syndecan interactions will exhibit a broad inhibitory spectrum against sexually transmitted pathogens.

Title: **Peptide Deformylase Inhibitor LBM415 for Sexually Transmitted Infections**
P.I.: **Huizhou Fan**
Institution: **University of Medicine and Dentistry of New Jersey, Johnson Medical School – Piscataway, NJ**
Grant No.: **1R21 AI071054-01A1**
Award: **$10,000**

This R21/R33 phased project will explore a novel strategy for combating sexually transmitted chlamydial and gonococcal infections. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most common sexually transmitted pathogens. In addition to acute urogenital inflammation, chlamydial and gonococcal infections frequently result in devastating complications, including infertility and chronic pelvic pain syndrome. Infection with these bacteria also increases the risk of HIV infection. Sexually transmitted chlamydial and gonococcal infections disproportionately affect the wellness of women. Therefore, there is an urgent need to develop effective self-administered, topical antimicrobials to combat the transmission of these organisms and other sexually transmitted pathogens. We have discovered that *C. trachomatis* and *N. gonorrhoeae* are highly susceptible to inhibitors of peptide deformylase (PDF), an enzyme that catalyzes the removal of the formyl group from newly synthesized proteins/peptides before they become biologically active. Lactobacilli and *Escherichia coli* are significantly resistant to PDF inhibitors. We hypothesize that PDF inhibitors may be used topically to prevent sexually transmitted chlamydial and gonococcal infections without disrupting normal microflora. The goal of the R21-phase research is to determine the feasibility of utilizing the lead PDF inhibitor, LBM415, topically for combating genital chlamydial and gonococcal infections. Thus, mice will be intravaginally exposed to a commercial gel containing LBM415 to determine whether LBM415 is free of acute and long-term toxicity and provides protection against vaginal chlamydial

and/or gonococcal infections upon its topical application. In addition, the effects of LBM415 on vaginal probiotic lactobacilli and bacterial vaginosis-associated pathogens will be determined. Frequencies of resistance to LBM415 in *Chlamydia trachomatis* and *N. gonorrhoeae* will also be assessed. If the R21 research meets its defined milestones (i.e., meaningful protection against chlamydial and gonococcal infections in vivo, a lack of in vivo toxicity, significant toleration by probiotic lactobacilli, and acceptable resistance frequencies), additional studies will be carried out to further determine the value of LBM415 for combating chlamydial and gonococcal infections in the R33 phase. During the R33 phase, dose-response, inhibition of pathogen shedding from animals with pre-established infection, possibility of early application, and potential synergism with another promising broad-spectrum topical microbicide candidate will be studied.

Title: **CVN-12p1 Chimeras and Combinations for AIDS Microbicides**
P.I.: **Irwin M. Chaiken**
Institution: **Drexel University – Philadelphia, PA**
Grant No.: **5 R21 A1071965-02**
Award: **$10,000**

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 protein cyanovirin-N (CV-N) is a highly stable protein that binds to HIV-1 Env gp120 and antagonizes viral entry into host cells and consequent infection. CV-N can be produced recombinantly at large scale, has been found to be effective in blocking HIV-1 transmission in animal studies, and is currently in preclinical development as a microbicide. Nonetheless, there are potential limitations, including amount of CV-N production required based on measured in vivo efficacy, reliance on a single mode of action, and CV-N–resistant strains of virus. Limitations of CV-N could be overcome by combining this protein with a second inhibitory agent that binds to a different interaction site in the same molecular target, gp120, and synergizes its antagonist activity with that of CV-N. Recently, we have found that a peptide denoted 12p1 functions as an allosteric dual antagonist of gp120 interactions with host cell receptors and can improve the antiviral activity of CV-N in combination mixtures. We have identified a chemical-modification strategy that yields strikingly higher affinity forms of 12p1 for gp120. Further, we have lead data demonstrating that a recombinant chimera of 12p1 and CV-N has enhanced antagonist activity vs. CV-N alone. The R21 part of this proposal is to examine the usefulness of evolving 12p1-based molecules as possible means to enhance the capability of CV-N as a microbicidal agent. The R33 phase will be to develop promising lead combinations and chimeras, including advanced agent design based on structural mechanism of action; to define in vitro and in vivo efficacy of lead chimeras and combinations and to examine synergies with other agents in the microbicide field; and to develop production approaches for the protein and peptide agents derived in this work. We will prioritize two specific aims in the R21 project. (1) Produce recombinant CV-N-12p1 chimeras with varying linkers and determine efficacy of chimera candidates versus that of the separate CV-N and 12p1 components. Work on this aim will identify CV-N-12p1 chimeras with optimized HIV-1 Env gp120 antagonism and potential as recombinant AIDS microbicide candidates. (2) Generate and screen affinity-enhanced conjugate 12p1 variants for noncovalent combination with CV-N and identify optimized mixture candidates. Work in this aim will provide alternative microbicide candidates that combine recombinant CV-N with synthetic 12p1 conjugates. The major milestone at the end of the R21 phase will be identification of 12p1/CV-N combinations, both chimeras and mixtures, that will have antagonist activities that are enhanced vs. CV-N alone and that hence will be recommended for development as microbicides in their own right. The CV-N-12p1 chimeras and noncovalent combinations will introduce a microbicide with a novel mechanism of action, substantially overcome potency and resistance limitations of CV-N alone, and hence lead to improved microbicide candidates to combat global AIDS transmission.

Title: Engineering Simian-Derived Lactobacilli to Secrete Anti-HIV-1 Microbicide
P.I.: Cecilia Cheng-Mayer
Institution: Aaron Diamond AIDS Research Center – New York, NY
Grant No.: 5 R21 AI071967-02
Award: $10,000

Every day, nearly 14,000 people are newly infected with HIV-1, and over 80% of these infections are transmitted by the mucosal route during unprotected rectal or vaginal intercourse. The development of a safe and effective topical microbicide may offer a preventive strategy that could have a major impact on the course of the HIV pandemic. Six candidate topical microbicides are currently undergoing clinical effectiveness trials and many others are under development. However, potential shortcomings of topical microbicides are the requirement of immediate precoital application; possible vaginal irritation/inflammation upon long-term use, which may result in enhanced HIV-1 transmission; and relatively high production costs. The strategy of using live microbial microbicides may solve the potential problems inherent in chemically based microbicides. Here, we seek to develop a live microbial anti-HIV microbicide based on simian-derived vaginal lactobacilli isolates. The cervicovaginal mucosa is primarily colonized by commensal lactobacilli, and the secretion of substantial quantities of an anti-HIV microbicide by genetically engineered lactobacilli may effectively block vaginal transmission of HIV-1. We will identify vaginal lactobacilli, isolates from macaques that demonstrate high hydrogen peroxide (H2O2) production and strong adherence to vaginal epithelial cells, critical factors for in situ colonization. Plasmid systems will be engineered to express and secrete anti-HIV compounds. The ability of recombinant lactobacilli strains to colonize the cervicovaginal tract will be tested in rhesus macaques. Finally, macaques will be inoculated with recombinant-*lactobacillus*-secreting anti-HIV microbicides and subsequently challenged with chimeric/simian immunodeficiency virus SHIV-162P3 to determine protective efficacy. The goal of this application is to develop a live microbial topical microbicide against HIV-1 based on vaginal *lactobacillus* isolates that may offer the following significant advantages over chemically based topical microbicides: (1) long-lasting protection due to bacterial colonization, thus eliminating the need for direct precoital application, and more control by the vulnerable receptive partner; (2) low potential to induce inflammatory reactions by using vaginal commensal bacteria; and (3) low production costs compared to protein-based microbicides.

Title: Topical Microbicide Against SIV and Chlamydia
P.I.: Ashley T. Haase
Institution: University of Minnesota, Twin Cities – Minneapolis, MN
Grant No.: 5 R21 AI71976-02
Award: $10,000

This application's major objective is to test the efficacy of a potential microbicidal agent to prevent transmission of HIV to women. Such an effective agent is urgently needed to combat the predominant rise globally of new HIV infections in women. Based on promising preliminary results in vitro, the specific aim of this application is to test in vivo the efficacy of glycerol monolaurate (GML) to prevent intravaginal transmission of simian immunodeficiency virus to rhesus macaques, a highly relevant nonhuman primate model of sexual mucosal transmission of HIV. Treated or control monkeys will be infected and biopsy and necropsy specimens will analyzed by immunohistochemical and in situ hybridization methods and viral loads in blood to assess the efficacy of GML in preventing transmission or altering viral replication in cervicovaginal and lymphatic tissues.

Title: Development of N-Peptides for Use in HIV-1 Topical Microbicides
P.I.: Min Lu
Institution: Weill Medical College of Cornell University – New York, NY
Grant No.: 5 R21 AI071979-02
Award: $10,000

HIV-1 continues to spread globally and no vaccine is available. Hence there is an urgent public health need for an effective microbicide to prevent sexual transmission of HIV-1. The topical application of potent combinations of viral fusion and entry inhibitors has been shown to exhibit microbicidal efficacy in the rhesus macaque vaginal transmission model. Peptides derived from the N- and C-terminal regions of the gp41 ectodomain (called N- and C-peptides, respectively) inhibit HIV-1 entry. N-peptides have generally proven far less potent than C-peptides. However, stabilization of a trimeric coiled-coil conformation of N peptides has been demonstrated to be a viable strategy to develop them as a new class of potent HIV-1 fusion inhibitors. We have recently identified and determined the crystal structure of an autonomously folded, N-peptide coiled-coil domain. The overall goal of this research plan is to gain a detailed understanding of the structural and thermodynamic properties of this novel coiled-coil domain and to use this knowledge to design and produce a bacterially expressed N-peptide fusion inhibitor for inclusion in an HIV-1 topical microbicide. Our central hypothesis is that the synergistic inhibition of different stages of the viral fusion and entry process can offer a powerful benefit in formulating an efficacious and more economical microbicide product. Specific aims of this research: (1) To use modern protein engineering methods to identify and develop stabilized variants of a trimeric coiled-coil domain that display potent inhibitory activity against HIV-1 membrane fusion. We will use isoleucine- and valine-scanning mutagenesis to identify and incorporate specific residue substitutions that increase both trimer stability and antiviral potency. We will also construct chimeric N-peptides by using an isoleucine-zipper sequence to stabilize the coiled-coil structure. Our emphasis is to generate potent N-peptide inhibitors suitable for development as an inexpensive component of a microbicide formulation. (2) To characterize the specificity, potency, and toxicity of improved N-peptide variants and their in vitro synergistic interactions with the virus-cell attachment inhibitors CMPD167 and BMS-378806 and the C-peptide fusion inhibitor C52L. We will conduct in vitro studies to determine inhibitory activity of select N-peptide variants against diverse primary HIV-1 isolates and their toxic or inflammatory effects using the rabbit vaginal irritation model and in human cells. We will also study synergistic antiviral effects in vitro in order to make rational predictions for lead inhibitor combinations for formulation and efficacy testing in rhesus macaques. (3) To use the rhesus macaque high-dose vaginal transmission model to assess the in vivo potency of an optimized N-peptide inhibitor alone and in combination with CMPD167, BMS-378806, and C52L. We will evaluate the protection of macaques from vaginal challenge with both CCR5 and CXCR4 SHIVs by a vaginally delivered N-peptide inhibitor alone and in synergistic combination with CMPD167, BMS-378806, and C52L.

Title: Stimulators of HIV-1 Integrase for Use in Combination Microbicide Regimes
P.I.: Michael Katzman
Institution: Pennsylvania State University, Hershey Medical Center – Hershey, PA
Grant No.: 1 R21 AI075929-01
Award: $10,000

The long-term goal of this project is to develop ways to interfere with HIV replication and transmission, which would have major implications for preventing the spread of HIV/AIDS. Any successful preventive strategy must work before infection becomes established, and the hallmark of an established retroviral infection is integration. The viral integrase enzyme catalyzes at least two endonuclease reactions in vivo: specific nicking to prepare the ends of viral DNA for integration and nonspecific insertion of the viral DNA into cellular DNA. Integrase also has a potent nonspecific endonuclease activity that can nick any DNA sequence in vitro, and this activity is dramatically stimulated by certain small compounds. These facts suggest a novel (and ironic) antiviral strategy in

which integrase is stimulated to destroy viral DNA before integration (with any damage to cellular DNA being limited to newly infected cells and also blocking infection). Thus, the objectives of this proposal are to identify potent stimulators of the nonspecific nicking activity of HIV-1 integrase and to bring at least one of these agents to the verge of clinical testing. The central hypothesis, based on known precedents and preliminary data, is that integrase's nonspecific endonuclease activity can be stimulated for a new antiviral strategy that can be part of a safe and effective combination microbicide regimen. In the R21 phase, Aim 1 will optimize a high-throughput assay for integrase-mediated nonspecific DNA nicking; Aim 2 will screen 50,000 chemicals in the Penn State Drug Development and Discovery Core for additional agents that stimulate HIV-1 integrase to nick DNA nonspecifically (with appropriate secondary assays to validate positive hits); and Aim 3 will use quantitative antiviral and cell toxicity studies to prioritize integrase stimulator (IS) compounds based on their therapeutic indices, all the while feeding back to organic chemists who will design and synthesize rational analogues of lead compounds for testing in an iterative fashion. In the R33 phase, Aim 4 will test the safety of each candidate IS compound in expanded toxicity studies, including a mouse model of cervicovaginal toxicity; and Aim 5 will test the range of antiviral activity against different subtypes of HIV-1 and in a NOD-SCID-hu mouse model of HIV-1 infection. These data will also feed back to the discovery pathway to make new derivatives of IS compounds. Finally, because the ideal microbicide regimen would combine agents that work outside cells to impede virus entry with agents that work inside cells to abort infection for any viruses that do gain entry, Aim 6 will evaluate microbicide combinations that include IS compounds for cooperative activity against HIV-1, in preparation for moving at least one drug candidate into future clinical trials.

Title: **Mucosal Protection Against HIV Transmission by Combinations of Anti-HIV Antibodies**
P.I.: **Lisa A. Cavacini**
Institution: **Beth Israel Deaconess Medical Center – Boston, MA**
Grant No.: **1 R21 AI075932-01**
Award: **$10,000**

There were approximately 5 million new infections with HIV-1 worldwide in 2005, with an increase in the prevalence of women becoming infected, especially in Africa, south and Southeast Asia, Eastern Europe, and central Asia, where social and cultural inequalities significantly impact a women's ability to prevent infection. While prevention programs can be successful at reducing the incidence of transmission, assuming they are long term and intensive, many individuals do not have access to prevention programs or are unaware of their partner's HIV status. Additional means of prevention must be developed to reduce the sexual transmission of HIV. A microbicide might be an effective means for women to use. It has been estimated that the regular use of a microbicide that is 60% efficacious by 20% of women in highly impacted countries would protect against hundreds of thousands of infections. Passive administration or local application of human monoclonal antibodies has been shown to be effective in preventing mucosal infection in nonhuman primate models. We hypothesize that the structure of these monoclonal antibodies can be altered to improve in vivo efficacy at mucosal surfaces formulated as a microbicide that can provide long-lasting, convenient, reliable, and locally effective prevention. To study these hypotheses, we propose to (1) determine the relationship of IgA subclass and monomeric or polymeric structure to functional activity of anti-HIV antibodies and stability in the mucosal environment, and (2) determine efficacy at preventing infection following vaginal challenge of nonhuman primates. Specific antibodies have been identified based on broad reactivity, structure-function relationships, epitope exposure, and availability and include F425A1g8, reactive with an epitope exposed by CD4 binding with neutralizing activity; b12, reactive with the CD4 binding site and neutralizes a broad range of isolates; F425B4e8, reactive with the V3 loop and neutralizes a broad range of isolates; and F240, reactive with gp41, binds to all clades of HIV and neutralizes infection when expressed as an IgA antibody. F240 represents a prototype of a class of antibodies that may include other broadly reactive antibodies to well-conserved sites that may mediate local destruction or sequestration of virus away from target cells for destruc-

tion by innate immune mediators prevalent at the mucosal surface or neutralize infection under specific conditions. The studies proposed explore the hypothesis that local expression of a combination of broadly anti-HIV-1 antibodies at the mucosa represents an efficacious method to block entry of the virus into the body.

Title: **Inhibitors of HIV-Dendritic Cell Interactions as Microbicides**
P.I.: **Philippe Gallay**
Institution: **Scripps Research Institute – La Jolla, CA**
Grant No.: **1 R21 AI076005-01**
Award: **$10,000**

The development of a safe, effective, and acceptable topical microbicide to prevent the sexual transmission of HIV could play a major role in worldwide reduction of the over 14,000 new HIV infections per day and potentially save millions of lives. Given that cell-free virus ineffectively crosses the genital epithelium in the absence of lesions, it is likely that HIV hijacks host cells as Trojan horses to cross the normally impermeable genital epithelium. It has been postulated that HIV exploits Langerhans (LC) and dendritic cells (DC) to facilitate its safe passage through the genital epithelium. In this application, we propose to develop compounds that prevent HIV-LC and HIV-DC interactions in vitro (R21 phase) and to test them as topical microbicides in vivo (R33 phase). We demonstrated that HIV uses three specific receptors to mediate its initial contact with vaginal LC and DC. We propose to generate reagents that target each of these receptors. These receptor antagonists will then be tested for their capacities to prevent HIV-LC and -DC interactions. The goal is to identify reagents that are the most potent at blocking in vitro HIV hijacking of vaginal LC and DC. These LC and DC receptor inhibitors will serve as microbicide candidates for subsequent in vivo studies proposed in the R33 phase. We demonstrated that gp120 mediates the contact between HIV and vaginal LC and DC. We propose to generate reagents that prevent gp120-LC and -DC interactions. Specifically, we propose to generate soluble reagents that mimic the receptors that HIV exploits to interact with LC and DC. These receptor mimics will serve as decoys to prevent gp120 contact with vaginal LC and DC. The goal is to identify receptor mimics that are the most potent at blocking in vitro HIV hijacking of vaginal LC and DC. These receptor mimics will serve as microbicide candidates for in vivo studies proposed in the R33 phase. One advantage of using compounds that prevent HIV-LC and -DC interactions is that many sexually transmitted pathogens also exploit LC and DC for host colonization, and thus the ability to block HIV-LC and -DC interactions may have the additional benefit of preventing other sexually transmitted pathogens. This approach may not only provide valuable novel microbicides, but it will also allow us to assess the contribution of LC and DC to HIV transmission.

Title: **Models for Testing Candidate Topical Microbicides for Cytotoxicity and Activity**
P.I.: **Mary F. Lampe**
Institution: **University of Washington – Seattle, WA**
Grant No.: **1 R21 AI076020-01**
Award: **$10,000**

Chlamydia trachomatis, an obligate intracellular parasite, is the most common sexually transmitted bacterial pathogen in the world. Infections are often asymptomatic and can cause serious complications, such as pelvic inflammatory disease, infertility, and ectopic pregnancy. In addition, chlamydial infections may increase the risk of HIV transmission. The development of topical microbicides to prevent sexually transmitted infections has recently gained attention. We have developed the in vitro minimal cidal concentration (MCC) assay to test the direct action of microbicides on the extracellular, infectious chlamydial EBs. We now propose to continue developing the MCC assay by studying the in vitro safety and efficacy of peptide and lipid topical microbicides and the effects of strain variation and the presence of human albumin, simulated vaginal fluid, or simulated semen. The MCC assay will further be employed to analyze the effect of novel antimicrobial agents, placed in formulation with universal placebo singly or in combination, for their activity against *C. tracho-*

matis. Finally, we will examine safe and active selected formulations of candidate topical microbicides in vivo in a nonhuman primate model for vaginal and rectal safety and efficacy. The mode of action of antichlamydial microbicides on the organism will be assessed as well as the possibility of *C. trachomatis* strains developing resistance to the selected microbicides. By providing these highly specialized laboratory tests and expertise not readily available in other laboratories, the chlamydia laboratory will contribute fundamentally to topical microbicide research that will ultimately help to prevent HIV and chlamydial infections around the world.

Title: **High-Resolution Optical Imaging Assessment of Microbicide Toxicity**
P.I.: **Massoud Motamedi**
Institution: **University of Texas Medical Branch – Galveston, TX**
Grant No.: **1 R21 AI076062-01**
Award: **$10,000**

Evaluation of safety and efficacy of microbicides requires an assessment of potential injury caused by microbicides in the epithelium of cervicovaginal tract and rectum. The development of imaging technology and protocols that can be used for endoscopic, rapid, and quantitative assessment of tissue injury following topical application of microbicides could have a significant impact on the development and testing of microbicides in animal models and clinical studies. Unfortunately, current imaging technology, such as white-light colposcopy or colonoscopy, cannot provide high-resolution images of epithelial injury and cannot probe below the surface, where epithelial injury and inflammation may be evident. However, in recent years, a new imaging technology has been developed where it is now possible to perform high-resolution imaging of epithelial tissue with microscopic resolution in vivo. Our overall goal is to develop an endoscopic image-based approach that can be used to (1) assess the degree of injury that may be induced by microbicides, and (2) correlate the results of imaging studies to susceptibility to genital infection in the mouse cervicovaginal tract and rectum caused by HSV-2. We will deploy emerging high-resolution imaging modalities, including confocal fluorescence microscopy and optical coherence tomography (OCT), to characterize the changes that occur in the architecture of cervical, vaginal, and rectal epithelium of untreated sexually naive mice as well as mice treated with known irritative microbicides. These results will be correlated to susceptibility to infection using a well-characterized mouse model of HSV-2 infection. This will allow us to assess the predictive value of confocal fluorescence and OCT imaging for observed HSV-2 susceptibility based on microbicide-induced epithelial changes, with attention to reproducibility/consistency of findings. In phase I of this project, we will demonstrate the capabilities of high-resolution optical imaging to quantitatively assess the response of cervicovaginal and rectal tissue to known microbicides and test the ability to predict the biological end point of microbicide-induced changes in susceptibility in cervicovaginal tract. In phase II, the proposed image-based assessment of rectal response will be extended to establish correlation between image-based markers and rectal susceptibility following application of microbicides. Furthermore, instrumentation and imaging parameters will be optimized to make the imaging protocol suitable for imaging of cervicovaginal and rectal epithelial response in large-animal models and humans. We also plan to use the developed imaging protocol to assess the performance of novel microbicides in small-animal models as new products are developed.

Title: **An In Vitro Model of Cell-Associated HIV-1 Transmission**
P.I.: **Deborah J. Anderson**
Institution: **Boston University Medical Campus – Boston, MA**
Grant No.: **8 R21 AI076966-02**
Award: **$10,000**

The long-term objectives of this project are to define molecular events underlying cell-associated (CA) HIV-1 transmission across human cervical and vaginal epithelia and to develop an in vitro model for testing the effects of vaginal microbicide formulations on CA HIV-1 transmission. The

aims of the first (R21) phase of this project are to define adhesion molecule receptor/ligand combinations that play a role in the attachment of HIV-1–infected cells to human cervicovaginal epithelial cells and chemokine/chemokine receptor (CR) combinations that promote penetration of infected cells into the vaginal epithelium. We will use multichannel cytofluorometric analysis to characterize adhesion molecule and CR expression on CD4+ lymphocytes and macrophages isolated from semen of HIV-infected men and immunohistochemistry and Bio-Plex/ELISA assays to characterize the expression of complementary adhesion molecules and chemokines by cells in human vaginal and cervical tissues. We will perform parallel studies on CD4+ lymphocyte and macrophage cell lines (HIV+ seminal cell surrogates) and on the MatTek EpiVag organotypic model (human vaginal epithelium surrogate) to validate their appropriate expression of these molecules as the first step toward establishing an authentic in vitro model of CA HIV-1 sexual transmission. In Phase II (R33), we will use the MatTek EpiVag model to further define mechanisms of CA HIV vaginal transmission and to develop and validate a quantitative CA HIV transmission assay. We will use this assay to test the efficacy of vaginal microbicide formulations and to screen for other factors that inhibit CA HIV transmission. This model system could accelerate the development of vaginal microbicides to prevent the sexual transmission of HIV-1 and lead to the identification of novel CA HIV blocking factors that could enhance the efficacy of vaginal microbicides.

Title: **Rational Development of Combination Microbicide Therapies**
P.I.: **Robert Walter Buckheit**
Institution: **ImQuest BioSciences – Frederick, MD**
Grant No.: **8 R21 AI076067-02**
Award: **$10,000**

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. The novel assays that will be developed and utilized in this application will specifically address the ability of the combination therapeutic to inhibit cell-free and cell-to-cell virus transmission in a microbicide-appropriate environment. The therapeutic drug combination will be developed using new microbicide candidate molecules licensed by ImQuest Pharmaceuticals. These candidate microbicides target HIV replication at three steps of the replication cycle, including inhibition of virus entry to the target cells through two distinct mechanisms of action (attachment and prefusion), and act as a highly potent nonnucleoside reverse-transcriptase inhibitor. Efficacious combinations identified in the in vitro analyses will be formulated for topical application using novel formulation techniques designed to place the agents at the correct place (intracellular, at the cell surface, or within the gel as it mixes with the viral inoculum) at the time they are required for maximal inhibitory activity and yield the most effective combination therapy. Additionally, since the development of an appropriate pharmaceutical product for use as a microbicide requires a formulation for the active pharmaceutical ingredient that will result in optimal efficacy while also including and emphasizing appropriate consideration for the social and behavioral concerns of acceptability and use of the formulated products, we propose to evaluate novel formulations to promote additional efficacy in the context of the social considerations of acceptability. Thus, this application will serve to develop an appropriately formulated and acceptable product 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: Development of Tissue Explant Models for Microbicide Evaluation
P.I.: Thomas J. Hope
Institution: Northwestern University – Evanston, IL
Grant No.: 8 R21 AI076968-02
Award: $10,000

Unsuccessful attempts to develop a vaccine against HIV have led to a great need for new preventive strategies, the most encouraging of which are microbicides. An effective microbicide would decrease the severity of the AIDS epidemic by decreasing the rate of sexual transmission. A number of model systems have been developed to provide insights into the mechanisms of male-to-female sexual transmission, including explant cultures and the rhesus macaque vaginal transmission model. These systems have been successfully used to evaluate and identify candidate microbicides. There has been much less progress in the development of systems to evaluate female-to-male sexual transmission. There are currently no model systems of female-to-male sexual transmission that can determine whether potential microbicides are capable of preventing infection via the penis. To fill this gap, this application seeks to develop an explant culture system using human penile tissue. This will enable the efficacy and safety of candidate microbicides that prevent the sexual transmission of HIV to males to be evaluated. Additionally, my laboratory has recently developed methodology that allows the detection of individual virions in tissue. This system will be further developed to determine how HIV normally interacts with human penile tissue. In the R21 component of this application, we will optimize these systems to determine the normal interaction of HIV with intact tissue and subsequent viral replication. In the R33 phase of the application, we will evaluate the potential of different candidate microbicides, individually and in combination, to alter HIV's interaction with the tissue and prevent HIV infection and replication. We will also determine if exposure to the microbicide causes any changes in the tissue that may have deleterious effects on normal cell function. The application seeks to develop new methods that determine whether chemicals can be used to prevent the sexual transmission of HIV. These methods will be used to determine the potency of protection from HIV infection and the safety of the compounds before they are tested in humans. It is hoped that preventing HIV infection will decrease the number of people in the world infected with HIV and slow the AIDS epidemic.

Title: Linking Biophysical Functions of Microbicides to User Perception and Acceptability
P.I.: Kathleen M. Morrow
Institution: Miriam Hospital – Providence, RI
Grant No.: 5 R21 MH080591
Award: $10,000

This project directly addresses RFA-AI-06-005's request for technologies, strategies, or models that contribute to new and more efficient ways of assessing and predicting microbicide acceptability within the preclinical framework of formulation development. Achieving this goal requires integration of behavioral and biophysical determinants of acceptability parameters. This project analyzes correspondence of cognitive and behavioral aspects of user ratings of microbicide characteristics and activity, with biophysical microbicide properties governing vaginal distribution/retention (deployment) and hypothesized to correlate with human perceptions of microbicide use. During the R21 project, qualitative interviews, item-development strategies, and cognitive interviews will enable behavioral investigators to develop a user rating scale for use within the framework of preclinical feasibility studies of candidate microbicides. In parallel, formulation scientists will compute measures of biophysical functioning of two current over-the-counter vaginal gels, hypothesized to correlate with the behavioral constructs. Once it is shown that the behavioral tool (i.e., scale) has good psychometric characteristics, relationships between user rating measures and biophysical measures will be evaluated. Correspondence between what users can perceive/evaluate with respect to their experiences using a gel and what biophysical properties/analysis can predict with respect to these

perceptions and user ratings will be delineated. The project goal is to demonstrate that these two measurement systems can be employed synergistically, toward optimization of (1) microbicide biophysical properties governing effective deployment and biofunctionality, and (2) user ratings of application- and vehicle-associated acceptability. In the R33, these measurement systems will be further evaluated and validated using novel GRAS gel formulations. Finally, a statistical framework that initiates prediction of user ratings of gels will be developed. The microbicide field's ability to codetermine microbicide function and acceptability will dramatically increase its ability to conceive and create optimal formulations in preclinical studies. By linking user ratings with biophysical properties, the resulting behavioral tool (scale) will better inform the preclinical microbicide pipeline, enabling products to be tailored to future users with greater certainty. In sum, this work will contribute methodology leading to rational design of microbicide formulations that co-optimize vaginal distribution and retention with user acceptability.

Immunity/Autoimmunity

Title: NARAC: The Genetics of Rheumatoid Arthritis
P.I.: Peter K. Gregersen
Institution: Feinstein Institute for Medical Research – Manhasset, NY
Grant No.: 2 R01 AR044422-09A1
Award: $182,442

This renewal application has the overall goal of identifying all of the major common genetic variants that underlie susceptibility to rheumatoid arthritis (RA) and to begin to identify rare susceptibility alleles, if they exist. In preliminary data, we have identified a number of candidate genes and regions on the basis of linkage analysis in multiplex RA families, as well as by whole-genome-association studies using approximately 550,000 SNPs on a panel of over 900 RA patients and matched controls. We now wish to identify the specific causal variants and understand their mode of action. In Specific Aim 1, we will identify the causal genetic variants within the common genes that confer risk for rheumatoid arthritis. We have already identified several genes and regions of interest, including STAT4 on chromosome 2q. In Specific Aim 1a, we will replicate these initial associations in case-control datasets totaling up to 5,000 patients. Various methods of genomic control for population stratification will be utilized for these replication studies. In Specific Aim 1b, we will carry out fine mapping of candidate regions. This will generally involve haplotypic analysis using custom sets of SNP markers. In Specific Aim 1c, we will utilize various approaches to identify the likely causative genetic variants in the gene under study. Examples of the approaches to be used in Specific Aim 1c are given for STAT4. In Specific Aim 2, we will apply a staged approach to identify gene–gene and gene–environment interactions that contribute to RA susceptibility. The top-performing markers in the univariate analyses of Specific Aims 1a and 1b will be examined for interactions using Classification and Regression Tree as well as traditional logistic regression methods. Top-performing models will be tested in replication datasets of cases and controls. In Specific Aim 3, we will identify rare genetic variants that contribute to RA susceptibility. This Specific Aim is based on preliminary analysis indicating that slightly deleterious SNPs (sdSNPs) are a significant component of the genetic burden underlying complex disease. These sdSNPs are enriched in the low-frequency (MAF < 5%) component of the SNP population. We will initially investigate a limited number of candidate genes with high-throughput sequencing on the Solexa platform, along with followup analysis in large case-control datasets. Larger scale and more comprehensive approaches to this issue may be employed in the later years, depending on technical advances in the field.

Title: **Predictors of Pregnancy Outcome in SLE and APS**
P.I.: **Jane E. Salmon**
Institution: **Hospital for Special Surgery – New York, NY**
Grant No.: **5 R01 AR049772**
Award: **$379,272**

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. Our 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. We propose a prospective observational study of over 400 pregnant patients enrolled at six major clinical centers and grouped and analyzed according to the presence or absence of aPL and preexisting SLE. We have assembled 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. We will obtain detailed medical and obstetrical information during the course of pregnancy and serial blood specimens for complement and cytokine assays and analyze these data to identify predictors of poor fetal outcome. We will study placentas 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. We believe that our 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 us 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: **Steroid Responsive Mechanisms in the Ear**
P.I.: **Dennis Trune**
Institution: **Royal Oregon Health and Science University – Portland, OR**
Grant No.: **5 R01 DC005593-06**
Award: **$19,420**

Although glucocorticoids have been employed for decades for control of hearing loss, little is known of the cellular mechanisms of the ear that are under their control. Knowledge of these steroid-responsive mechanisms is critical for our understanding of normal cochlear function, as well as the design of appropriate clinical therapies. Therefore, the long-term goal of this research is to fully characterize the steroid-driven cellular and molecular mechanisms of the ear. Progress on this study has shown that hearing loss in the MRL/MpJ-Fas1pr autoimmune mouse responds to steroid treatments by regulating cochlear gene expression with both the glucocorticoid prednisolone and the mineralocorticoid aldosterone. Therefore, our working hypothesis is that two steroid-responsive mechanisms

exist in the ear: a direct sodium and potassium transport (homeostatic) gene expression mediated by the mineralocorticoid receptor, and an indirect inflammatory gene-suppression mechanism mediated by the glucocorticoid receptor. The planned studies will characterize these steroid-driven cellular and molecular processes with steroid treatments that will selectively isolate these receptors and measure changes in cochlear homeostatic and inflammatory genes and proteins they control. The specific aims to investigate these steroid mechanisms of the ear are Aim 1: Determine the dose-dependent control of inner ear ion homeostatic and inflammatory gene expression by the mineralocorticoid aldosterone and the glucocorticoid prednisolone; Aim 2: Determine the most effective control of both inner ear ion homeostatic and inflammatory gene expression processes by combination doses of the two steroids; Aim 3: Determine which cochlear cellular and molecular functions are mediated by each steroid receptor; and Aim 4: Determine if effective inner ear homeostatic and anti-inflammatory gene expression can be induced by middle ear steroid delivery. In all studies, (1) inner ear function will be assessed by auditory brainstem response audiometry. The endocochlear potential will be measured in some experiments; (2) inner ear morphology will be assessed by light and electron microscopy; (3) systemic autoimmune disease will be assessed by serum immune complexes, hematocrits, and antinuclear antibodies; (4) cochlear-specific autoantibodies will be assessed with ELISA; and (5) steroid-mediated cochlear gene products will be assessed with ELISA, Western blot, cytokine RNA expression, and quantitative RT-PCR. The results from these studies will provide new findings regarding the cellular and molecular mechanisms of the ear that are under the control of steroids. This also will lay important groundwork for the potential development of steroid therapies that are more effective than those currently employed.

Title: **New Assay for MRBC-Specific Autoantibody Responses**
P.I.: **Catherine E. Calkins**
Institution: **Thomas Jefferson University – Philadelphia, PA**
Grant No.: **1 R03 AI064636-01A2**
Award: **$77,499**

The NZB mouse model of autoimmune hemolytic anemia was one of the first animal models of autoimmunity and has been important in contributing to our understanding of genetic control of anti-self responses and some of the cell interactions involved in these responses. The 100% incidence of disease in the NZB mice and their ability to control this response until middle age allows study of the model prior to, as well as after initiation of, specific autoantibody production. Yet the mechanisms of induction of the antierythrocyte autoantibodies in this mouse model are not known. Cellular studies of the controlling elements in this response have so far been limited by the use of an intact erythrocyte as the target antigen, for which assays of specific responses are complex and not very sensitive for low-affinity antibodies. The use of target peptide MRBC epitopes could simplify and enhance the sensitivity of assays for this autoimmune response, making possible mechanistic studies of this autoantibody reaction that have not so far been approachable. A major portion of the pathogenic autoantibodies produced in these mice bind to erythrocyte band 3; however, the actual target epitopes have not been defined, and band 3, as an integral membrane protein, is difficult to obtain with structural integrity. Therefore, we propose a pilot study to focus on identifying the specific band 3 target epitopes of the NZB autoantibodies and then using these epitopes to develop assays that will be usable to detect individual autoantibody responses to each target epitope. Linear epitopes will be identified by testing selected peptide sequences deduced from DNA sequences of the extracellular loops of the erythrocyte band 3 for binding to a panel of pathogenic NZB monoclonal autoantibodies as well as to polyclonal autoantibodies extracted from autoimmune NZB mice. Target conformational epitopes of band 3 will be identified as mimotopes using a phage display approach for epitope discovery. ELISPOT assays for epitope-specific, autoantibody-secreting cells will be developed using the selected target peptide epitopes as detection probes for secreted antibody. These assays will then be used to determine the importance of identified band 3 epitopes or mimotopes at each stage of NZB disease, focusing on the earliest stage identifiable to determine which epitope target(s) is/are involved in the initiation of this autoimmunity. This pilot study should make

possible future investigations into the regulation of each epitope-specific autoantibody response in normal as well as preautoimmune and actively autoimmune NZB mice and into potential causes of the failure of these regulatory mechanisms in autoimmune NZB mice. The ultimate goal of these investigations into regulatory mechanisms that control the anti-MRBC response in NZB mice is to open up and test therapeutic opportunities for human autoimmune disease. NZB mice provide an animal model of human autoimmune disease in which anti-self erythrocyte (MRBC) antibodies are spontaneously produced and detectable in midlife. The goal of the proposed work is to identify the MRBC peptide targets of the anti-MRBC autoantibodies made by these mice and to use these target peptides to develop assays for the autoreactive cells. Such assays will facilitate studies of the mechanisms of control versus induction of these autoantibody responses that will lead ultimately to therapeutic interventions in human autoimmune disease.

Title: **Delineating the Role of Selected Genes in Lupus Induced by CD8+Ti and CD4+CD25 T**
P.I.: **Ram Pyare Singh**
Institution: **University of California, Los Angeles – Los Angeles, CA**
Grant No.: **1 R03 AR054034-01A1**
Award: **$76,999**

The goal of this project is to identify and explore the molecular mechanisms of suppression of autoimmunity utilizing CD8+ Ti, CD4+CD25+ T regulatory cells with specific targeted genes differentially expressed by CD8+ inhibitory T cells (Ti) and CD4+ CD25+ T regulatory cells from tolerized mice compared to naive littermates in our murine model of SLE. Tolerization of young BWF1 mice with an artificial peptide that contains MHC Class I and Class II T cell determinants from Ig induces two sets of regulatory/inhibitory T cells that suppress autoantibody production. Genome scans of the first, pCONS-binding CD4+CD25+ Treg, show large numbers of genes upregulated and downregulated. The second, CD8+CD28- inhibitory T cells, suppress autoantibody production in vitro—an effect that depends on secretion of TGFa1 and IFN—and on adoptive transfer to prevent disease in vivo. The number of genes upregulated or downregulated in those CD8+ Ti compared to CD8+CD28- T cells from unmanipulated littermates is small. We chose four upregulated genes from CD8+Ti to study their role in suppressive function, which is directed against CD4+CD25- helper T cells. Upregulation of those genes in the CD8+Ti was identified by genome scan and then confirmed by real-time PCR in multiple experiments. The four genes are Ifi202B, Trp53, bcl2, and Foxp3. Each gene is known to play a role in cell apoptosis, and each is influenced by levels of IFN and/or TGFa. Our strategy is to silence each of the four genes, alone or in combination, in CD8+ Ti, then measure the effect of that silencing on expression of Foxp3 and on cytokine production in the CD8+Ti cell itself and in its CD4+ helper T cell target. We will study the effects of silencing the genes of interest in vivo in adoptive transfer experiments. The overall purpose is to understand the molecular mechanisms by which these CD8+ inhibitory T cells and CD4+ T regulatory cells suppress autoimmunity; results may identify new targets for therapies for SLE in patients.

Title: **Nanoparticle Targeting of ICAM-1 as a Potential Treatment for Rheumatoid Arthritis**
P.I.: **Cory Berkland**
Institution: **University of Kansas – Lawrence, KS**
Grant No.: **1 R03 AR054035-01A1**
Award: **$69,095**

Intercellular cell-adhesion molecule-1 (ICAM-1) is upregulated on the vascular endothelium in response to proinflammatory cytokines produced in the synovial cavity of patients with rheumatoid arthritis (RA). Nanoparticles that interact specifically with ICAM-1 may preferentially pool to sites of inflammation, potentially interrupting this signal and/or facilitating the delivery of therapeutics, such as methotrexate. The objective of this application is to identify the performance of

methotrexate-loaded nanoparticles targeted to ICAM-1 for rescuing rodents with collagen-induced arthritis (CIA). Our central hypothesis is that nanoparticles loaded with 10% methotrexate will significantly reduce arthritis scores in the CIA rodent model compared to an equivalent intravenous dose of methotrexate or nanoparticles alone. We propose two Specific Aims: Specific Aim 1: Identify nanoparticle formulations that specifically target ICAM-1 on HUVECs. Our working hypothesis, based upon strong preliminary data, is that nanoparticles displaying the cLABL peptide will preferentially bind HUVECs overexpressing ICAM-1. Specific Aim 2: Identify cLABL-nanoparticle disease mitigation in the CIA rodent model. Our working hypothesis, also based upon strong preliminary data, is that cLABL-nanoparticles targeted to ICAM-1 and delivering methotrexate will significantly disrupt the progression of CIA compared to methotrexate or cLABL-nanoparticles alone. The FDA has approved combination therapy using mAbs against TNF-a (infliximab) with methotrexate and results have been encouraging. Here, we propose a potentially more selective approach for treating RA by attempting to localize drugs to molecular markers of inflammation (ICAM-1) as an alternative to systemic immunosuppression.

Title: **Treatment of Autoimmune Disease by Costimulatory Signal**
P.I.: **Samia J. Khoury**
Institution: **Brigham and Women's Hospital – Boston, MA**
Grant No.: **5 U19 AI046130-09**
Award: **$58,260**

There have been tremendous advances in the field of autoimmunity in the past 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 multispecialty approach for evaluating new and emerging therapies would provide the opportunity to integrate knowledge from the various specialties. We have chosen to study therapy of autoimmune disease by blocking costimulatory signals with CTLA4Ig and by blocking T cell activation with rapamycin. This strategy has two advantages. First, these are antigen nonspecific 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 2 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, we 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 and 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: Modulation of B Cell Responses in Autoimmunity
P.I.: Eugene W. St. Clair
Institution: Duke University – Durham, NC
Grant No.: 5 U19 AI056363-05
Award: $55,891

The proposed center will focus on the modulation of B cell responses in autoimmunity and will be under the leadership of Dr. E. William St. Clair, Professor of Medicine, Division of Rheumatology. It unites a team of outstanding and experienced basic and clinical investigators. 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 antigens, including CD20 and CD22. Growing evidence, including our results, indicates that CD20 and CD22 are attractive targets for immunotherapy of autoimmune diseases. In addition, we have shown that inflammatory stimuli, such as tumor necrosis factor alpha (TNFalpha), can promote the emigration of B cells from the bone marrow, transferring large numbers of developing B lymphocytes to the periphery. We hypothesize that 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 TNFalpha, 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-TNFalpha) 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: UCSF Autoimmunity Center of Excellence
P.I.: David Wofsy
Institution: University of California, San Francisco – San Francisco, CA
Grant No.: 5 U19 AI056388-05
Award: $56,891

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, we will participate in collaborative clinical trials of novel immunotherapies, and we will conduct basic research into the mechanisms that leads 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 (David Wofsy, PI). 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. Project 1 – Activation and functions of regulatory T lymphocytes (Abul Abbas and Jeffrey Bluestone, co-PIs): The principal goals of this project are (1) to clarify the signals involved in the induction and maintenance of regulatory T cells (Treg) and (2) to understand the mechanisms by which Treg control potentially pathogenic effector cells. Project 2 – Targeting antigen-specific T cells in SLE (David Daikh, PI): The principal goals of this project are (1) to use murine models for SLE to clarify the mechanisms of disease and to understand the basis for the efficacy of specific therapeutic interventions and (2) to develop novel antigen-specific approaches to the treatment of autoimmune disease in murine models as a prelude to clinical trials in humans. Immune Function Monitoring Core (Lawrence Fong, PI). This core facility will provide the capability for developing and performing cellular and antibody-based immune assays on samples (e.g., blood, lymph node, etc.) derived from patients participating in ACE trials. Assays that will be available include flow cytometry; MHC/peptide tetramer production and staining; cytokine analysis by ELISA, ELISPOT, and flow; T cell proliferation; and cytotoxicity assays. This core will support the Clinical Center and Project 2. Together, the Clinical Center, individual projects, and Immune Monitoring Core comprise a tightly linked program to bring novel therapies from bench to bedside and to investigate the mechanisms by which these therapies retard autoimmune disease.

Title: **Suppression and Exacerbation of B and T Cell Responses**
P.I.: **Ignacio E. Sanz**
Institution: **University of Rochester – Rochester, NY**
Grant No.: **5 U19 AI056390-06**
Award: **$56,891**

The overarching goal of this proposal is to establish an Autoimmunity Center of Excellence at the University of Rochester. This goal is based on 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: UAB Autoimmunity Center for Excellence
P.I.: Robert H. Carter
Institution: University of Alabama at Birmingham – Birmingham, AL
Grant No.: 5 U19 AI056542-05
Award: $56,891

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 breadth of experience in clinical trials in a range of immune-mediated diseases to jointly develop new therapies for autoimmunity.

Menopause

Title: Staging Reproductive Aging in Four Cohorts: Issues of Hormone Use Spotting Bias
P.I.: Sioban D. Harlow
Institution: University of Michigan at Ann Arbor – Ann Arbor, MI
Grant No.: 2 R01 AG021543-03A2
Award: $472,098

Menopause marks a period of critical change in women's biology and health. Establishing a staging system for reproductive aging would enable providers to better counsel women about menopausal symptoms and preventive therapy and permit researchers to accurately classify women's reproductive status. The Stages of Reproductive Aging Workshop (STRAW) proposed such a staging system. STRAW'S recommendations, although based on emerging results of ongoing cohort studies, were not data driven and included important departures from clinical and research practice. ReSTAGE is a collaboration among four large cohort studies of the menopausal transition (TREMIN, Melbourne Women's Midlife Health Project, Seattle Midlife Women's Health Study, and Study of Women's Health Across the Nation). Our goal has been to empirically evaluate bleeding criteria for the menopausal transition that were the basis for STRAW's recommendations using menstrual calendars, hormones, and symptom data. The original grant focused only on the natural history of the menopausal transition. This competitive renewal addresses three methodological issues critical

to specifying inclusive staging criteria broadly applicable to a heterogeneous population of women. It will extend staging criteria to include women who use hormones (HT) during the midlife, address misclassification associated with intermenstrual bleeding/spotting (1MB), and characterize the problem of left truncation and left censoring biases in studies of the menopausal transition. We aim first to develop and compare two approaches for modifying bleeding criteria for the menopausal transition to account for the case where women use HT and assess the effect of including HT users on estimates of age and duration of the menopausal transition in the four cohort studies. Second, as 1MB makes assessment of bleeding criteria difficult, we aim to develop an algorithm for distinguishing 1MB from menstrual episodes in menstrual calendars and to assess IMB's impact on estimates of age at and duration of the transition in the four cohorts. Third, we aim to develop likelihood methods to correct for left censoring and left truncation biases associated with the differential age at entry criteria in cohort studies of midlife women and assess the impact of these biases on estimates of age at and duration of the menopausal transition. This research will extend staging systems for reproductive aging to include HT users and provide definitive guidance regarding criteria for staging reproductive aging in HT users and women with 1MB. Results will facilitate clinical decision making for women and providers relevant to contraception, symptomatic treatment, and preventive therapy.

Title: **Neurobiology of the Menopausal Transition**
P.I.: **Yolanda R. Smith**
Institution: **University of Michigan at Ann Arbor – Ann Arbor, MI**
Grant No.: **5 R01 AG027675-02**
Award: **$48,550**

The menopausal transition is an important life process, significantly impacting the cognitive and psychological health of women. Postmenopausal neuroimaging studies of hormone therapy indicate that estrogen levels have significant effects on brain neural circuitry. However, mechanistic studies of the neurobiology of the menopausal transition are lacking. This proposal combines the rich historical data from and access to a uniquely well-characterized population of women, transitioning to the menopause, with neuropsychological testing and state-of-the-art neuroimaging techniques, to characterize the neurobiology of the menopausal transition. To test hypotheses concerning mechanisms of menopausal cognitive and affective changes, we will recruit from a well-characterized population of women at midlife who have been participants in a bone health and metabolism study involving extensive hormone and cycle monitoring since 1992. Recruits will be women aged 40–55 years, stratified into panels representing premenopause, early perimenopause, late perimenopause, and natural postmenopause defined by follicle-stimulating hormone levels and menstrual bleeding patterns. This collaboration will involve extensive neuropsychological testing combined with a validated functional magnetic resonance imaging (fMRI) paradigm to determine brain activation patterns during cognitive and emotional tasks among women of each panel. The Specific Aims include (1) Identify if specific stages or characteristics of the menopausal transition are associated with alterations in brain functioning as manifested either by fMRI-BOLD activation during cognitive and emotional tasks or by neuropsychological testing; (2) Delineate the relative contribution of ovarian aging vs. chronological aging in brain functioning as manifested either by fMRI-BOLD activation during cognitive and emotional tasks or by neuropsychological testing; and (3) Demonstrate whether cognitive processing changes noted on fMRI-BOLD precede, occur concurrently with, or follow observable changes in neuropsychological testing. These studies will determine the contributions of hormones and aging to changes in cognitive and emotional processing. A better understanding of the areas and sequence of brain processing changes will allow the health community to plan interventions that most effectively preserve cognitive and emotional health for women.

Title: Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO
P.I.: Puliyur S. Mohankumar
Institution: Michigan State University – East Lansing, MI
Grant No.: 5 R01 AG027697-02
Award: $48,550

Perimenopause is one of the most complex and least understood states of a woman's life. Many of the health risks associated with this state were believed to be due to decreases in estrogen levels and that estrogen could protect against health risks faced by perimenopausal women. However, estrogen fluctuates during perimenopause and, if at all, increases during the premenstrual and follicular phases. Recent clinical trials have shown that chronic administration of estrogenic compounds in postmenopausal women may increase the risk for several diseases. Therefore, it is important to investigate the effects of estrogen exposure on various organ systems. Studies so far indicate that estrogen's effects in the brain are beneficial. These reported effects, however, deal with nonhypothalamic regions of the brain. The effects of chronic estrogen exposure on the hypothalamus, which regulates several key body functions, have not been investigated. This is critical because women use estrogenic preparations on a prolonged basis and are exposed to endogenous estrogen throughout their adulthood. This proposal focuses on the effects of chronic estrogen exposure on one of the estrogen-sensitive neuronal systems of the hypothalamus, namely, the tuberoinfundibular dopaminergic (TIDA) system. Dopamine (DA) released from TIDA neurons inhibits prolactin (PRL) secretion from the anterior pituitary. Age-related reductions in TIDA activity are associated with hyperprolactinemia and appearance of mammary and pituitary tumors in animal models. The mechanisms behind the loss of TIDA neuronal function are not clear. In this application, we are proposing a novel hypothesis and an interesting model to study how estrogen could affect TIDA neurons and increase PRL levels. This series of studies is important because women not only use estrogen on a long-term basis in HRT but are also exposed to environmental estrogens. Prolonged exposure to estrogen and elevated levels of PRL may promote the risk for breast cancer.

Title: Estrogen: Neuroprotection in the Perimenopause
P.I.: Anne M. Etgen
Institution: Yeshiva University – Bronx, NY
Grant No.: 5 R01 AG027702-02
Award: $48,550

Alterations in the hypothalamic-pituitary-ovarian axis in perimenopausal women are associated with multiorgan risk factors for disease, yet the biological mechanisms underlying this increased disease risk are largely unknown. This proposal addresses unanswered questions regarding the vulnerability of the middle-aged brain to global ischemia. In young female rats, the presence of physiological levels of estradiol before and after global ischemia, as might occur during cardiac arrest, reduces hippocampal CA1 neuron loss and associated cognitive impairments. Whether estradiol retains its neuroprotective actions in middle-aged females and whether the age-related decline in insulin-like growth factor-l (IGF-I) increases vulnerability to ischemia-induced neurodegeneration and cognitive impairment are unknown. This proposal aims to examine the roles of age, estrogen, and IGF-I in the survival and function of hippocampal neurons in a rat model of global ischemia. The underlying hypotheses are (1) that the middle-aged brain retains its responsiveness to the neuroprotective actions of estradiol if the duration of estrogen withdrawal is brief (critical period hypothesis) or circulating levels of IGF-I are maintained; and (2) that estrogen acts in the middle-aged brain to activate specific cell survival pathways and thereby intervenes in apoptotic cascades to prevent death of neurons otherwise destined to die. Specific Aim 1 uses stereological cell counting and behavioral tests to evaluate the outcome of global ischemia in middle-aged female rats that are intact, ovariectomized at various intervals prior to insult, or ovariectomized and treated with estradiol at various intervals after ovariectomy. If estradiol does not preserve neurons and cognitive function in older hormone-deprived animals, we will also determine if IGF-I can reinstate estrogen protection. Specif-

ic Aim 2 examines the apoptotic death cascades triggered by global ischemia and identifies the site at which estrogen intervenes in these cascades. We will examine (1) mitogen-activated protein kinase and cAMP response element binding protein at early times after ischemia, (2) the antiapoptotic gene Bcl-2 and activation of caspase 3 at later times after ischemia, and (3) inactivation of Akt and subsequent activation of the forkhead transcription factor FKHRL1 at early times after ischemia. These experiments will provide new information on the potential for hormone therapy instituted during the perimenopausal transition to protect the brain from damage due to global ischemia.

Title: **Menopause: Decreased Response to Increasing Inflammation**
P.I.: **Caterina Adriana Maggi**
Institution: **University of Milan – Milan, Italy**
Grant No.: **5 R01 AG027713-02**
Award: **$47,142**

The long-term goal of our research is to find treatments for the prevention of the disorders associated with menopause that are safer and more efficacious than present hormone replacement therapy (HRT). The failure of present HRT to fulfill medical and women's needs has to be ascribed to an insufficient knowledge of the biology of menopause. The aim of our research is focused on understanding the consequences of cessation of ovarian functions on the physiology of nonreproductive organs such as bone, brain, arteries, and fat. In particular, our studies and the studies proposed in the present project will focus on the effects of estrogen-decreased production at menopause transition and after in nonreproductive organs. Given recent results demonstrating that, in nonreproductive organs of fertile female mice, estrogen receptors (ERs) are activated by factors other than estrogens, our Specific Aim 1 will focus on assessing the extent to which ERs are transcriptionally active during menopause transition and after. We will then try to identify the factor(s) involved in ER activation. This part of the project relates to questions that so far could be addressed only partially with current technology. The generation of a novel model of reporter system, the ERE-Luc mouse, will enable us to precisely quantify ER activity in the organs of interest and facilitate the search for factors involved in ER-unliganded activation. Specific Aim 2 will give us the opportunity to test an original hypothesis that would explain the widespread protective effects provided by the estrogen-ER system. This hypothesis is based on numerous, very recent observations made in our group and several others showing that estrogens and cognate receptors may exert a strong anti-inflammatory action by inhibiting the immune response of cells of the monocyte lineage. We propose here that menopause consists of a decreased response to increased inflammation. We will test this hypothesis by the direct assessment of ER's relevance to macrophage activity through the generation of a novel conditional ERalpha KO mouse. Furthermore, using brain as a paradigmatic nonreproductive organ, we will measure basal and induced activity of brain inflammatory cells. Finally, the specific involvement of ER anti-inflammatory activity in the development of menopause-associated diseases will be tested with the study of the activity in menopause of another class of intracellular receptors devoted to the control of inflammation, the PPARs.

Title: **Cytokine Modulation by Follicle-Stimulating Hormone**
P.I.: **Joseph G. Cannon**
Institution: **Medical College of Georgia – Augusta, GA**
Grant No.: **5 R21 AG027714-02**
Award: **$48,550**

The menopausal transition involves dramatic decreases in circulating ovarian steroids and dramatic increases in circulating hypothalamic gonadotropins. The biological consequences of estrogen loss on health problems associated with aging and menopause, such as osteoporosis and cardiovascular disease, have been studied extensively. One consequence is that tonic inhibition of inflammatory cytokine synthesis by estradiol is lost. These cytokines, including interleukin-1B (IL-1B), interleukin-6 (IL-6), and tumor necrosis factor-a (TNFa), contribute to bone resorption and development

of atherogenic lesions. Although the fundamental influence of estradiol on postmenopausal health is unquestioned, the potential influence of increased gonadotropin concentrations, particularly follicle-stimulating hormone (FSH), has received less attention. This project will investigate potential mechanisms by which FSH may affect skeletal and vascular health, namely, by stimulating IL-1B, IL-6, and TNFa secretion and inhibiting the shedding of receptors for these cytokines. These mechanisms will be studied using leukocytes isolated from the peripheral blood of pre-and perimenopausal women. In addition, the biological significance of these mechanisms will be assessed by comparing plasma FSH, cytokine, and cytokine receptor concentrations with circulating markers of bone turnover (N-telopeptide and osteocalcin), bone densities measured by dual energy x-ray absorptionmetry, and indices of vascular health (carotid intimal-medial thickness and pulse wave velocity measured by ultrasound). A better understanding of FSH-mediated mechanisms in peri-and postmenopausal health may lead to new therapies directed at modulation of FSH that can alleviate menopausal health problems without the attendant risks associated with steroid hormone replacement therapy.

Mental Health

Title: **Antimanic Use During Pregnancy**
P.I.: **Katherine L. Wisner**
Institution: **University of Pittsburgh – Pittsburgh, PA**
Grant No.: **5 R01 MH075921-02**
Award: **$194,200**

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 postbirth. 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 have 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 nonexistent in women with either 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 the 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 decisionmaking to a new level of sophistication. This is a prospective observational study of women with BP during pregnancy and the mother-infant pairs in the first postpartum year. We 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 12–16 weeks, 20–24 weeks, and 32–36 weeks after birth. No such PK data are currently available.

Title: Emotions Are Emergent Events Constrained by Affective and Conceptual Processes
P.I.: Lisa Feldman Barrett
Institution: Boston College – Chestnut Hill, MA
Grant No.: 1 DP1 OD003312-01
Award: $78,625

Title: Parenting and the Brain
P.I.: Robert Bridges
Institution: Stafford Tufts University Boston – Boston, MA
Grant No.: 1 R13 MH080562-01
Award: $3,000

The "Parenting and the Brain" conference to be held in Boston, Massachusetts, in June 2007 is the third conference in a series of international scientific meetings devoted to the study of maternal and paternal caregiving and its underlying biological substrates. The initial meeting in this series of conferences was held in Bristol, England, in 1999 and focused on the maternal brain. In 2003, a second meeting entitled "The Mothers and Infants Conference" was held in Montreal, Canada. The mission of the upcoming "Parenting and the Brain" conference is to bring together internationally recognized basic and clinical researchers who use state-of-the-art scientific approaches to examine the role of the central nervous system in both maternal and paternal caregiving and thereby increase our understanding of how the biology of the brain influences mental health. Researchers will discuss variations in parental behavior and responses during critical biological periods associated with raising offspring. A central focus of this meeting will be consideration of underlying mechanisms that regulate adaptations of the brain toward parenting. Translational aspects of parenting will be a second key component of the program. The conference will consider issues related to postpartum mood disorders, such as postpartum depression, anxiety, maternal aggression, as well as insufficient parental bonding to infants in an effort to identify novel linkages between the basic and clinical sciences on these crucial topics and to advance our understanding and treatment of mental health issues. The conference proceedings will be published as an integrated text.

Musculoskeletal

Title: Genomic Convergence for Female Osteoporosis Risk Genes
P.I.: Hong-Wen Deng
Institution: University of Missouri–Kansas City – Kansas City, MO
Grant No.: 1 P50 AR055081-01
Award: $100,000

Osteoporosis is the most prevalent metabolic bone disease responsible for a major public health problem. Osteoporosis is mainly characterized by low bone mineral density (BMD). In general, women have lower BMD and higher risk of osteoporosis than men. Most BMD variation is determined by genetic factors, with heritability greater than 60%. However, the specific genes involved are largely unknown. Our studies and the studies of others have demonstrated that some osteoporosis risk genes/genomic regions are gender specific. The goal of this SCOR is primarily to identify osteoporosis risk genes and their functional aspects in females and, secondarily, to assess the female specificity of these identified genes/functions in male samples. In addition, we will also perform in-depth molecular and cellular functional studies for specific mechanisms and confirmation of the risk genes identified by studying two novel genes we discovered recently. This SCOR will pioneer a comprehensive and novel approach in bone genetics by investigating osteoporosis at the genome-, transcriptome-, and proteome-wide levels simultaneously. We will use the samples largely recruited or archived for targeted recruitment and adopt state-of-the-art technologies proven successful in our recent pilot studies. This genomic convergence approach will pinpoint and consolidate the most

significant genes identified in each of the individual projects. The genes identified will be subject to replication studies within and across populations by ourselves and our collaborators. All the genes identified in the genomic convergence approach will be subject to in-depth functional studies for confirmation and functional mechanisms as exemplified in Stage 2 of Project 2 of this SCOR. This SCOR is composed of three projects, all aimed at identifying osteoporosis risk genes, but from different genomic approaches. Project 1 is to perform a whole-genome-association scan using dense SNPs to identify those genes/regions that are associated with risk of osteoporosis. Project 2 is to perform a DMA microarray study to scan >40,000 known human genes and ESTs to identify those mRNAs and corresponding genes associated with osteoporosis. Project 3 is to perform proteomics studies to identify those proteins (and corresponding genes) associated with osteoporosis. The SCOR has three cores: A) Administrative Core, B) Clinical Core, and C) Biostatistics and Bioinformatics Core. Each core serves all the three projects. For example, the Clinical Core recruits samples that are shared by Projects 2 and 3 and provides support for clinically related issues (e.g., choice of important medical and environmental factors for covariate analyses) and for human subject research issues in Project 1. Identifying genes and their functions for human BMD variation, especially for women, is important for (1) gaining insights into the fundamental molecular mechanisms underlying risk of osteoporosis; (2) discovering new pathways and targets for therapeutic cures; and (3) identifying genetically susceptible individuals, so that future preventions and interventions can be targeted to and based on individuals' specific genotypes.

Title: **Bone-Sparing Effects of Soy Phytoestrogens in Menopause**
P.I.: **Silvina Levis**
Institution: **University of Miami School of Medicine – Coral Gables, FL**
Grant No.: **5 R01 AR048932-04**
Award: **$97,100**

Women will live a third of their lives in 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 them from 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. We propose 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. Our study will also explore the effectiveness of oral isoflavones in preventing menopausal symptoms and other changes associated with estrogen deficiency. The study will characterize the actions of a defined preparation of soy isoflavones in humans and will correlate these actions with the circulating serum levels of the principal isoflavone metabolites, providing new insights on their long-term biological actions. This 5-year study will provide a foundation of knowledge from which menopausal women can begin to make more informed decisions regarding HRT and menopausal signs and symptoms.

Neurology/Neurosciences

Title: Estradiol and Glutamate in the Developing Hypothalamus
P.I.: Jaclyn Marie Schwarz
Institution: University of Maryland, Baltimore – Baltimore, MD
Grant No.: 1 F31 NS055518-01A2
Award: $30,705

Male and female brains exhibit fundamental morphological differences thought to underlie sex differences in physiology and behavior. Development of the male rodent brain includes the completion of two distinct processes: masculinization and defeminization. In the rodent, estradiol initiates both processes during a restricted sensitive period. During development and adulthood, the medial basal hypothalamus (MBH) is a key target for estradiol. The MBH is important for female sex behavior and a possible site of defeminization in the male brain. Dendritic spines are the major sites of excitatory synapses. In the MBH, newborn males have more dendritic spines than females and treatment of females with testosterone, which is aromatized to estradiol, increases dendritic spines in this region to levels seen in males. Recent work has begun to investigate the mechanism of masculinization. However, little is known about the mechanism by which estradiol induces defeminization and establishes sexually dimorphic patterning in the MBH. Based on preliminary data and previous findings, we propose a novel role for glutamate release and the NMDA receptor in the process of defeminization of the brain and behavior. The goal of this proposal is to elucidate the mechanism by which estradiol induces defeminization of the rodent brain, to increase understanding of sex differences in brain development. Many neurological and psychiatric disorders, including autism, affective disorder, and schizophrenia, exhibit a sex-biased prevalence and/or characteristics. These diseases are frequently disorders of neurochemicals or wiring. Understanding how sex affects normal brain development is necessary to understand how it may develop abnormally in psychiatric disorders.

Obesity/Overweight

Title: Altered Glucose and Lipid Metabolism in Obesity and CVD
P.I.: Maureen J. Charron
Institution: Yeshiva University – Bronx, NY
Grant No.: 5 R01 HL073163-05
Award: $194,200

Obesity is associated with metabolic abnormalities that increase the risk of type 2 diabetes and cardiovascular disease (CVD). Obese patients with a substantial accumulation of visceral adipose tissue are characterized by higher insulinemic and glycemic responses during an oral glucose challenge and a deteriorated plasma lipoprotein-lipid profile compared to normal body weight or obese individuals with low-level visceral adiposity. We will use a mouse model with a primary impairment in insulin-mediated glucose flux into adipocytes to define the molecular mechanisms underlying the pathogenesis of obesity-associated CVD. Male mice carrying only one functional copy of the insulin-stimulatable GLUT4 transporter (GLUT4) first display reduced GLUT4 expression specifically in white adipose tissue (WAT). Reduced GLUT4 in WAT leads to visceral obesity, progressive impairment in insulin sensitivity, altered lipid metabolism, and eventually to type 2 diabetes with associated CVD. As such, male GLUT4 mice represent an excellent model to study pathophysiological changes associated with visceral obesity in humans. Interestingly, changes in adipose cell-secretory proteins, such as the adipocyte-specific Acrp30, precede the onset of measurable changes in other metabolic parameters in GLUT4 mice. We and others have demonstrated profound effects of Acrp30 on insulin resistance in liver and muscle through specific effects on carbohydrate and lipid metabolism. The objectives of this proposal are (1) to understand the molecular mechanisms underlying the metabolic changes that specifically affect male, but not female, GLUT4 mice or GLUT4 mice that overexpress GLUT4 in muscle; and (2) to test genetically whether correction of Acrp30 downregulation in male GLUT4 will prevent or delay the onset of insulin resistance, visceral obesity, and/or

CVD. Additionally, we 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. Other objectives are (3) to assess the effects of high-fat diet-induced changes in disease progression in GLUT4 compared to C57BL/6J mice, and (4) to determine transcriptional and translational changes in WAT associated with visceral obesity and alterations following treatment with thiazolidinedione insulin sensitizers in the 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: **Estradiol Regulation of In Vivo Adipose Tissue Glucocorticoid Metabolism**
P.I.: **Wendolyn S. Gozansky**
Institution: **University of Colorado Denver – Denver, CO**
Grant No.: **5 R21 AG027687-02**
Award: **$48,550**

Premenopausal women are protected against abdominal obesity and this appears to be estrogen mediated. Pharmacologic suppression of sex hormones in premenopausal women increases total body fat, with disproportionate increases in trunk fat. Randomized controlled trials provide strong evidence that estrogen-based hormone therapy attenuates weight gain and abdominal fat accumulation in postmenopausal women; the mechanisms for these actions remain unknown. Thus, our global aim is to employ an experimental model to evaluate a potential biological mechanism by which the withdrawal of estradiol (E2) triggers an increase in abdominal adiposity. Glucocorticoids are a potent stimulus of abdominal fat accumulation. In animals, estrogen deficiency increases conversion of the inactive glucocorticoid, cortisone, to the active glucocorticoid, cortisol, thereby amplifying tissue exposure to cortisol; this action is mediated by the enzyme 11-beta-hydroxysteroid dehydrogenase type 1. We propose to study both whole-body and abdominal adipose tissue-specific (using a novel in vivo microdialysis technique) glucocorticoid metabolism in 30 healthy, premenopausal women after 5 days of sex hormone suppression (GnRH antagonist [GnRHant]). To isolate the effect of E2, we will continue GnRHant and randomize women to 5 days of add-back therapy with low- or high-dose transdermal E2 or placebo. We hypothesize that sex hormone suppression will increase both whole-body and subcutaneous abdominal fat conversion of cortisone to cortisol compared with the early and late follicular menstrual cycle phases (expected dose response: GnRHant > early follicular > late follicular). Further, we postulate that E2 add-back will reverse the effects of sex hormone suppression. Our studies will evaluate a biological mechanism that we believe is responsible for the menopausal increase in abdominal adiposity and its associated metabolic sequelae. Importantly, the mechanism that we will study, E2-mediated regulation of glucocorticoid metabolism, likely has relevance to other conditions that also increase after the menopause transition (e.g., osteoporosis, cognitive impairment). Therefore, this proposal is highly responsive to the RFA goal of addressing the underlying biology of endogenous hypothalamic-pituitary-ovarian axis hormones and their interactions with nonreproductive organ systems.

Title: **Markers of Autonomic and Metabolic Control in Childhood Obesity**
P.I.: **Michael C. K. Khoo**
Institution: **University of Southern California – Los Angeles, CA**
Grant No.: **1 R21 HL090451**
Award: **$101,842**

Diet, physical activity, glucose-insulin control, and autonomic activity are tied together in a delicate balance that, if disrupted, can lead to obesity and obesity-related disorders. Sleep-disordered breathing (SDB), which is highly prevalent in obesity, can also contribute independently to autonomic imbalance and insulin resistance. Recent studies also suggest that the vicious cycle of interplay among these factors in childhood predisposes to the emergence of metabolic syndrome, a clustering

of obesity, hypertension, insulin resistance, and dyslipidemia. Based on extensive preliminary data, we hypothesize that the strong association between autonomic and metabolic function enables the use of autonomic markers as noninvasive surrogate measures of insulin sensitivity in obese children that could be applied in clinical and community settings. To test this hypothesis, we will (1) develop a method for noninvasive assessment of autonomic function, based on a computational model of pulse transit time variability and heart rate variability; (2) determine the quantitative relationships between the parameters of the autonomic control model and insulin sensitivity in childhood obesity; and (3) determine how SDB alters these relationships. The study employs a multidisciplinary approach with expertise in computational bioengineering, cardiopulmonary physiology, pediatric sleep disorders, and pediatric obesity research. We will initiate this study in a homogeneous sample of obese male Hispanic children aged 13–17 years, with and without SDB. Autonomic measurements (respiration, heart rate, blood pressure, and pulse transit time) will be monitored during supine wakefulness and following exposure to autonomic challenges (cold face test and orthostatic stress). From these measurements, the parameters of a computational model of heart rate and pulse transit variability will be estimated and used to quantify baseline autonomic function and cardiovascular autonomic reactivity. Metabolic measurements will include body composition; fasting levels of insulin, glucose, and triglyceride; and a frequently sampled intravenous glucose tolerance test. Regression analysis will be used to determine the correlations between the parameters representing autonomic and metabolic function, as well as how these correlations are affected by SDB. The knowledge derived from this study may lead to the development of a low-cost, portable device that can be used for early detection/monitoring of autonomic and metabolic abnormalities and sleep disruption in large populations of obese children.

Pain

Title: Chemokine Receptor Function in the Nervous System
P.I.: Richard J. Miller
Institution: Northwestern University – Evanston, IL
Grant No.: 3 R01 DA13141-8S1
Award: $20,000

Title: Brain Serotonin and Angiotensin II Systems in Migraine
P.I.: Jose A. Terron
Institution: Cinvestav–IPN – Mexico City, Mexico
Grant No.: 5 R01 TW006622-05
Award: $39,060

Long-term objectives. The brain serotonin (5-HT) system plays an important role in cerebrovascular and neuroendocrine control. These systems have been implicated in migraine. Migraine is a low 5-HT syndrome and attacks may be triggered by a massive release of 5-HT acting on sensitized receptors. This proposal will elucidate the association between the phenomena of decreased 5-HT neurotransmission and altered cerebrovascular and neuroendocrine responsiveness. The focus will be on 5-HT receptors recently implicated in migraine pathogenesis and/or prophylactic treatment (5-HT1A, 5-HTT, 5-HT2s, and 5-HT2c). As a key activator of the hypothalamic-pituitary-adrenal (HPA) axis, the role of the brain angiotensin II (Ang II) system will be addressed. The proposal intends to shed light on the pathophysiological mechanisms of migraine and the mechanism of action of migraine prophylactic 5-HT and Ang II drugs. Specific Aims: The following hypotheses will be challenged: (1) A decreased 5-HT transmission in the brain will cause sensitization and/or upregulation of 5-HT receptor subtypes in the cerebral vasculature and the HPA axis; treatment with a migraine prophylactic compound that targets these receptors will restore 5-HT receptor function and/or expression. This may be a useful animal model for drug screening in migraine prophylaxis. (2) The response to stress, which involves sequential activation of the brain Ang II and the HPA systems,

will lead to decreased brain 5-HT levels, upregulation of 5-HT receptors, and/or amplified neuroendocrine and cerebrovascular responses to 5-HT receptor activation; treatment with an inhibitor of Ang II synthesis will restore serotonergic function. Design: (1) Cerebrovascular and neuroendocrine responses to 5-HT agonists and expression of 5-HT receptors in the cerebral vasculature and the HPA axis will be determined in control and 5-HT-depleted Wistar rats. It will be determined whether chronic treatment with a migraine prophylactic 5-HT antagonist restores 5-HT receptor function and/or expression. (2) Brain 5-HT content, expression of 5-HT receptors in the HPA axis, and neuroendocrine and cerebrovascular responses will be determined in control and stressed (acute and chronic isolation and restraint) Wistar rats. Reversal of stress-induced changes in these variables will be attempted by chronic treatment with the angiotensin-converting enzyme inhibitor, lisinopril (i.e., a migraine prophylactic agent). In vivo cerebrovascular reactivity will be assessed by laser-Doppler flowmetry (cortical blood flow) and the 4-iodo-[N-methyl-14C]-antipyrine method (regional cerebral blood flow). In vitro cerebrovascular reactivity will be analyzed with an arteriographic chamber system. The hormonal response (ACTH, corticosterone, and prolactin) will be measured by radioimmunoassay in blood samples and 5-HT receptor expression will be determined by quantitative receptor autoradiography in tissue sections. 5-HT content will be measured by HPLC in brain homogenates.

Title: **Long-Term Behavioral Effect of Neonatal Pain**
P.I.: **Christine A. Gleason**
Institution: **University of Washington – Seattle, WA**
Grant No.: **1 R21 DA022573-01**
Award: **$175,218**

Critically ill premature infants in neonatal intenisive care units (ICUs) are severely stressed and undergo numerous painful procedures, so they are often treated with narcotics such as morphine to try and relieve their stress and pain responses—sometimes for weeks or months. This is an important healthcare issue for two reasons: (1) neonatal stress/pain is believed to have long-term adverse effects on the developing brain, including behavioral disorders such as depression and addiction; and (2) there are also concerns about the neurodevelopmental effects of prolonged narcotic exposure used to try and ameliorate neonatal stress/pain responses. This exploratory grant application is written in response to RFA-DA-06-005, Prescription Opioid Use and Abuse in the Treatment of Pain. For these studies, we have developed a unique mouse model of preterm neonatal pain/stress and narcotic exposure that mimics the clinical condition of critically ill preterm infants in the neonatal ICU. We have also developed a new collaboration between our developmental neuropharmacology group and the Chavkin lab that is focused on understanding mechanisms of the effects of pain/stress on adult addiction/reward behavior. The overall objective of our application is to use our unique mouse model to improve our understanding of the long-term effects of neonatal stress and chronic narcotic exposure on adult addictive behavior and to explore mechanisms for these long-term effects. Our central hypothesis is that repeated neonatal pain/stress induces release of endogenous dynorphin peptides, which persistently activate kappa opioid receptors, which causes a subsequent sensitization to the rewarding properties of narcotics experienced later in life. Further, we hypothesize that neonatal morphine treatment ameliorates these long-term effects of neonatal pain/stress on adult addictive and depressive behavior by decreasing the neonatal release of endogenous dynorphin. We will address the following Specific Aims: (1) To examine long-term, gender-specific effects of neonatal pain/stress, with or without morphine treatment, on adult addictive and depressive behavior; and (2) Using prodynorphin and kappa opioid receptor knockout mice, we will test our central hypothesis regarding potential mechanisms for the long-term effects of neonatal pain/stress and its treatment on adult addictive and depressive behaviors. Understanding the long-term effects of neonatal stress and narcotics on adult addictive and depressive behaviors will help clinicians who manage these vulnerable infants to care for them more safely and effectively.

Physical Activity

Title: Exercise-Based Motivational Interviewing for Fibromyalgia
P.I.: Dennis Chua Ang
Institution: Indiana University–Purdue University at Indianapolis – Indianapolis, IN
Grant No.: 1 R01 AR054324-01A1
Award: $493,749

Fibromyalgia (FMS), defined as the presence of both chronic widespread pain and the finding of 11/18 tender points on examination, affects 2% of the general population. Drug therapy for FMS is largely symptomatic as there is not yet a complete understanding of the pathogenesis of the disease. In the past 17 years, supervised aerobic exercise has emerged as an important treatment modality to improve pain, aerobic capacity, function, and well-being. Individuals who are able to adhere to exercise almost always maintain the symptomatic benefits of exercise. Unfortunately, the rate of exercise adherence 6 months after the completion of a well-structured supervised exercise program is disappointingly low. Furthermore, although the efficacy of supervised aerobic exercise in the research setting is well documented, the applicability of such interventions in the clinic setting is doubtful. Therefore, we propose to conduct the Research to Encourage Exercise for Fibromyalgia (REEF), a randomized attention-controlled trial whose primary aim is to evaluate the efficacy of telephone-delivered motivational interviewing (MI) to encourage exercise in improving exercise adherence and self-reported physical function (coprimary outcome measures) for FMS patients. REEF will enroll 200 FMS patients, randomizing them to either the MI group or the attention-control (AC) group. Participants from each group will receive a total of 6 telephone calls within a 12-week period. Prior to the phone calls, participants from both groups will receive an individualized exercise prescription and two supervised exercise training sessions to get them started on an exercise program. All subjects will undergo comprehensive outcome assessment at baseline, week 12, week 24, and week 36. The secondary aim of this application is to determine the mediators between MI and improvement in self-reported physical function. The proposed research is significant because our focus is the promotion of adherence to an exercise program, of adequate intensity, in order to maximize functioning and well-being for patients with FMS. The use of a predominantly home-based exercise program and telephone-delivered MI by a trained licensed practice nurse (LPN) could potentially make the proposed intervention more accessible to the greater majority of FMS patients. Furthermore, if proven efficacious, MI could readily be applied to other chronically painful conditions (e.g., chronic back pain).

Title: Young Adult Environmental and Physical Activity Dynamics
P.I.: Barry M. Popkin
Institution: University of North Carolina at Chapel Hill – Chapel Hill, NC
Grant No.: 5 R01 CA109831
Award: $97,100

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. We will use four study years (1985, 1992, 1995, and 2001) of the Coronary Artery Risk Development in Young Adults Study (CARDIA), 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. We will use complex longitudinal and spatial analytical models 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. We will model physical activity as a function of covariates, some of which may be endogenous choices made by the individual. We will examine race/ethnic differentials in these effects and the impact of the environment shifts over

time and through the lifecycle. The focus will be on examining how modifiable environmental factors will affect physical activity patterns among underserved communities and consequently will reduce ethnic and socioeconomic differentials in health status. The longitudinal analysis and the vast array of environmental measures used, coupled with the very high-quality physical activity measures of CARDIA, allow us to capture the effects of the environment (and changes in location) on physical activity shifts. No study heretofore has had large-scale groupings and in-depth environmental measures over time to examine these issues in a dynamic manner.

Title: **Mediators and Moderators of Exercise Behavior Change**
P.I.: **Sara Anne Tompkins**
Institution: **University of Colorado at Boulder – Boulder, CO**
Grant No.: **5 R01 CA109858-04**
Award: **$94,818**

Rates of cancer and cardiovascular disease have shown very little improvement over the past two decades, and the incidence of type 2 diabetes mellitus is increasing at an alarming rate. Recent reports estimate that approximately 30% 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 (Booth et al., 2002). Despite the benefit of regular physical activity in the prevention of cancer and other debilitating illnesses, 75% of the U.S. population does not get the recommended amount of physical activity as defined by 30 minutes of moderate-intensity physical activity 5 or more days per week (CDC, 2001), and 40% of the population is completely sedentary (USDHHS, 1996). 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 hypotheses and one secondary hypothesis: (1) A previously tested and validated exercise promotion intervention (c.f., Marcus et al., 1998) is successful at helping sedentary individuals initiate and maintain a moderate-intensity physical activity regimen, compared to a health and wellness control intervention; (2) Increases in positive attitudes, perceived normative support, self-efficacy, and intentions to exercise will mediate the effectiveness of the intervention; (3) Increased positive mood and better temperature, stress, and lactate regulation immediately after exercise challenge (assessed in the laboratory) will moderate the effectiveness of the intervention; and (4) Secondarily, we 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.

Reproductive Health/Developmental Biology

Title: **Childhood Exposure to Disadvantage and Adult Pregnancy Outcomes**
P.I.: **Janine Liana Richardson**
Institution: **University of North Carolina at Chapel Hill – Chapel Hill, NC**
Grant No.: **1 F21 HD056549-01**
Award: **$30,096**

Among the most challenging perinatal health problems in public health is the prediction and prevention of preterm birth (PTB). PTB is a major contributor to infant mortality, particularly among African-Americans, who have historically experienced higher rates of PTB than other racial/ethnic groups. During the past several decades, efforts to predict and prevent PTB—which mostly focused on behavioral, psychological, and medical risk factors—have had little impact on this racial disparity. The proposed study instead focuses on the role of social ecological factors in PTB and the mecha-

nisms by which these factors are related to more proximal causes of PTB. The study has four Specific Aims. First, it will determine whether the experience of structural disadvantage during childhood is associated with increased risk of PTB in adulthood, independent of adulthood socioeconomic status. Second, it will assess whether the effects of experiencing disadvantage in childhood and adulthood on PTB are multiplicative or cumulative. Third, it will explore potential behavioral, psychosocial, and biological mediators of these relationships. Finally, the study will examine whether differential experiences of structural disadvantage during childhood explain racial differences in rates of PTB in adulthood. To accomplish these aims, the study will use data from the public-use dataset of the National Longitudinal Study of Adolescent Health—a study that collected data from a nationally representative sample of adolescents between 1994 and 1995 (Wave I), 1 year later (Wave II), and 6 years later (Wave III), when they were adults, as well as contextual information about their childhood neighborhoods. The proposed study will entail secondary analyses of data from a sample of females who reported at least one live birth at Wave III (n = 1,357 live births, 947 women). This study is consistent with the mission of NICHD, where the underlying causes of infant mortality and where structural factors related to the health of women, their families, and their communities during their adolescent and childbearing years, are clear research priorities. Relevance: The proposed study responds to the Healthy People 2010 objective to eliminate racial disparities in pregnancy outcomes and to the lOM's 2004 report on racial and ethnic differences in health over the life course, which called for identifying mediating variables between childhood deprivation and adult health, including environmental conditions. Moreover, the study will attempt to identify the actions that public health professionals must take and the appropriate targets and timing for those actions in order to prevent PTB.

Title: **Protein Tyrosine Kinases in Leiomyomata Uteri**
P.I.: **Jean Y. Wang**
Institution: **University of California, San Diego – La Jolla, CA**
Grant No.: **5 R01 HD046225-05**
Award: **$70,427**

Uterine leiomyomas or fibroids are benign pelvic tumors that originate from uterine cells. The clinically apparent incidence of leiomyoma in women of productive age is about 25%, whereas pathological examination places the rate of incidence as high as 75%. The growth of leiomyoma is dependent on the female sex hormones, estrogen and progesterone. We propose that hormones stimulate the expression and/or activation of protein tyrosine kinases (YKs) to promote the growth of fibroids. This hypothesis predicts that inhibition of YKs involved in the proliferation of uterine cells would halt the growth of fibroids. Therefore, we propose to survey the expression and the activity of YKs in normal uterine myometrium and leiomyomas. We propose to create microarrays that are suitable for profiling the expression of all 90 human YK genes (Aim 1). Using these microarrays, we will profile the expression of YKs in specimens of normal myometrium and leiomyoma procured from patients in different age and ethnic groups because these factors are known to affect the risk for fibroids (Aim 2). In addition to the static view of YK expression profiles in patient samples, we will determine the influence of hormones on YK expression (Aim 3). We will examine the protein levels and kinase activities of YKs that are expressed in normal and fibroid tissues (Aim 4). We will develop the necessary anti-YK and phospho-specific antibodies if commercial antibodies are not available. We will disrupt the activity of YKs that are expressed and/or activated in fibroids by small-molecule inhibitors, if available, or by siRNA, and then measure the hormone-dependent proliferative response of leiomyomas in athymic nude mice (Aim 5). Results from the proposed study will identify tyrosine kinases that are important for the proliferation of fibroids. Tyrosine kinases have been successfully targeted in the development of rational therapy for human cancers. Information gathered from the proposed research may therefore lead to the development of new therapeutics to control the growth of fibroids.

Title: **Finding Genes for Uterine Fibroids**
P.I.: **Cynthia Casson Morton**
Institution: **Brigham and Women's Hospital – Boston, MA**
Grant No.: **5 R01 HD 46226-05**
Award: **$72,750**

Uterine leiomyomata (UL), also called fibroids, are the most common pelvic tumors in females. Although they are benign neoplasms, UL constitute a major public health problem as 20–25% of affected women experience debilitating symptoms, including excessive menstrual bleeding, pelvic discomfort, and reproductive failure. Medical treatment options for UL are limited, and surgery is the mainstay of therapy. In fact, UL are the most common indication for hysterectomy, accounting for over 200,000 procedures annually in the United States. Although it is well recognized that UL are steroid-dependent tumors, much remains to be known about their growth and development. Compelling evidence suggests a genetic liability to develop UL. These tumors are at least three times more frequent in Black than in White women, and twin-pair correlations for hysterectomy in monozygotic twins are about twice those observed in dizygous twins. Studies of familial aggregation indicate a 2.5-fold increased risk for UL among first-degree relatives of affected probands compared to relatives of unaffected probands; this odds ratio increases to 5.7 after stratifying cases by age of proband (< 45 years) and of relatives (less than or equal to 40 years). About 25–40% of UL are karyotypically abnormal, and several genes involved in the pathobiology of the tumors have been identified using positional cloning approaches based on chromosome rearrangements. Genetic linkage analysis in two rare Mendelian disorders, Reed syndrome (MIM150800), characterized by UL in association with multiple cutaneous leiomyomata, and hereditary leiomyomatosis and renal cell cancer (HLRCC, MIM605839), a cancer syndrome characterized by uterine leiomyomas and papillary renal cell carcinoma, resulted in the surprising finding of mutations in the gene for fumarate hydratase. Despite these important findings, we remain ignorant of the genes that predispose millions of women to develop these tumors. Experiments in this application will focus on identification, isolation, and characterization of genes involved in the pathogenesis of UL. Specifically, we propose to identify genes that predispose women to develop UL by performing a genome-wide scan (www.fibroids.net: Finding Genes for Fibroids). Ultimately, understanding genetic pathways involved in the formation of UL may lead to improved treatment options for affected women and lifestyle changes for at-risk individuals.

Title: **Estrogen Dependency of Uterine Leiomyoma**
P.I.: **Ayman Al-Hendy**
Institution: **University of Texas Medical Branch – Galveston, TX**
Grant No.: **5 R01 HD046228-05**
Award: **$70,427**

Uterine leiomyomas arise from the uterine smooth muscle compartment (myometrium) and are the most common gynecologic tumor in premenopausal women, occurring in up to 77% of all women. They are a significant cause of pelvic pain, menorrhagia, infertility, and pregnancy-related complications. These estrogen-dependent tumors are the leading indication for hysterectomy in reproductive-aged women. Currently, no medicinal therapy exists. Prolonged use of GnRH agonists, which can shrink tumors but induce a chemical menopause, is restricted due to serious side effects. The hormone-dependent phenotype of uterine leiomyoma suggests that interventions targeting the estrogen receptor (ER)-signaling pathway may have therapeutic efficacy. Proof-of-principal experiments have now established that treatment with antiestrogen medications (e.g., tamoxifen and raloxifene) can significantly reduce tumor incidence, size, and proliferative index in the Eker rat, the only animal model known to acquire spontaneous uterine leiomyoma. Adenovirus-mediated delivery of a mutated dominant-negative ER (Ad-ER-DN) inhibited cell proliferation and induced apoptosis in human and rat leiomyoma cell lines. In a pilot experiment, Ad-ER-DN injected directly

intratumor in nude mice with preexisting fibroids induced immediate arrest and regression of tumor growth due to extensive apoptosis. In this project, we will (Specific Aim 1) determine if Ad-ER-DN transduction inhibits endogenous ER signaling in estrogen-responsive rat and human leiomyoma cells, (Specific Aim 2) expand pilot results and evaluate the ability of Ad-ER-DN to ablate preestablished subcutaneous leiomyoma mice, and (Specific Aim 3) conduct a preclinical trial to assess the ability of Ad-ER-DN to ablate uterine leiomyoma when delivered by direct intratumor injection in the immune-competent Eker rat. Tumor response will be correlated to proliferative and apoptotic indices, to markers of tumor angiogenesis, and to several estrogen-regulated genes. We will examine immune response and the safety of single vs. repeated recombinant adenovirus treatment alone or in combination with SERM (raloxifene). Evident therapeutic potential aside, this project will add to our understanding of the molecular mechanisms of estrogen dependence in this common uterine tumor. It will also show, in a well-characterized natural rat model, the effects of specific perturbing of ER signaling on several cellular functions (i.e., angiogenesis, apoptosis, and cell cycle). This knowledge will impact many other estrogen-related conditions (e.g., breast and endometrial cancer, cardiovascular disease, osteoporosis).

Title: **Leiomyomata Uteri: Apoptosis and Cell Survival Pathways**
P.I.: **Gregory M. Christman**
Institution: **University of Michigan at Ann Arbor – Ann Arbor, MI**
Grant No.: **5 R01 HD046249-05**
Award: **$73,237**

Leiomyomas are benign monoclonal proliferations of uterine smooth muscle cells occurring in one of every three women of reproductive age. Twenty to 50 percent of women with leiomyomas develop symptoms, including abnormal bleeding, pelvic pain and pressure, urinary frequency, reduced fertility, and miscarriage. Leiomyomas represent the leading indication for hysterectomy in the United States. The development and severity of symptoms is related to the size and position of the tumors. The proliferation of uterine leiomyoma cells exceeds the limited number of cells undergoing apoptosis, resulting in tumor enlargement. Studies from our laboratory have demonstrated the effectiveness of a cytotoxic gene therapy approach known to induce apoptosis to reduce leiomyoma proliferation and volume using human leiomyocytes and leiomyoma cells derived from the Eker rat strain (ELT-3 cells). A strong bystander effect was demonstrated where transfection of a small percentage of leiomyoma cells was able to mediate marked cellular death of the nontransfected cells and in vivo tumor regression of uterine leiomyomas. In vitro experiments using the dietary triphenolic stilbene resveratrol, an estrogen alpha receptor antagonist, inhibited proliferation of the ELT-3 uterine leiomyoma cell line in a hypoestrogenic environment. Uterine leiomyomas generally exhibit minimal apoptosis despite evidence that cellular mediators of both the intrinsic and extrinsic pathways of apoptosis are expressed. The antiapoptosis factor Bcl-2 is highly expressed in leiomyoma cells in comparison to normal myometrium. Bcl-2 protein expression is reduced by estrogen exposure and increased by progesterone exposure. GnRH agonists administered in vivo cause a marked reduction in leiomyoma size without evidence of apoptosis. In contrast, in vitro exposure of leiomyoma cells to GnRH agonists causes marked apoptosis and induction of Fas and Fas ligand. We propose the following Specific Aims. Specific Aim 1: To study the effect of HSV-tk/ganciclovir, the dietary ER-alpha receptor antagonist resveratrol, and GNRH agonist on cell proliferation and apoptosis in ELT-3 and human leiomyoma cells; Specific Aim 2: To study the effect of HSVtk/ganciclovir, the dietary ER-alpha receptor antagonist resveratrol, and GNRH agonist on cell proliferation and apoptosis in the ELT-3/nude mouse model of leiomyoma; and Specific Aim 3: To study the effect of HSV-tk/ganciclovir, the dietary ER-alpha receptor antagonist resveratrol and GNRH agonist on cell proliferation and apoptosis in a human leiomyoma xenograft model. A detailed understanding of the apoptosis and cell survival pathways active in uterine leiomyomas will allow us to better promote long-term tumor regression in response to evolving minimally invasive therapies in development for uterine leiomyomas, including vascular embolization, high-intensity focused ultrasound, and evolving targeted molecular and pharmacologic therapies.

Title: Regulation of Uterine Fibroids by CCN5
P.I.: John J. Castellot
Institution: Tufts University – Boston, MA
Grant No.: 5 R01 HD046251-05
Award: $73,238

The long-term goal of this project is to elucidate the cellular, molecular, and biochemical mechanisms regulating the proliferation and motility of human uterine smooth muscle cells (UtSMC). UtSMC hyperproliferation is the cause of fibroids, a condition that afflicts 20–25% of all women and 75% of African-American women. Fibroids cause severe pain and bleeding, impair fertility, and result in >200,000 hysterectomies annually in the United States. There is no known treatment—medical or surgical—that permanently reduces or eliminates fibroids, other than hysterectomy. Clearly, a detailed understanding of the mechanisms and molecules that regulate UtSMC mitogenesis and migration will provide a therapeutic rationale for controlling fibroids and may provide important insights into the pathophysiologic basis for fibroid formation. Our laboratory has provided strong evidence that CCN5, an estrogen-induced, growth-arrest–specific gene, inhibits proliferation and motility in cultured UtSMC. Furthermore, we have demonstrated that human leiomyomas have greatly reduced levels of CCN5 mRNA and protein compared to normal myometrium from the same uterus. Based on this evidence, the following hypothesis will be tested: CCN5 is an autocrine regulator of UtSMC proliferation and motility in culture and in vivo and exerts its antiproliferative and antimotility effects, at least in part, through regulation of extracellular matrix synthesis and composition. To test this hypothesis, we will (1) Continue our functional analysis of CCN5 and its regulation by estrogen on proliferation, motility, and extracellular matrix in SMC cultured from matched pairs of normal and fibroid human uterine tissue. To do this we will use adenovirus vectors, recombinant CCN5, and small inhibitory RNA approaches. (2) Examine the physiologic functions and estrogen regulation of CCN5 in animal models, including normal cycling rats, ovariectomized rats, pregnant rats, wild-type mice, and genetically manipulated mice that either under- or overexpress CCN5. Quantitative PCR, Western blot analysis, and immunohistochemistry will be used to determine the spatial and temporal expression pattern and estrogen regulation of CCN5 in each of these animal models. We will also explore the possibility that CCN5 gene or protein therapy might be a useful approach for suppressing human fibroids in a novel nude mouse model system. The experiments proposed in this application should provide new and important insights into UtSMC pathophysiology in humans.

Title: Estrogen Biosynthesis and Uterine Leiomyomata
P.I.: Serdar E. Bulun
Institution: Northwestern University – Evanston, IL
Grant No.: 5 R01 HD046260-05
Award: $73,237

The long-range objective of this application is to determine cellular and molecular mechanisms responsible for aberrant aromatase P450 (P450arom) expression in uterine leiomyomata. The pathologic significance of this application is underscored by the fact that estrogen is essential for the growth of leiomyomata. P450arom is the key enzyme for estrogen biosynthesis in a number of human tissues. We demonstrated local estrogen biosynthesis via P450arom expression in tissue samples and cultured leiomyoma smooth muscle (LSM) cells, but not in normal myometrial tissues or cells. We hypothesize that aberrant expression of stimulatory transcription factors and downregulation of inhibitory transcription factors in LSM cells are critical mechanisms for PGE2-dependent induction of P450arom promoter II activity, mRNA levels, and enzyme activity in these cells. The clinical relevance of these findings was recently emphasized by the successful treatment of a leiomyoma in a menopausal woman with an aromatase inhibitor. We propose the following Aims: (1) To determine the molecular mechanisms responsible for PGE2-dependent regulation of P450arom enzyme, protein, and mRNA levels in LSM cells. We will test the hypothesis that PGE2 acts via EP1 and EP2 receptor subtypes to stimulate both PKC and PKA pathways, which induce

P450arom expression. (2) To define the DNA motifs that mediate PGE2-dependent activation of P450arom promoter II in LSM cells. We hypothesize that an LRH-l-binding site, a cAMP response element, and a C/EBP-binding site mediate PGE2-dependent promoter activation. (3) To determine the roles of transcription factors in aberrant P450arom expression in LSM cells. The effects of overexpression and reduction of coregulators of LRH-1 on P450arom promoter will be studied. In vivo spatial and temporal association between these transcription factors and P450arom in leiomyoma samples will be determined. (4) To define the basic composition of the multimeric complex that occupies P450arom promoter II and enhances its activity in response to PGE2. We will employ immunoprecipitation-PCR to determine the association of LRH-1, its coregulators, a C/EBP isoform, and p300/CBP showing histone acetyl transferase activity with P450arom promoter in response to PGE2. Protein–protein interactions will be demonstrated by immunoprecipitation-Western analyses. We predict that these studies will establish the critical role of P450arom in uterine leiomyomata and lead to identification of novel therapeutic targets.

Title: **Molecular Etiology of Leiomyoma Uteri**
P.I.: **Cheryl L. Walker**
Institution: **University of Texas–M.D. Anderson Cancer Center – Houston, TX**
Grant No.: **5 R01 HD046282-05**
Award: **$73,237**

Very little is known about the molecular mechanisms that underlie the pathophysiology of leiomyoma uteri. In contrast to carcinomas, which are generally singular and for which the stages of tumorigenesis and associated molecular alterations are well described, leiomyoma uteri are usually multiple and events that determine their long-term sequelae have not been elucidated. Furthermore, the natural history of individual leiomyomas within a single woman may be quite different. This indicates that even though tumors within a given woman are exposed to the same hormonal milieu, intertumor heterogeneity in hormone responsiveness must exist. Such intertumor heterogeneity may be the result of differences in molecular etiology, which could also determine responsiveness to hormonal therapy and the impact of environmental estrogen exposure. Loss of the tuberous sclerosis complex 2 (TSC-2) tumor-suppressor gene results in the development of leiomyoma uteri in the Eker rat model for this disease. However, defects in TSC-2 or the pathways in which this tumor-suppressor gene participate have not been investigated in human leiomyomas. Recently, the TSC-2 gene product tuberin has been shown to play an important role in PI3K signaling, which can impact both estrogen receptor signaling and cell cycle control via p27. Our preliminary data from the Eker rat model and translational studies utilizing primary human tumors suggest that TSC-2 and p27 play important, and possibly interrelated, roles in the molecular etiology of leiomyoma uteri. Recognition of the involvement of TSC-2, PI3K signaling, and p27 in the etiology of leiomyoma uteri now provides a unique avenue for understanding the molecular basis of aberrant cell cycle regulation and hormonal responsiveness in this disease. The goal of this proposal is to identify the mechanisms responsible for differential cell cycle regulation in leiomyoma uteri that may underlie intertumor heterogeneity and responsiveness. To accomplish this goal, the Specific Aims of this proposal are (1) Determine the mechanism responsible for diminished p27 function in leiomyoma uteri and the role of PI3K signaling and tuberin in this process, (2) Test the hypothesis that alteration of p27 expression levels is a critical regulator of normal and neoplastic myometrial cell growth that can determine natural history of this disease, and (3) Determine if diminished p27 levels and/or aberrant P13K/AKT signaling enhances estrogen-receptor signaling in leiomyomas and potentiates the activity of SERMs and environmental estrogens in these tumors. Data generated from these experiments will help elucidate how defective cell cycle regulation and estrogen receptor signaling contribute to the pathophysiology of leiomyoma uteri.

Title: Sixteenth Ovarian Workshop
P.I.: Teresa K. Woodruff
Institution: Northwestern University – Chicago, IL
Grant No.: 1 R13 HD056944-01
Award: $5,000

The Sixteenth Ovarian Workshop, The Ovary: Signaling Mechanisms Regulating Development and Dysfunction was held on July 19–21, 2007, in San Antonio, Texas, at the Sheraton Hotel. The Ovarian Workshop provided a forum for clinicians, scientists, and students to exchange ideas and current concepts on the development, regulation, and maintenance of the ovary without regard to disciplinary boundaries. The Workshop promoted the presentation and exchange of ideas at the frontiers of research in female reproductive biology. The scientific program has evolved into an internationally respected conference, attracting scientists from diverse backgrounds who share a common interest in understanding the function of cells in the ovary. The format at this Workshop expanded on the theme of translational research that reaches from bench to bedside by incorporating new basic science together with clinically relevant issues and presentations by clinical scientists. The theme of the workshop was ovarian development and included a variety of topics on sex determination, follicle assembly, new concepts in follicle engineering, and diseases that impact ovarian formation or function. The program included two keynote addresses and poster sessions related to the theme of the Workshop. New investigators were invited to submit expanded abstracts that were evaluated for scientific merit and competition for travel awards and the Cornelia P. Channing New Investigator Award. The program had an outstanding list of speakers who were new to this venue and provided transdisciplinary topics with clinical relevance and a focus on fellows and cutting-edge science. These ingredients made the Ovarian Workshop the premiere program in ovarian biology in the Nation. The goal of this Ovarian Workshop was to advance our understanding of ovarian function so that this basic knowledge could be translated into clinical applications to enhance or control fertility and treat, reduce, and/or eliminate ovarian dysfunction and cancer. These conditions include sex reversal; metabolic disease that adversely impacts ovarian function; steroid excess, including hyperandrogenic states leading to hirsutism; acne and alopecia; infertility treatments for women with ovarian dysfunction; preservation of fertility for women with cancer; the prevention and treatment of gynecological cancers related to ovarian dysfunction, including endometrial and ovarian cancer; and environmental threats to reproductive function. Further, given the public controversies that surround many of these treatments, our goal was to provide all participants with the ethical framework to understand the varying positions of the many constituents who weigh in on these issues.

Title: Reproductive Medicine and the Law Workshops
P.I.: Robert William Rebar
Institution: American Society for Reproductive Medicine – Birmingham, AL
Grant No.: 1 R13 HD056978-01
Award: $6,000

Infertility affects approximately 13–14% of couples of reproductive age in the United States. Although this rate has remained stable over the past few years, the demand for infertility services has increased substantially as refinements in assisted reproductive technologies (ARTs), including in vitro fertilization (IVF), have extended family-building potential to patients who previously had little hope of conception. Presently, approximately 1% of all children born in the United States are born using ART. The advent of IVF and the ability to produce a live baby using spermatozoa, oocytes, embryos, and gestational carriers from heterologous sources has led to a myriad of complicated legal issues pertaining to embryos, children, parents, families, and reproductive rights. Patients and their physicians often are confused by seemingly contradictory State laws and State and Federal judicial rulings pertaining to rights and responsibilities of infertility patients and health care providers. There is an urgent public health need in the United States for medical and legal scholars and professionals to develop enlightened and coherent approaches to jurisprudence in the area of reproductive medi-

cine so that this increasing segment of the population is able to maximize its family-building potential. The American Society for Reproductive Medicine and the Association of American Law Schools have collaborated to develop a program consisting of two workshops to address the gap between ART and existing laws. The objectives of the workshops are to (1) facilitate dialogue among medical and legal professionals that will lead to increased understanding in the medical profession of the legal ramifications of advances in assisted reproductive technologies and to increased understanding in the legal profession of the need for novel legal strategies to justly and humanely govern the rapidly changing variations in approaches to family building; (2) review jointly the current status of assisted reproductive technologies and the body of Federal, State, and local laws and judicial decisions pertaining to gametes, embryos, parenting, and reproductive rights and responsibilities; and (3) produce and disseminate scholarly expert guidance that increases knowledge and informs public policy in the realm of reproductive medicine and the law. These workshops are expected to be the first in an ongoing dialogue between medical and legal scholars in their efforts to provide sound legal guidance for patients undergoing ART.

Title: **17a-OH Progesterone Caproate and Progesterone Actions in Human Myometrial Cells**
P.I.: **Melvyn S. Soloff**
Institution: **University of Texas Medical Branch – Galveston, TX**
Grant No.: **1 R21 HD056399-01**
Award: **$226,500**

Preterm birth is the leading cause of infant mortality and has been targeted for funding by the NICHD Pregnancy and Perinatalogy Branch. Two large, independent, randomized clinical trials showed that administration of 17a-hydroxyprogesterone caproate (17P) or progesterone (P4) during the second trimester to women at risk of spontaneous preterm birth resulted in a significant reduction in the incidence of preterm labor. Progestins induce myometrial quiescence, likely due in part to alterations in P4 receptor-mediated gene expression in myometrial cells. However, the effects of P4 signaling on the gene expression profile of myometrial cells are largely unknown. The objective of this project is to define progestin-regulated gene networks in human myometrial cells to provide a deeper understanding of progestin control of myometrial contractility. Unraveling these intricate pathways is essential to understanding biological mechanisms that control myometrial function and could lead to the development of improved and/or novel tocolytics. A standard approach to profiling transcriptomes has been to use cultured cells. However, myometrial cells in primary culture rapidly lose P4 (and estrogen) receptors. Both estrogen and P4 signaling are essential in reproductive processes, and estrogens upregulate both estrogen and P4 receptor gene expression in all mammalian species. We will use recombinant methods to reengineer immortalized myometrial cell lines developed in our laboratory so that they conditionally express estrogen receptors. Endogenous P4 receptors will then be induced by the administration of estrogen. Using GeneChip microarray analysis, the cells will be used to characterize the human myometrial cell transcriptome before and after 17P or P4 administration. Changes in expression of transcripts that show a likely relationship to uterine contractile activity will be confirmed by real-time PCR. PCR will also be used to verify gene repression, using intron/exon oligonucleotides to probe newly synthesized transcripts. The recognition of progestin target genes in human myometrial cells, coupled with the use of knowledge-based analysis tools to model and understand complex biological systems, will allow us to begin to identify biological networks involved in progestin maintenance of uterine quiescence and serve to guide more elaborative biochemical studies on the interplay between progestin-regulated processes. Two large, independent, randomized clinical trials showed that administration of 17a-hydroxyprogesterone caproate or progesterone during the second trimester to women at risk of spontaneous preterm birth resulted in a significant reduction in the incidence of preterm labor. The objective of this project is to define progestin-regulated gene networks in human myometrial cells to provide a deeper understanding of progestin control of myometrial contractility. Unraveling these

intricate pathways is essential to understanding biological mechanisms that control myometrial function and could lead to the development of improved and/or novel tocolytics.

Title: Pelvic Floor Disorders Network–Data Coordinating Center
P.I.: Catherine A. Spino
Institution: University of Michigan at Ann Arbor – Ann Arbor, MI
Grant No.: 5 U01 HD041249-07
Award: $24,275

Pelvic floor disorders, such as urinary incontinence, pelvic organ prolapse, and fecal incontinence, are common and significant health-related problems for women in the United States. Outcomes following surgical and nonsurgical intervention for pelvic floor disorders have not been adequately evaluated. As a result, data necessary to fully inform patients and to make important policy decisions are unavailable. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to systematically evaluate these outcomes. This application to be the Data Coordinating Center (DCC) for the PFDN brings together experienced investigators from biostatistics, urogynecology, urology, quality-of-life, and health services research to prospectively assess the outcomes from various surgical interventions for female pelvic floor disorders. The specific aims of the DCC are to (1) Assist in protocol development by providing expertise in the design, conduct, and analysis of clinical trials conducted by the PFDN; (2) Provide expertise in measurement of quality of life and in the selection of the appropriate instruments to assess treatment outcomes and, when appropriate, to perform the interviews; (3) Coordinate the implementation of the study protocols approved by the Steering Committee, including design of the case report forms and interviewing protocols, development of a manual of operations, centralized database management with either centralized or remote data entry, submission of an IND to the FDA when necessary, and by organizing training and certification sessions, as needed; (4) Establish a database for each study conducted by the PFDN; (5) Implement either centralized or Web-based data entry and verification; (6) Monitor the clinical sites with respect to data quality; (7) Provide infrastructure for monitoring adverse events and regulatory oversight for the network; (8) Provide logistical support for the Steering Committee, Advisory Board, and DSMB, for both face-to-face meetings and teleconferences; (9) Maintain a Web site for the PFDN that includes Web pages with content for the public and a password-protected site with all study documentation and databases; and (10) Manage and distribute protocol funds to the Clinical Centers. To illustrate the work of the DCC, a randomized clinical trial is proposed to compare surgical procedures for pelvic organ prolapse using a vaginal approach.

Title: The Pelvic Floor Disorders Network
P.I.: Linda Brubaker
Institution: Loyola University of Chicago – Maywood, IL
Grant No.: 5 U10 HD041250-07
Award: $24,275

Loyola is a productive, innovative clinical research institution that has contributed to the first cycle of the Pelvic Floor Disorders Network (PFDN)and we are eager to build on the PFDN's excellent start. Our application documents the following: (1) The qualifications and commitment of institution and key personnel at Loyola, a qualified and committed institution with a multidisciplinary faculty with experience in clinical trials design and conduct, along with a highly qualified and committed research team led by the same PI, Dr. Brubaker. This research team also employs urogynecologists and urologists. Two of the faculty members received master's degrees in clinical research design and statistical analysis and one is currently in this degree program. A cadre of study coordinators are crosstrained to meet the needs of the PFDN study roster. The team has excellent collaborations within the Loyola faculty. (2) Loyola's Participation in PFDN Protocols and Procedures. High-quality participation in PFDN protocols with excellent and consistent recruitment. We also demonstrate our consistent contributions in PFDN work, including dissemination of PFDN

scientific findings. Loyola has been productive and has worked well with the PFDN team. Our first-cycle application proposed the essence of the CARE trial, which was completed ahead of schedule and is under consideration for publication. (3) A Feasible, Scientifically Relevant Concept Protocol (Randomized Surgical Trial). We believe we have demonstrated our ability to design and conduct high-quality clinical trials. This application also describes a randomized surgical trial for women who select vaginal apical reconstruction. A comparison of the two most common techniques may inform a future study that seeks to determine which route of surgery (abdominal vs. vaginal) is best suited for an individual woman. This trial is a feasible, scientifically relevant, randomized surgical trial. The draft protocol is suitable for PFDN Steering Committee discussion and revision prior to implementation.

Title: **The Pelvic Floor Disorders Network**
P.I.: **Anthony G. Visco**
Institution: **Duke University – Durham, NC**
Grant No.: **5 U10 HD041267-08**
Award: **$25,000**

Women's health research at the University of North Carolina (UNC) is sophisticated and widespread, with many committed investigators addressing issues of fundamental importance to women. UNC has a tradition of excellence in clinical care, training, and research in pelvic floor disorders and includes one of the nation's first accredited fellowship programs in the Division of Urogynecology and Reconstructive Pelvic Surgery. We offer comprehensive evaluation and treatment options in a high-volume care setting that serves as a tertiary referral center for women from across the State. Women sought consultation or treatment for more than 2,700 pelvic floor disorders by Urogynecologists at UNC in the previous 2 years. Seventy-eight percent of the women were Caucasian and 15% were African-American, predominantly from rural and suburban communities with stable care and followup patterns. Approximately 427 women had multichannel urodynamic studies annually. UNC providers have extensive expertise in both surgical and nonsurgical management of urinary incontinence, pelvic organ prolapse, and defecatory dysfunction. The Division of Urogynecology performs an average of 106 surgical procedures for the primary indication of urinary incontinence and 300 for prolapse and provides medical management for over 1,464 women with these conditions each year. The UNC Pelvic Floor Disorders Research Collaborative, led by the Division of Urogynecology, is a multidisciplinary team of outstanding investigators in urogynecology, urology, gastroenterology, radiology, maternal–fetal medicine, and clinical research methodology. They have a history of strong clinical ties and dedication to interdisciplinary research. Diagnostic resources include mutichannel urodynamic testing, cystoscopy, defecography, pelvic MRI, 360-degree endoanal ultrasound, anal manometry, and needle electromyography. Clinical services include surgical treatment of complex pelvic floor disorders and a wide range of nonsurgical options. As an active PFDN clinical network site, UNC has an established research infrastructure with the proven ability to support large-scale, multicentered clinical research. The collaborative is well equipped and uniquely qualified to continue as a valuable member of the Pelvic Floor Disorders Network. Given the exceptional quality of the research opportunities and resources available at UNC, the stable and diverse patient population, the strength of the investigator pool, our proven high-level recruitment, and the commitment of the institution to the stated goals of this RFA, we look forward to continuing to make substantial contributions to advancing women's health related to pelvic floor disorders.

Title: Washington Obstetric–Fetal Pharmacology Research Unit
P.I.: Menachem Miodovnik
Institution: Georgetown University – Washington, DC
Grant No.: 5 U10 HD047890-04
Award: $50,000

The Washington Obstetric Pharmacology Research Unit (WOPRU) represents a collaboration among two universities and four medical centers in the Nation's capital that is uniquely positioned to use population pharmacokinetic, pharmacokinetic-pharmacodynamic, clinical trials simulation, and cutting-edge in vivo and in vitro techniques to assess the clinical pharmacology of important therapeutic agents and their effects in pregnant women and their offspring. Specifically, the WOPRU combines the basic research resources of Georgetown University (lead agency) and George Washington University (GWU) with the clinical strengths of MedStar Health (Washington Hospital Center and Georgetown University Hospital), GWU Hospital, and Children's National Medical Center (CNMC). Our hospitals are strategically placed throughout the DC metropolitan area and are closely associated with their 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 our diverse community. The faculty of the WOPRU represents a team of highly motivated basic scientists and clinical investigators who are enthusiastically approaching the prospect of becoming a new center for OPRU. They are experienced investigators in a multitude of basic science and clinical disciplines with a unique combination of strengths in pharmacometrics, pharmacodynamics, pharmacogenetics, drug metabolism, therapeutic drug monitoring, proteomics, genomics, and biostatistics in conjunction with significant experience in multicenter clinical trials. The administration and the basic science and clinical investigators of the WOPRU institutions are unanimous in their eagerness to support and participate in the future OPRU network.

Title: Obstetric–Fetal Pharmacology Research Units Network
P.I.: Gary D. Hankins
Institution: University of Texas Medical Branch – Galveston, TX
Grant No.: 5 U10 HD047891-04
Award: $48,550

The University of Texas Medical Branch (UTMB) has the capability to participate actively as a member of the Obstetric-Fetal Pharmacology Research Unit (OPRU) Network. Gary Hankins, M.D., as PI, is responsible for the proposed clinical trial on the use of hypoglycemic drugs in the treatment of diabetes during pregnancy. He has extensive experience within several NIH multicenter trials, such as First and Second Trimester Evaluation of Risk of Aneuploidy (FASTER), Beneficial Effects of Antenatal Magnesium Sulfate Study (BEAM), and the Vaginal Ultrasound Cerclage Trial. Dr. Hankins has achieved successful patient recruitment and retention by involvement with UTMB's Regional Maternal & Child Health Program (RMCHP). All RMCHP clinics follow protocols established by the Maternal-Fetal Medicine division, headed by Dr. Hankins. Over 12,000 pregnant women are cared for annually within the RMCHP clinic system, approximately 7,000 of whom deliver at UTMB. The Pharmacology/Pharmacokinetics (PK) Coinvestigator, Mahmoud S. Ahmed, Ph.D., has over 25 years of expertise in utilizing human placenta and derived preparations in his investigations. Dr. Ahmed is a laboratory pioneer investigator in placental receptors, their natural ligands and mediated responses, as well as the mechanism of hCG release from trophoblast tissue. They 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 metabolicenzymes on the PK for placental transfer of opiates. They identified placental aromatase as a drug-metabolizing enzyme and are investigating its polymorphism. Kenneth D. Carey, D.V.M., Ph.D., as Animal Model Coinvestigator, 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. Dr. Hankins is an adjunct investigator at the SNPRC and has had extensive involvement with the Primate research staff. The Department of Ob/Gyn has well-funded scientists with expertise in areas relevant to this RFA, including infection, vascular physiology, and placental functions. Clinical PK Coonvestigators Susan Abdel-Rahman, Pharm. D., and Wayne Snodgrass, M.D., Ph.D., have over 30 years of combined experience in the development of protocols for PK studies, evaluation of data obtained, and PK/PD modeling. The Division of Neonatology, the GCRC, and other departments at UTMB will provide support for this project.

Title: **Obstetric–Fetal Pharmacology Research Unit**
P.I.: **Mary F. Hebert**
Institution: **University of Washington – Seattle, WA**
Grant No.: **5 U10 HD047892-04**
Award: **$50,000**

The overall objective of this grant proposal 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 on cytochrome P450 enzymes and membrane transporters. This proposal describes the available environment and resources at the University of Washington for establishing a successful and productive Obstetric-Fetal Pharmacology Research Unit. As a demonstration of our research interests and capabilities, the following translational research studies that integrate our strengths in clinical and basic sciences are proposed to evaluate the following Study Aims. (1) We aim 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) We aim 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

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Title: **Pregnancy and Drug Metabolizing Enzymes and Transporters**
P.I.: **Steve N. Caritis**
Institution: **Magee-Womens Research Institute and Foundation – Pittsburgh, PA**
Grant No.: **5 U10 HD047905-04**
Award: **$45,750**

The purpose of this proposal is to establish an Obstetric-Fetal Pharmacology Research Unit (OPRU) at the University of Pittsburgh and to summarize the components of the applicants' 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. They provide three protocols for assessment by the Network for future exploration. The Pittsburgh OPRU is composed of a large clinical facility (Magee-Womens Hospital) with more than 8,000 deliveries and a wide array of women with medical or obstetric complications. A CRC satellite at Magee provides an optimal site for recruitment and study of pregnant women. These clinical facilities are linked to the Center for Clinical Pharmacology (CCP), which provides a core laboratory for classical pharmacology analyses and a pharmacogenetic laboratory for genotyping, mRNA expres-

sion, 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-Womens 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: **Utah Pelvic Floor Disorders Network**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah – Salt Lake City, UT**
Grant No.: **5 U10 HD054136-02**
Award: **$24,275**

Pelvic floor disorders are common, bothersome, and inadequately treated. The overarching aim of the investigators from the proposed University of Utah Pelvic Floor Disorders Clinical Site is to improve women's health in the area of pelvic floor dysfunction. To this end, site-Specific Aims include (1) Identifying priority areas of research, (2) Developing assessment tools, (3) Developing and implementing PFDN protocols, (4) Recruiting and enrolling subjects in PFDN protocols, (5) Achieving on-target recruitment goals and high subject retention, (6) Ensuring high-quality data, (7) Transmitting data accurately to the Data Coordinating Center, (8) Participating in data analysis, (9) Disseminating results to the research community, and (10) Producing high-quality publications. The broad scientific aim for the randomized clinical trial outlined in this proposal is to evaluate whether postoperative pelvic floor muscle training following surgery for pelvic organ prolapse and/or stress urinary incontinence improves postoperative outcomes (anatomic, symptomatic, and quality-of-life outcomes) at 3 months, 1 year, and 2 years postoperatively.

Title: **Pelvic Floor Disorders Network**
P.I.: **Charles W. Nager**
Institution: **University of California San Diego – La Jolla, CA**
Grant No.: **5 U10 HD054214-02**
Award: **$24,275**

The objectives and aims of this application are for San Diego to become the first western U.S. clinical site in the Pelvic Floor Disorders Network (PFDN). The San Diego Clinical Site is a collaboration of three medical centers, (1) the University of California, San Diego (UCSD); (2) Kaiser Permanente, San Diego (Kaiser); and (3) the Naval Medical Center, San Diego (NMCSD). This same collaboration in the Urinary Incontinence Treatment Network (UITN) led all sites in patient recruitment for the Stress Incontinence Surgery Treatment Efficacy (UITN SISTEr) trial. The efficiency of the San Diego Clinical Site's efforts was recognized by the PFDN and we were asked to become a subcontract site for the University of Alabama for the Colpopexy and Reduction Efforts (CARE) study. In the brief 9 months available before the CARE study ended, San Diego (UCSD and Kaiser only) recruited 19 patients to CARE. This total was more than all but one center during those 9 months. We were the third UITN site to reach recruitment goals in the UITN's Behavior Enhances Drug Reduction Incontinence (BE-DRI) study. Additionally, in the UITN, our site has led efforts in the design, protocol development, and workgroup leadership for the UITN's current study, Trial Of Midurethral Slings (TOMUS). Urodynamic studies are commonly performed in the United States at an annual cost of approximately $400 million. These urodynamic studies are routine preoperative investigations in most centers that have urodynamic capability, yet we do not have evidence that these tests improve outcomes. Our concept proposal is a randomized trial of preoperative urodynamic studies in women with predominant stress urinary incontinence. The primary aim is to determine if preoperative urodynamic studies improve treatment success rates in all women considered candidates for

SUI surgery after an office evaluation. We believe that this proposed urodynamics study requires a multicenter randomized clinical trial and has significant relevance to the appropriate evaluation and care of women with pelvic floor disorders, namely, urinary incontinence. The proposed study also has potentially significant importance for national health care resource allocation and expenditures. The work that the San Diego investigators have done for the UITN in the past 5 years to develop standardized, quality urodynamic studies make them the ideal investigators to lead this effort. We believe that the PFDN will benefit greatly from the proven ability of the San Diego Clinical Site's demonstrated energy, skills, and leadership.

Title:	**The Cleveland Clinic Clinical Site**
P.I.:	**Matthew Barber**
Institution:	**Cleveland Clinic Lerner College of Medicine of Case Western Reserve University – Cleveland, OH**
Grant No.:	**5 U10 HD054215-02**
Award:	**$24,275**

Pelvic floor disorders (PFD)—including urinary incontinence, pelvic organ prolapse (POP), and fecal incontinence—affect a substantial proportion of women in the United States. PFD result in significant psychosocial costs to an individual, and their aggregate social and economic costs to society are enormous. Despite their substantial health impact, the quality of the evidence supporting most of the commonly used treatments, especially surgical interventions, is limited by the lack of standardization of diagnostic and therapeutic interventions, use of nonstandardized and nonvalidated outcome measures, poor-quality research designs, and inadequate power to detect clinically meaningful differences. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with PFD using the highest quality research methods available. The specific aims of this application are (1) To demonstrate that the Cleveland Clinic Foundation (CCF) possesses the personnel, patient, clinical, and administrative resources needed for successful participation as a Clinical Site in the PFDN and that our participation would be advantageous to the successful attainment of the Network's scientific goals and (2) To present a concept application for potential conduct by the PFDN. The broad, long-term objectives of our concept application are (1) to compare sacrospinous ligament fixation (SSLF) to uterosacral vaginal vault fixation (USWS) and (2) to assess the role of perioperative pelvic floor physiotherapy (PFPT) in women undergoing transvaginal surgery for apical or uterine POP. Our specific aims are to (1) Compare the anatomic outcomes of SSLF to USWS in women undergoing transvaginal surgery for Stage 2-4 POP involving the vaginal apex or uterus 3 years after surgery; (2) Compare functional, sexual, and health-related quality of life (HRQOL) outcomes of SSLF to USWS in the same women 3 years after surgery; (3) Assess whether short-term functional, sexual, and HRQOL outcomes improve in women receiving PFPT perioperatively compared to those who receive surgery alone; (4) Assess whether perioperative PFPT improves anatomic, functional, sexual, and HRQOL outcomes 3 years after surgery (long term) compared to surgery alone; and (5) Determine the incremental cost-effectiveness of perioperative PFPT at the time of transvaginal surgery for POP. We present a collaborative, multicentered randomized trial comparing SSLF to USSVS with or without perioperative PFPT using a 2x2 factorial study design. A standardized common protocol for enrollment, treatment, and data collection will be employed by six to eight Clinical Sites within the PFDN coordinated by the data coordinating center.

Title: Pelvic Floor Disorders Network
P.I.: Joseph I. Schaffer
Institution: University of Texas Southwestern Medical Center – Dallas, TX
Grant No.: 5 U10 HD054241-02
Award: $24,275

This application describes the qualifications and experience of the urogynecology and urology faculty and research teams at the University of Texas Southwestern Medical Center and Parkland Hospital and the facilities and patient population available to carry out clinical protocols sponsored by the Pelvic Floor Disorders Network (PFDN). In 2004, there were more than 2,100 women with pelvic floor disorders seen in our clinics and 617 women underwent surgical procedures for correction of pelvic floor disorders. The Departments of Obstetrics and Gynecology and Urology have increasingly collaborated since 1997 to offer comprehensive care of women with pelvic floor disorders. In addition to urogynecology and urology, collaboration includes faculty from colorectal surgery, radiology, physical therapy, and maternal–fetal medicine. The clinical research teams described in this application have successful prior as well as ongoing experience in NIH-sponsored national multicenter trials. Centerpieces in this application are two existing research clinics, one targeted at private patients (operated by the Urology Department) and the other focused on medically indigent patients (operated by the Obstetrics and Gynecology Department). Also included in this application is a concept application for a randomized trial designed to assess the efficacy of end-to-end versus overlapping repair of the external anal sphincter lacerated during childbirth. The primary outcome is anal incontinence, which is a significant consequence of such lacerations. This trial would permit accurate evaluation of the outcome of specific surgical procedures, which is one of the prime areas of interest leading to creation of the PFDN. We are of the view that along with strategies for prevention of anal sphincter laceration during childbirth, optimal management of the torn sphincter should also be studied because more than 200,000 women sustain such pelvic floor injuries each year in the United States.

Title: SGI Annual Meeting: Fostering a Multidisciplinary Approach to Research in Women
P.I.: Kelle H. Moley
Institution: Society for Gynecologic Investigation – Washington, DC
Grant No.: 2 U13 HD044185-04A1
Award: $5,000

Physicians and other health professionals face new challenges in obstetrics, gynecology, developmental biology, and reproductive biology and medicine. A multidisciplinary approach to translational research in women's health is needed to make significant advances in the subspecialties of gynecologic oncology, maternal–fetal medicine, and reproductive endocrinology, as well as reproductive and developmental biology. While the need for professionals devoted to women's health escalates, we are simultaneously confronted with a steadily growing shortage of academic physicians and scientists who work in the fields of translational reproductive biology and medicine. The shortfall is due both to fewer physicians and scientists entering these fields and to the attrition of trained researchers from earlier generations. As the preeminent national and international professional organization for clinicians and researchers involved in reproductive biology and medicine, the Society for Gynecologic Investigation (SGI) must play a major role in addressing these issues and providing a forum for the exchange of ideas, presentation of the best science, networking, and mentoring. The SGI is the only organization in this field that represents the breadth of clinicians and scientific investigators in all areas of women's health dedicated to translational reproductive medicine. This proposal sought funds to support future SGI Annual Scientific Meetings to fulfill, in cooperation with NICHD staff, the following Specific Aims: (1) To provide support to young investigators in all aspects of reproductive sciences and encourage them to attend the SGI Annual Scientific Meeting by educational, collegial, and meritorious incentives; and (2) To provide outstanding speakers at the annual

SGI meeting whose research exemplifies cutting-edge science in the collective fields of reproductive biology, genomics, and genetics, in an attempt to introduce trainees to the high quality of science conducted in these areas. The 54th Annual SGI Scientific Meeting, held in Reno, NV, in March 2007, was entitled "Multidisciplinary Approach to Translational Research in Reproduction, Development and Women's Health," and this theme prevailed throughout the 4-day meeting. The objective of this proposal was to continue support for the outstanding scientific content of the meeting and to attract young investigators to attend and join this unique society. Throughout the meeting, the contributions of trainees to research was emphasized; there was a plenary session at which the top-ranked trainee abstracts were presented and awards granted to authors of top-ranked abstracts. A new ad hoc trainee committee has been created by the SGI Council for supportive infrastructure for trainees within the SGI membership. The rationale for these efforts is that by presenting interdisciplinary research in women's health to young investigators in the community of the society, more trainees will be encouraged to pursue these areas and translational reproductive science will advance. The rationale for this proposal was to support the Annual Meeting of the SGI in order to present interdisciplinary research in women's health to young investigators as a means to attract more young physician-scientists to these biomedical research areas. The SGI is the premiere organization in this field and is the only one that represents the breadth of clinicians and scientific investigators in all areas of women's health dedicated to translational reproductive medicine. Our goal is to make a significant impact on the training of young investigators in order to advance reproductive science.

Title: **Cooperative Center for Research in Reproduction**
P.I.: **Bogdan J. Nowicki**
Institution: **Meharry Medical College – Nashville, TN**
Grant No.: **5 U54 HD 044315-05**
Award: **$194,000**

The collaborative partnership of Pennsylvania State University (PSU) and Meharry Medical College (MMC) proposes the development of a Cooperative Center for Research in Reproduction at MMC. The proposal addresses two goals. First, the Center will conduct scientifically sound, clinically relevant research in a thematically focused area of gynecologic endocrinology. Specifically, the research development core will study (1) the role of sex steroid hormones as determinants of bone mineral density score in Black 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 hyperandrogenemia and its associated symptomatology. These studies will generate knowledge and comparisons across race. Secondly, the compelling need to strengthen research infrastructure at a historically Black medical school through development of minority-initiated research proposals, collaboration, and mentorship with a research-intensive institutional network of experienced investigators, toward the eventual capacity to build an independent clinical research team at MMC will be facilitated. Additionally, core research support resources will be enhanced at MMC.

Appendix C

ORWH-Cofunded Research Summaries, FY 2008

Aging

Title: National Social Life, Health, and Aging Project
P.I.: Linda J. White
Institution: National Opinion Research Center – Chicago, IL
Grant No.: 1 R37 AG030481-01A1
Award: $400,000

The National Social Life, Health, and Aging Project (NSHAP) was established as an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally representative sample of 3,005 community-dwelling adults aged 57–85 in 2005–06. The second wave in NSHAP is designed to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal dataset will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. We propose to revisit respondents 4 years after their initial interview. Using these data, we can describe and model the distribution of changes in health, well-being, social networks, social participation, and social context. In each case, we shall examine the distributions both for the entire sample and within subgroups defined by key sociodemographic characteristics such as gender, race/ethnicity, and socioeconomic status. We also propose to augment the sample by interviewing the spouse/cohabitating romantic partner. These data will allow us to characterize the impact of marital and romantic relationships on health by examining the effects of one person's characteristics and behaviors on the health of the other. We will also analyze the partnerships themselves and assess the relationship between characteristics of the partnership, such as support, closeness, and mistreatment, and the health of each of the partners. In sum, we will explore our overarching hypothesis that older adults with strong, functioning intimate relationships will show more positive (or less negative) health trajectories than those who have weaker relationships or lack such relationships altogether. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age.

Title: Phytoestrogens and Aging: Dose, Timing, and Tissue
P.I.: William G. Helferich
Institution: University of Illnois, Urbana-Champaign – Champaign, IL
Grant No.: 5 P01 AG024387-05
Award: $92,922

The overall research objective of this project 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 research focus is on dosage, timing, and duration of exposure and the de-

terminants of the biological outcome of phytoestrogen exposure in different target tissues. Because 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. These 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's effects on these different target tissues. In summary, the overall goal is to conduct highly interactive investigations of the effects of phytoestrogen dietary exposure using well-established animal models, each having specific advantages for the study of breast cancer progression to hormone independence, obesity and risk of diabetes, and cognitive function. This goal will be achieved through four complementary, synergistic projects: (1) Genistein and Endocrine Resistance in Breast Tumors, (2) Dietary Phytoestrogens and Adipocyte Development, (3) Dietary Estrogens and Cognitive Function During Aging, and (4) Phytoestrogen Action Through Estrogen Receptors Alpha and Beta. An Analytical and Bioavailability Core will provide analysis and standardization of blood and tissue isoflavone levels for Projects 1–3, and a Dietary, Genomics and Chemistry Synthesis Core that will provide uniform diets, gene expression profiling analysis by microarray and quantitative PCR methods, and chemical synthesis of phytoestrogens and phytoestrogen metabolites.

Title: **End-of-Life Quality of Care in Nursing Homes**
P.I.: **Helena Temkin-Greener**
Institution: **University of Rochester – Rochester, NY**
Grant No.: **1 R01 NR010727-01A1**
Award: **$120,000**

Nursing homes are increasingly the place of care and death for older persons. However, the quality of care provided to nursing home residents at the end of life (EOL) has been reported to be inadequate. Comparative empirical evidence on the quality of EOL care in U.S. nursing homes is lacking and there are currently no risk-adjusted measures of EOL quality of care in nursing homes. The objective of the proposed study is to develop and validate individual indicators and a composite measure for assessing EOL quality of care in nursing homes and to identify characteristics of facilities associated with superior EOL quality of care. The specific aims of this project are to (1) Develop and validate individual and composite EOL indicators of quality; (2) Examine cross-sectional and longitudinal variations in individual indicators and in the composite quality measure, for example, across States, facility ownership type, etc.; and (3) Identify EOL practice patterns and characteristics of nursing homes that are associated with better individual and composite quality measures. The measures developed in the course of this study could provide a prototype for EOL quality measures to be incorporated into publicly disseminated report cards, such as the Medicare Nursing Home Compare. Empirical insights gained from this project may be used to test and implement strategies for improving the quality of EOL care in nursing homes. This project will improve public health by developing a prototype for EOL quality measures that could be incorporated into publicly disseminated report cards, such as the Nursing Home Compare. Lessons learned from this project may be used to implement and test strategies for improving the quality of EOL care in nursing homes.

Title: **Neuromuscular Fatigue in Older Adults**
P.I.: **Sandra K. Hunter**
Institution: **Marquette University – Milwaukee, WI**
Grant No.: **1 R15 AG030730-01A1**
Award: **$223,500**

This project examines the cause of age-associated neuromuscular fatigue in tasks that are more functionally relevant to daily activities and that are important for maintenance of independence in older adults, within an aging American population. This project brings a new and innovative approach to understanding fatigability of the neuromuscular system in older adults by examining functionally relevant tasks that require control of a load with limited limb support and maintenance of power

for a dynamic task. Recent studies indicate that older adults experience greater muscle fatigue than young adults during these more functionally relevant tasks. However, the causes of the increase in age-related muscle fatigue in older adults during submaximal dynamic and postural contractions with limited limb support are not understood. Based on preliminary data, we hypothesize that neural mechanisms are responsible for greater fatigue exhibited by older adults compared with young adults for submaximal fatiguing contractions that require supporting an inertial load. First, we examine the mechanisms for age-related changes in muscle fatigue of dynamic and postural tasks that involve supporting an inertial load. Specifically, we will compare the time to task failure between young and older adults for a postural isometric and dynamic task and establish the association between the age-related fatigue and functional ability in old adults. We will also determine neural mechanisms that contribute to time to task failure for these tasks in young and old adults. To accomplish this, we will use transcranial magnetic stimulation to examine cortico-spinal excitability before, during, and after fatigue and this will be quantified as the size of the motor-evoked potential normalized to the changes in neuromuscular propagation (M wave). By understanding the magnitude and mechanisms that contribute to age-related fatigue during functionally relevant tasks, we can identify appropriate and simple rehabilitative techniques to improve the increased fatigue experienced by older adults. Our preliminary data suggests that "practice" of a fatiguing task will improve performance via neural adaptations. Therefore, we will determine the change in time-to-task failure and cortico-spinal excitability with practice of a postural isometric and dynamic task performed by young and older adults. This project will evaluate the efficacy of "practice" as a rehabilitative technique, to ameliorate neuromuscular function deficits and minimize impairments in old adults, and also to provide evidence of age-related neural impairments in performance.

Adolescent Health

Title: The National Longitudinal Study of Adolescent Health (Add Health)
P.I.: Kathleen Mullan Harris
Institution: University of North Carolina, Chapel Hill – Chapel Hill, NC
Grant No.: 5 P01 HD031921-13
Award: $390,316

Add Health is currently funded for Wave IV data collection. At the time the project began, in 1994–1995, investigators selected a nationally representative sample of adolescents in grades 7 through 12. Participants have been followed through adolescence and the transition to adulthood with three in-home interviews. Wave IV 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.

Alcohol and Other Substance Abuse

Title: Effects of Alcohol on Gene Expression and Epigenetics of Progeny
P.I.: Carrie L. Marin
Institution: Jackson Laboratory – Bar Harbor, ME
Grant No.: 1 R21 AA017244-01
Award: $125,000

Alcoholism and alcohol-related illness affect multitudes of American families with a significant financial impact on annual medical and caregiver costs. Furthermore, it is recognized and publicized that chronic alcohol consumption during gestation produces a variety of adverse pregnancy outcomes and birth defects. Yet, the influence of acute alcohol consumption near the time of conception is relatively unknown. Around this early developmental stage, the epigenetic marks, which govern gene expression, are initially established along the genome for all mammals, from mice to humans. Consequently, the oocyte-to-embryo transition is a critical period of development because

the totipotent embryo gives rise to the entire individual and any "epigenetic misprints" occurring during this stage are inherited throughout the body. The purpose is to study the effect of ethanol exposure on the alterations of gene expression and epigenetic mechanisms in oocytes and pre-implantation embryos in a mouse model. This novel research project could identify and characterize the epigenetic mechanisms of ethanol-induced changes in genetic profiles during early maternal and embryonic environments that may predispose individuals to metabolic diseases during adulthood (e.g., obesity).

Title: **Sex Differences in Vulnerability to Cocaine Addiction**
P.I.: **Therese A. Kosten**
Institution: **Baylor College of Medicine – Houston, TX**
Grant No.: **1 R21 DA020117-01A2**
Award: **$230,250**

Understanding sex differences in the initiation of addiction is an important goal that needs to be addressed. The study proposes a novel yet hypothesis-based approach to examine sex differences in stress responsivity and addiction using established animal procedures. Stress responsivity relates to acquisition of cocaine self-administration, an animal model of vulnerability to addiction. Stress responsivity shows sex differences, but reports on self-administration are conflicting. Links between maternal care and stress responsivity of offspring are proposed; greater care relates to lower stress responsivity of adults. Maternal care differs by pup sex; male pups receive more care than female pups. Adult males show lower stress responsivity than females, consistent with the link of maternal care with stress responsivity. The proposal hypothesizes that sex-dependent maternal care influences sex differences in stress responsivity and cocaine self-administration in the adult. The investigators will test this by manipulating maternal care by altering litter gender composition (LGC; single- vs. mixed-sex litters) because pups of single-sex litters receive more care than pups of mixed-sex litters. LGC influences stress responsivity in infant mice and juvenile and maternal behaviors in rats and mice. They predict that both male and female adult rats of single-sex litters will show lower stress responsivity than offspring of mixed-sex litters.

Title: **Women and Smoking: Understanding Socieconomic Influences**
P.I.: **Stephen T. Higgins**
Institution: **University of Vermont and State Agricultural College – Burlington, VT**
Grant No.: **1 R13 DA024956-01**
Award: **$5,000**

Health disparities among disadvantaged women are a concern shared throughout the NIH, including NIDA, NCI, and the ORWH. Over 170,000 deaths per year among women in the United States are attributable to smoking-related causes. The proportion of those women who are socioeconomically disadvantaged is growing, and these women, on average, are least likely to respond to prevention and treatment interventions. Greater scientific understanding of the important social, behavioral, pharmacological, and biological controlling variables involved in this problem are needed if more effective interventions and policies are to be developed. Researchers from a number of different disciplines are studying the problem, but interdisciplinary efforts are lacking. This conference has the potential to enhance recognition of the urgency of the problem; embed the problem in a broader context with regard to other types of substance abuse, as well as other non-substance-related public health problems; and perhaps, most importantly, foster interdisciplinary research efforts. For example, how the strong socioeconomic influences on smoking are to be reconciled with the strong heritability estimates coming out of genetics studies on smoking is unclear, and investigators from the relevant disciplines need to be discussing those challenges. As another example, sociological and epidemiological research documents an important potential moderating effect of education on the risk of smoking, but says little about how education would produce those effects. Research being conducted on executive function and risky choice among smokers by behavioral neuroscientists has

the potential to advance understanding in that area. There are many other examples where research on this general problem could be advanced through interdisciplinary efforts. By inviting leaders from these different disciplines to participate in a single-track conference where they will listen to each other's presentations and have ample opportunity to ask each other questions has the potential to significantly improve that situation. By publishing the proceedings in a peer-reviewed journal, that opportunity is enhanced even further because now interested professionals who did and did not attend the conference have the opportunity to examine each other's work in careful detail.

Cancer

Title: **Pharmacogenomics Research Network and Knowledge Base**
P.I.: **David Alastair Flockhart**
Institution: **Indiana University–Purdue University at Indianapolis – Indianapolis, IN**
Grant No.: **5 U01 GM061373-09**
Award: **$230,171**

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 will 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's effects. This 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 Aims 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; and (5) To test the hypothesis that variants in candidate genes identified in Specific 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 that are key to optimizing drug selection for women with breast cancer and to our understanding of the mechanisms of estrogen action.

Title: **Novel Ovarian Cancer Detection Agents from Phage Display**
P.I.: **Susan L. Deutscher**
Institution: **University of Missouri – Columbia, MO**
Grant No.: **1 R21 CA134960-01**
Award: **$184,400**

Ovarian adenocarcinomas are the largest class of gynecologic malignancies in the United States with respect to incidence and mortality. While treatable in their earliest stage, advanced or metastatic forms of ovarian cancer are usually deadly. Because ovarian cancer is often asymptomatic in its early stages, approximately 70% of patients have advanced or metastatic disease at the time of diagnosis. Current screening methods include ultrasonography, pelvic exam, and serum screening for CA125. Unfortunately, these tests are not specific for ovarian cancer and invasive surgical biopsy is required for proper diagnosis. Improved early diagnosis and therapy will result from a more directed approach in which antigens specific to or overexpressed on ovarian tumor cells are targeted. New

peptide-based molecular probes to facilitate cancer detection and imaging are rapidly evolving due to implementation of bacteriophage (phage) display approaches. Here, it is hypothesized that phage selected in vivo, in human ovarian tumor-bearing mice, once fluorescently labeled, can be easily rescreened in vivo for tumor-homing propensity, thus streamlining the process of development of peptide-based ovarian cancer imaging and therapeutic agents. Radiolabeled versions of the identified peptides will be examined for their ability to image ovarian tumors in mice using single photon emission computed tomography (SPECT). A long-term goal of this work is to translate the radiolabeled peptides into the clinic for the noninvasive screening and detection of ovarian cancer. Specifically, the study proposes to obtain new classes of ovarian-cancer-targeting peptides by performing in vivo phage display selections in human ovarian-carcinoma-bearing mice. Second, phage selected from the screens will be fluorescently labeled and employed in in vivo optical imaging screens to expedite discovery of new ovarian tumor imaging agents. Lastly, peptides corresponding to phage with optimal in vivo imaging properties will be synthesized and radiolabeled with 111In and 99mTc and examined for their SPECT imaging efficacy in vivo. Novel phage display and peptide radiochemistry approaches are described to advance the detection of ovarian cancer, a cancer that deserves much more research and attention.

Title: **Understanding Decisionmaking in Breast Cancer Reconstruction**
P.I.: **Amy K. Alderman**
Institution: **University of Michigan at Ann Arbor – Ann Arbor, MI**
Grant No.: **1 R21 CA122467-01A2**
Award: **$125,000**

This study addresses important quality-of-life and health services delivery issues for breast cancer patients of all ages. It has the potential to inform breast cancer health policy and clinical practice. The multidisciplinary investigative team includes researchers from the fields of behavioral science, internal medicine, plastic surgery, epidemiology, and health services research. Breast reconstruction after mastectomy is an important treatment for women with breast cancer. However, there is virtually no information about whether there is an unmet need for reconstructive surgery after the initial treatment period. The goal of this study is to examine the decisionmaking process of breast cancer reconstruction after the initial diagnosis and treatment period. The results of this exploratory study will improve informed decisionmaking regarding breast cancer reconstruction by evaluating barriers to and unmet need for treatment. A population-based cohort of 500 women in Los Angeles who underwent a mastectomy in 2005–06 will be surveyed to determine clinical, demographic, and psychosocial correlates of immediate, delayed, and no reconstruction. Decisional satisfaction and health-related quality of life will be evaluated in women who did and did not receive reconstruction. It is anticipated that the study sample will comprise 45% Hispanic, 25% African-American, and 30% Caucasian women.

Title: **Participatory Research To Understand the Translation of HPV Vaccine Policy**
P.I.: **Andrew Louis Sussman**
Institution: **University of New Mexico, Albuquerque – Albuquerque, NM**
Grant No.: **1 R21 CA134259-01**
Award: **$125,000**

This project will study the process of implementing policy regarding the HPV vaccine in the State of New Mexico and related programmatic efforts to offer the vaccine and relevant education to parents and the public. The goal is to interpret the data and develop and disseminate health policy recommendations regarding initiatives to support HPV vaccine dissemination and informed decisionmaking, leading to the reduction of cervical cancer health disparities in New Mexico. The recent approval of the HPV vaccine is an important scientific advance, but faces challenges in dissemination and implementation. This study will help to develop a better understanding of the factors that contribute to the development of HPV vaccine policy. These findings will be used to work toward the creation of

strategies, both at the primary care and health policy levels, to promote informed decisions among patients with regard to the HPV vaccine that are consistent with community.

Title: **Caregivers' Strengths–Skills: Managing Older Cancer Patients**
P.I.: **Victoria H. Raveis**
Institution: **Columbia University Health Sciences – New York, NY**
Grant No.: **5 R01 CA115315-04**
Award: **$46,488**

This project will implement and evaluate the efficacy of a short-term problem-solving skills training program for familial caregivers to lower income older (60+ years) posttreatment 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 experience during the cancer survivorship period. By focusing attention on families' potential role in palliative care efforts during the posttreatment 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 10 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 posttreatment 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, and perceptions of and satisfaction with care (patient outcomes) and b) Change in caregivers' depressive symptomology, anxiety, quality of life, and perceptions of and satisfaction with patient care (caregiver outcomes); and (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.

Title: **Dietary Lignan Effects on Hormone, Growth, and Signaling Factors in Breast Tumors**
P.I.: **Susan E. McCann**
Institution: **Roswell Park Cancer Institute – Buffalo, NY**
Grant No.: **1 R03 CA128035-01A1**
Award: **$125,000**

Several epidemiologic studies have shown reduced breast cancer risks associated with higher exposure to dietary lignans. Recent studies also have shown reduced risks of estrogen receptor (ER) negative breast cancer in women with high versus low dietary intakes, suggesting that the protective effects might be more effective in certain subtypes of cancer. ER status, as well as a number of other tumor characteristics, has been associated with breast cancer prognosis. Although experimental evidence supports the potential for dietary lignans to favorably affect many of these tumor markers, much of the laboratory work has used pharmacologic doses of lignans from flaxseed. Besides the limited data regarding lignan intakes and ER status, an examination of the effect of commonly consumed ranges of dietary lignan intakes on other prognostic and predictive tumor characteristics has not been conducted. Lignans constitute the largest contribution to phytoestrogen intakes among Western populations, where soy intake is generally low and intakes can range widely, depending upon which foods are consumed. The wide range of possible intakes is important as experimental

evidence suggests that phytoestrogen actions often are concentration dependent, and it is unclear whether amounts consumed via diet produce the same effects as pharmacologic doses available as dietary supplements. The proposed study will investigate the association of dietary lignan intakes, as amounts commonly consumed in usual diets, with several hormone- and growth-related tumor characteristics, many of which are related to breast cancer prognosis. The results of this study may provide us with important information that can be useful in understanding the effect of diet on the development of different breast cancer subtypes.

Title: **Human Papillomavirus (HPV) Types 16/18 Phase III Vaccine Clinical Trial in Costa Rica**
P.I.: **Allan Hildesheim**
Institution: **NCI Intramural Program – Bethesda, MD**
Grant No.: **Z01 CP010177**
Award: **$600,000**

Following successful completion of recruitment, blind randomization, and vaccination of 7,466 women in our trial, participants have been actively followed for adverse events and for the development of HPV infections and cervical lesions with annual or semiannual clinic visits. The initial plan was to actively follow participants for a period of 4 years to allow for the evaluation of short-term vaccine safety and efficacy. Followup of participants to date has been very successful, with a study discontinuation rate of about 5%. Over 85% of participants have completed a study visit at least once annually. In addition to routine followup screening visits, women with evidence of persistent low-grade cervical lesions or incident high-grade cervical precancer lesions have been referred to colposcopy for evaluation and treatment. Beginning in mid-2008, women will reach their 4-year anniversary in the study and will be invited to their final clinical evaluation. Completion of this initial 4 years of followup will ensue over the coming 1.5–2 years and will provide the complete data required for evaluation of short-term vaccine safety and efficacy in our population. While the NCI remains masked to arm randomization at this time, analyses of data for outcomes other than the primary efficacy outcome have been initiated, whenever approved by the external scientific working group and data and safety monitoring board that oversee the trial. Of particular note is the analysis conducted to evaluate any possible therapeutic effect of the HPV-16/18 vaccine on prevalent infections. Results from this analysis, published last year in the *Journal of the American Medical Association*, indicate that the vaccine does not affect rates of clearance of already established infections. As discussed in the past, this is an important finding that has helped clarify whether women with established infections and/or cytological abnormalities should be offered vaccination as treatment for their conditions.

Title: **Immunogenicity of Quadrivalent Human Papillomavirus Vaccine (HPV Types 6, 11, 16, and 18) in Recipients of Reduced Intensity Hematologic Stem Cell Transplantation (HSCT)**
P.I.: **A. Chenoy, P. Stratton, L. Pinto, and L. Wood**
Institution: **National Heart, Lung, and Blood Institute and National Cancer Institute – Bethesda, MD**
Award: **$200,000**

This project investigates the use of the recently licensed quadrivalent human papillomavirus (HPV) vaccine against HPV types 6, 11, 16, and 18 in females aged 12 years or older undergoing allogeneic, hematopoietic stem cell transplantation (HSCT) as an approach to reduce posttransplant HPV-related comorbidity, anogenital dysplasia, and malignancy. This population is at excess risk for HPV-related anogenital dysplasia and malignancy following transplantation and stands to benefit greatly from prophylactic HPV vaccination. In addition to determining whether the quadrivalent vaccine is immunogenic in the posttransplant population, this investigation will also determine, in a subset of patients, whether there are differences in HPV vaccine immunogenicity in individuals with identi-

cal T-cell immunity that have nonidentical host cell backgrounds, that is, HSCT donors (male or female) and their respective/paired female transplant recipients.

Cardiovascular Disease

Title: Cardiovascular Events in Women's Ischemia Syndrome Evaluation
P.I.: Sheryl F. Kelsey
Institution: University of Pittsburgh – Pittsburgh, PA
Grant No.: 1 R03 AG032631-01
Award: $75,357

Much attention has been focused on the differences between men and women presenting with heart attacks and angina pain. The Women's Ischemia Syndrome Evaluation (WISE) study has been a successful and productive four-center prospective study of women clinically referred for coronary angiography for evaluation of symptoms suggestive of ischemia. The goals of WISE were to improve diagnostic testing for ischemic heart disease and to explore female-specific ischemic heart disease pathophysiology. A National Death Index (NDI) search will be used to extend mortality followup for WISE women to an average of 8 years (maximum 10). Experienced site coordinators will prepare materials to submit to NDI and send results to the coordinating center, where updated mortality data will be added to the WISE database. Using the existing database, coronary risk factors, hormonal status, psychosocial factors, genetic factors, and results of diagnostic tests will be evaluated as predictors of long-term mortality. Initiated in September 1996, recruitment of 936 women was completed in a timely manner by March 2000. Support was awarded for an additional 5 years of followup, and the database was closed in March 2006. A rich longitudinal database on these women is thus available. Patient names reside at the clinical sites, but to maintain confidentiality, are not included in the WISE database at the coordinating center. Extension of cardiovascular mortality data will more clearly define prognostic factors for long-term mortality in women with ischemia with and without obstructive disease. With an additional targeted analysis, development of a simple, reproducible, angiographic technique to identify microvascular dysfunction, by correlating TIMI frame count with Doppler-wire-determined coronary flow reserve measured in response to adenosine in WISE women with suspected ischemia but no significant coronary artery disease, is possible. Availability of a simple diagnostic technique allows clinicians to target these women for aggressive medical therapy aimed at early coronary artery disease and improved prognosis.

Chronic Fatigue Syndrome

Title: HERV-K18 as a Risk Factor for CFIDS
P.I.: Brigitte T. Huber
Institution: Tufts University – Boston, MA
Grant No.: 5 R01 AR053821-02
Award: $160,777

The etiology of chronic fatigue syndrome (CFS) is far from understood and is likely due to multiple genetic components. Infection with EBV and treatment with IFN-a have been implicated in the pathogenesis. Our laboratory has shown that EBV infection, and exogenous IFN-a activate transcription of the env gene of a human endogenous retrovirus, HERV-K18. This provirus is normally silent but, when induced, it encodes a superantigen (SAg), which is a class of proteins that is capable of deregulating the immune system. Three alleles of HERV-K18 env have been documented, K18.1, K18.2, and K18.3, whose gene products have SAg activity, but are predicted to differ biochemically and functionally. Our working hypothesis is that HERV-K18 is a risk factor for CFS. In a pilot study, the allele and genotype distributions of the HERV-K18 env gene were compared between various groups of CFS patients and healthy controls. Although only a limited number of samples were available in the various cohorts, the odds ratios that were obtained were statistically significant. The most

intriguing interpretation of these data is that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the coinvestigator, Dr. Renee Taylor. Dr. Ben Katz, board certified in both pediatrics and pediatric infectious diseases, will clinically evaluate the patient cohort, and Dr. Inga Peter, a genetic epidemiologist and biostatistician, will oversee the statistical analyses. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T-cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during the course of the disease, will be tested ex vivo using a T-cell hybridoma reporter assay that has been developed in our lab. Since SAg-activated T-cells produce massive quantities of chemokines, lymphokines, and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of this chronic disease. CFS is a disease that affects a significant number of people worldwide, yet the underlying mechanism(s) of pathogenesis remains unclear. The herpesvirus EBV and IFN-a have been suggested to be associated with CFS, although these concepts are far from accepted. We propose a novel genetic aspect in the EBV/CFS association, namely, the presence of certain HERV-K18 alleles that differ in their superantigen activity.

Title: **Autonomic Nervous System in Chronic Fatigue Syndrome**
P.I.: **Italo Biaggioni**
Institution: **Vanderbilt University – Nashville, TN**
Grant No.: **5 R01 NS055670-03**
Award: **$365,169**

The overall goal of this application is to determine the role of the autonomic nervous system in the abnormalities associated with chronic fatigue syndrome (CFS). We propose to test the hypothesis that the sympathetic nervous system contributes to the cardiovascular and inflammatory abnormalities present in the CFS and, in particular, in the subset of patients characterized by postural tachycardia (POTS). CFS and POTS are seen mostly in otherwise normal young women and are the cause of significant disability. Our preliminary analysis indicates a decrease in plasma volume in patients with POTS, which can contribute to, and be the consequence of, sympathetic activation. Our preliminary studies also indicate an interaction between the sympathetic nervous system and nitric oxide mechanisms; this may also create a negative feedback mechanism whereby a decrease in nitric oxide results in sympathetic activation and increased sympathetic activity results in impaired nitric oxide mechanisms. We have developed a paradigm that will allow us to define selectively the contribution of endothelial nitric oxide to blood pressure regulation and will apply this approach to patients with CFS and POTS. In addition, our preliminary studies indicate that sympathetic activity is associated with inflammatory processes. In particular, C-reactive proteins are increased in patients with POTS and, conversely, decreased in patients with low sympathetic tone due to pure autonomic unsuccessful undertaking. We propose to measure validated indices of sympathetic activity, inflammation, and oxidative stress in patients with CFS and POTS and compare them to appropriate control groups, including patients with CFS without POTS, POTS without CFS, and normal controls. If our hypothesis is correct and sympathetic activity contributes to the pathophysiology of CFS, then chronic inhibition of sympathetic tone will result in improvement of symptoms, cardiovascular alterations, volume defects, and inflammatory abnormalities present in CFS.

Title: Cognitive Behavioral Stress Management for Chronic Fatigue Syndrome
P.I.: Michael Howard Antoni
Institution: University of Miami – Coral Gables, FL
Grant No.: 5 R01 NS055672-03
Award: $327,582

This is a 4-year study that uses a 10-week, telephone-based, cognitive behavioral stress management intervention (T-CBSM) to illuminate neuroimmune mechanisms underlying the effects of stress and stress management on physical health status and immune regulation in individuals with chronic fatigue syndrome (CFS) relative to participants receiving a health promotion telephone (T-HP) intervention. CFS is characterized by physical symptoms that bring about severe limitations in lifestyle behaviors and vocational activities. Associated symptoms include debilitating fatigue, low-grade fever, lymph node pain and tenderness, cognitive difficulties, and mood changes. There is growing evidence that CFS patients may also show abnormalities in HPA axis functioning and on several indices of immune functioning. Chronic stress is also associated with a flattened diurnal secretion pattern for cortisol. An inability to maintain regulation in the HPA axis may contribute to the pathophysiology of CFS via diminished control of proinflammatory cytokines and associated physical symptoms related to chronic immune activation and inflammation. Given the debilitating nature of CFS, we propose to deliver the T-CBSM intervention through a telecommunications system (i.e., Telecare) designed to enhance access to formal and informal care for a population that may have difficulty accessing traditional psychotherapeutic settings. In our prior work with individuals with CFS, we have shown that individuals in a structured group CBSM intervention report significantly improved quality of life, perceived stress, fatigue, memory, muscle pain, and postexertional malaise compared to individuals in the control condition. The Telecare system has been successful in delivering a supportive intervention for older caregivers of dementia patients. This study is novel in expanding our prior work to individuals with CFS who have reported difficulty participating in structured groups due to physical burden. The study design is a 2 X 3 randomized experimental design with group (T-CBSM, n=60 vs. T-HP, n=60) as the between-group factor, and time (preintervention, postintervention, and 6-month followup) as the within-group factor. Our primary objective is to evaluate the extent to which a T-CBSM intervention aimed at building skills in anxiety reduction, distress tolerance, stressor appraisals, and adaptive coping strategies may improve physical health status and immune regulation in CFS by modulating neuroimmune interactions.

Craniofacial

Title: Hormonal Cycles in Women: Effects on TMD Pain and Symptoms
P.I.: Linda A. Leresche
Institution: University of Washington – Seattle, WA
Grant No.: 5 R01 DE016212-05
Award: $139,383

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Thus, pain is, inevitably, a product of the interaction of mind and body. This project will study the interactions of mind and body related to temporomandibular disorders (TMDs), 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. Specifically, normally cycling women with TMD experience rising levels of TMD pain premenstrually during a time of precipitous drop in estrogen and show peak TMD pain during menses. Interestingly, a secondary peak of TMD pain occurs at about the time of ovulation, another phase corresponding to rapid estrogen change. These data demonstrate a system-

atic relationship between levels of TMD pain and phases of the menstrual cycle. We propose two related studies to further 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 (n = 35), as well as appropriate comparison groups of the same size—normally cycling women with episodic headache and normally cycling control women without TMD, headache, or other chronic pain problems. Study 1 is designed to test the hypothesis that increases in clinical pain and symptoms across the menstrual cycle are associated with estrogen withdrawal and increased perceived stress. 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. Thus, the proposed studies will provide important and unique information on the relationships of biological and psychosocial aspects of pain perception in women.

Title: **Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?**
P.I.: **Allen W. Cowley**
Institution: **TMJ Association, Ltd. – Brookfield, WI**
Grant No.: **1 R13 DE019079-01**
Award: **$5,000**

The fifth scientific meeting of The TMJ Association, Can Studies of Co-morbidities with TMJDs Reveal Common Mechanisms of Disease?, was held in 2008. The need for this meeting and that of previous meetings has been based on two important factors. First, the number of people affected by temporomandibular joint and muscle disorders (TMJDs) is estimated to be more than 10 million in the United States. Ninety percent are women in their childbearing years. The physical, psychological, and financial burdens on these patients are compelling. Second, there continues to be a dearth of scientific understanding of the etiology of these conditions upon which to base diagnoses and develop safe and effective treatments. To stimulate research in this field, The TMJ Association has organized biennial scientific meetings beginning in the year 2000. These meetings have convened experts in TMJDs and other fields to characterize and address the multiple symptoms and comorbid conditions found in TMJD patients. The theme of the fifth scientific meeting builds upon evidence from the four previous meetings, showing that TMJDs are a complex family of conditions influenced by genetics, gender, and environmental and behavioral triggers mediating the vulnerability of patients to TMJDs and manifesting as more than jaw and muscle pain and jaw dysfunction. The 2008 proposed meeting will bring together clinical and basic scientists who have made advances in the diagnosis and treatment of TMJDs with scientists knowledgeable about other chronic pain conditions, such as chronic headache, generalized pain conditions, irritable bowel syndrome, fibromyalgia, low back pain, chronic fatigue syndrome, and rheumatoid arthritis, with which TMJD patients frequently share common symptoms. The Specific Aims of the proposed meeting are to (1) Identify similarities across these diseases, perhaps finding common pathways that could elucidate the underlying pathophysiology of TMJDs and point to novel targets for diagnosis and treatment; (2) Promote and engage new and young investigators in TMJD research; and (3) Develop recommendations for research initiatives in TMJDs that would synergize the work of scientists at multiple Institutes and Centers of the National Institutes of Health and that of academic health centers. Project Narrative: The variety of current treatments for TMJDs lacks a coherent body of scientific knowledge. It is imperative that the underlying pathophysiological processes that drive these conditions be understood in order to provide accurate and predictable diagnostics and safe and effective therapies. This scientific meeting brings clinical and basic scientists together with patients to consider common underlying mecha-

nisms that may be responsible for TMJDs and other shared comorbidities, as are seen in chronic headache, generalized pain conditions, irritable bowel syndrome, fibromyalgia, low back pain, chronic fatigue syndrome, and rheumatoid arthritis. A major goal of this meeting is to identify common therapeutic targets related to shared comorbidities.

Diabetes

Title: Post-DPP Followup Study
P.I.: Sarah E. Fowler
Institution: George Washington University – Washington, DC
Grant No.: 5 U01 DK048489-15
Award: $484,454

The Diabetes Prevention Program (DPP) is a multicenter, controlled clinical trial examining the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome, while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of approximately 3 years (range 2 to 5) with a total of approximately 10,000 patient-years in the 3,234 volunteers in the three-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the lifestyle intervention and metformin-treated groups (58% and 31% reductions, respectively) compared with the placebo-treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May 2001, 1 year earlier than originally planned. This application is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the subcohort that has developed diabetes (n of approximately 700) has been followed from nearly the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific Aims include (1) Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes, including diabetes, clinical cardiovascular disease, atherosclerosis, cardiovascular disease (CVD) risk factors, quality of life, and cost–benefit; (2) Determine the clinical course of new-onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; (3) Determine the incidence of CVD, CVD risk factors, and atherosclerosis in new-onset type 2 diabetes and IGT; and (4) Examine topics 1–3 in minority populations, men vs. women, and older subjects in the DPP.

Title: Look AHEAD: Action for Health in Diabetes
P.I.: Mark Andrew Espeland
Institution: Wake Forest University Health Sciences – Winston-Salem, NC
Grant No.: 5 U01 DK057136-10
Award: $94,818

Look AHEAD is randomized clinical trial examining the long-term health effects of an intensive weight-loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and nonfatal MI, stroke, and cardiovascular deaths) over a planned followup of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an

additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well—the sample of 5,145 was recruited on time, retention has been excellent, and the intervention has been effective in producing initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific aims are to retain the cohort over time, continue to complete annual in-person visits and semiannual telephone interviews for outcome assessments, and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular-related factors and complications and on the cost-effectiveness of the intervention.

Dietary Supplements/CAM

Title: **Botanical Dietary Supplements for Women's Health**
P.I.: **Norman R. Farnsworth**
Institution: **University of Illinois – Chicago, IL**
Grant No.: **5 P50 AT000155-09**
Award: **$95,158**

The UIC/NIH Center for Botanical Dietary Supplements Research was established in the fall of 1999 to address the issues of standardization, quality, safety, and efficacy of botanical dietary supplements. The Center then adopted and will continue to implement a multidisciplinary strategy to achieve its basic and clinical research objectives. Participating faculty coinvestigators and collaborators are drawn from the Departments of Medicinal Chemistry and Pharmacognosy and Biopharmaceutical Sciences in the College of Pharmacy; the Department of Medicine (Section of Endocrinology and Metabolism) in the College of Medicine; and the Department of Math, Statistics, and Computer Science in the College of Liberal Arts. The Center studies botanicals with potential benefits for women's health, focusing on plants that are reported to alleviate the symptoms of menopause and premenstrual syndrome. Botanical extracts are subjected to rigorous chemical evaluation followed by both in vitro and in vivo biological testing. Standardized botanical extracts that appear efficacious and demonstrate adequate safety profiles in in vitro and animal models will be candidates for clinical Phase I trials. Hops (Humulus lupulus L.) will undergo Phase I evaluation in this grant cycle. In order to achieve this comprehensive agenda for the development of chemically and biologically standardized botanical dietary supplements, the renewed BRC research program will be organized as follows: Standardization of Botanicals; Mechanism of Action of Botanicals (Menopause); and Studies of Metabolism, Bioavailability, and Toxicity. Two additional programs will be undertaken, a Pilot Project Program and a Training and Career Development Program. The experiments proposed in this application will greatly enhance our understanding of the mechanism of action of botanicals and whether they are safe and efficacious for women's health.

Title: **North American Integrative Medicine Scientific Conference**
P.I.: **David M. Eisenberg**
Institution: **Harvard University Medical School – Boston, MA**
Grant No.: **1 R13 AT005049-01**
Award: **$50,000**

This R13 application requests support for a conference entitled North American Conference on Complementary and Integrative Medical Research, which will be held on May 12–15, 2009. This conference is sponsored by the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM), which represents 39 medical schools in the United States and Canada with programs focusing on complementary therapies and models of integrative medicine. The site host for the conference is the University of Minnesota, Center for Spirituality and Healing, a member of CAHCIM. This research conference is intended to showcase the highest quality, peer-reviewed, original research in this field. Its faculty is composed of leaders from the conventional and complementary medical

research communities of both the United States and Canada, including federally and provincially funded investigators, directors of integrative centers, educators, and policy researchers. Expert reviewers of original abstracts are nominated by a process governed by the Consortium's Research Steering Committee. This is the fourth in a series of highly successful conferences, with a similar focus and audience and peer-review process that were originally cosponsored by Harvard Medical School and the University of California, San Francisco. The most recent conference (and the first sponsored by the Consortium) was held in Edmonton, AB, Canada in May 2006. This conference is meant to showcase, by way of keynote and plenary presentations, posters, symposia, and workshops, original scientific research involving complementary and integrative medical therapies. Basic science, clinical, and health service researchers will present original research and moderate panel presentations selected through a peer-review process. Leaders in the field will be invited to provide keynote addresses and to moderate concurrent research presentations. Public scientific meetings where new peer-reviewed work is presented and discussed are crucial for the advancement of all research disciplines as they allow scientists, regulators, funders, researchers in training, and commercial entities to come together in a focused setting to explore data from important recent work in their respective disciplines, address issues of common concern, and inspect new resources that offer to make their work more efficient. The general public benefits enormously by way of the improved therapeutic and other scientific advances that make their first appearance at these meetings.

Genitourinary

Title: **Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome**
P.I.: **Sandra Berry**
Institution: **RAND Corporation – Santa Monica, CA**
Grant No.: **5 U01 DK070234-05**
Award: **$191,394**

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 it difficult to meet patients' needs for medical and nonmedical care. This project will establish (1) a case definition of IC in women for patient screening or epidemiological studies using a Delphi panel of experts in IC and diseases with similar symptoms; (2) develop and validate a symptom questionnaire that can be used to identify female IC patients and distinguish them from those with similar conditions (e.g., overactive bladder, urinary tract infection, and endometriosis); (3) develop an IC-specific measure of self-reported functional status, including physical, mental, social, sexual/relationship, role functioning, and other factors identified by IC patients as important; (4) survey more than 300,000 women for urinary symptoms and, using the validated symptom questionnaire, screen more than 23,000 to estimate prevalence of IC in the United States and provide a sample of 354 women over age 18 who fit the case definition for IC and 300 who have IC-like symptoms; and (5) describe the impact of IC on patients' 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.

Global Health Partnerships

Title: Fogarty International Clinical Research Scholars Support Center
P.I.: Sten H. Vermund
Institution: Vanderbilt University – Nashville, TN
Grant No.: 5 R24 TW007988-02
Award: $150,000

The Vanderbilt–MMC Fogarty International Clinical Research Scholars Support Center (FICRS) seeks to nurture and manage global health research training within centers of excellence identified by the NIH in developing countries. Our goal is to help train and inspire both U.S. and foreign graduate students in research techniques and topic areas applicable to resource-limited and/or tropical countries. This RFA builds on our experience as the current partner of the Association of American Medical Colleges (AAMC) in the management of the FIC/Ellison Medical Foundation Overseas Fellowships in Global Health and Clinical Research, now terminating. Our proposed FICRS will have expanded responsibilities, as delineated by the RFA, including direct funding of the sites responsible for the mentorship of the Fogarty International Scholars (FIS), funding the stipends and expenses of the scholars, and operating substantial Web-based information systems. These duties join the incumbent responsibilities of organizing the selection and matching process for FIS yearly, providing the orientation training at the NIH in July, and establishing a very long-term (20-year) trainee-tracking system. The substantial administrative role of funding the sponsoring sites and the FIS will also be centralized into the FICRS. One vision underlying our application is efficient administration of career-transforming experiences designed to nurture careers in international clinical and public health research. To further maximize the number of trainees that can be supported and the quality of research that they can do, we propose to seek copayments from the graduate schools of the selected students, investing the schools themselves with a concrete interest in the training outcome, and seeking to institutionalize this program, at least in part, in U.S. academia to ensure its sustainability. The specific aims focus on facilitating all aspects of mentored clinical research training for graduate-level U.S. health sciences students and host country counterparts at international sites collaborating with competitively funded U.S. investigators of renown. We have reached out to schools of medicine (allopathic, osteopathic, and veterinary), nursing, public health, dentistry, optometry, and pharmacy so far, including minority-serving institutions and FIC/NIH Global Framework grantees.

HIV/AIDS

Title: International Training in AIDS-Related Epidemiology
P.I.: Myron E. Essex
Institution: Harvard University School of Public Health – Boston, MA
Grant No.: 3 D43 TW000004-21S1
Award: $100,000

Working in partnership, the ORWH and the Fogarty International Center (FIC) will facilitate the inclusion of investigators from resource-poor countries who are interested in women's health and HIV/AIDS to attend a major scientific conference in this area. One of the most important ways that new investigators from low- and middle-income country receive recognition for their research and network with researchers in their field from other countries is through attending and presenting at scientific meetings. The grantees under the FIC research training programs are encouraged to find and support opportunities for their trainees, both current and former, to present their research conducted with support from the AITRP grant. The regional meeting in Africa will be held in Dakar, Senegal, on December 3–8, 2008, as the 15th International Conference on AIDS and SDS in Africa. The meeting is being chaired by Dr. Souleymane MBoup, who has been the foreign collaborator for over 20 years with the Harvard AITRP activities in Senegal. The theme of this meeting is "Africa's Response: Face the Facts." ORWH and FIC will be providing scholarships for this meeting. The recipients will be selected by the Scientific Advisory Committee, using three criteria: (1) have submitted an

abstract that received a high score in the external review, (2) the research abstract deals with pertinent operational or implementation research (interest of FIC and the ORWH), and (3) the recipients has no other means of support.

Title: **The Risk of Cardiovascular Disease Among Women in the Women's Interagency HIV Study Initiating Abacavir**
P.I.: **Mardge H. Cohen**
Institution: **Hektoen Institute for Medical Research – Chicago, IL**
Grant No.: **2 U01 AI034993-15**
Award: **$150,000**

The WIHS is a multisite prospective epidemiology cohort study of women enrolled in 1994 and 2002 who either are infected with HIV or are at increased risk for acquiring HIV infection. The purpose of the study is to continue followup of the WIHS cohort, thereby supporting studies of the natural and treated history of HIV infection in representative, primarily minority, adult women in the United States, as well as supporting studies of emerging questions related to long-term HIV infection and treatment. Women with HIV have a number of risk factors for cardiovascular disease (CVD) that are under study by the WIHS. Traditional risk factors have a similar impact on CVD in HIV-infected women as they do in the general population. Women with HIV have high underlying risk for CVD, including high rates of smoking, high BMIs, and higher rates of diabetes. Furthermore, in HIV-infected women, both HIV replication and antiretroviral therapy (ART) may contribute independently to cardiovascular risk. One antiretroviral drug is under particular scrutiny for its potential role as an inducer of inflammation.

Recently, an observational study, D:A:D, detected a 90% (95% CI: 47%–145%) increase in the risk of myocardial infarction (MI) in patients who were currently receiving or who had recently received abacavir compared to patients who had not recently received this drug. In the same report, a less statistically robust finding of a 49% (95% CI: 14% to 95%) increased risk of MI associated with current use of didanosine was also reported. These findings were unexpected, because abacavir is not known to adversely affect lipids and glucose metabolism. The MI risk associated with abacavir use was characterized epidemiologically as emerging quickly once the drug was initiated (within the first year of use), did not appear to be affected by duration of use of the drug, and was no longer present in patients who had ceased to take the drug for some months. These findings suggest that the mechanism by which abacavir might increase the risk of MI is more likely through an increased propensity for subclinical atherosclerosis to manifest itself as an MI other than a direct effect on the underlying atherosclerotic process per se. Analysis of specimens from the SMART study (in press AIDS) suggests a plausible biologic mechanism. At study entry, patients on abacavir had higher levels of hsCRP and IL-6 compared with patients receiving other NRTIs. Conversely, for the four other biomarkers considered, all of which have previously been associated with CVD, significant differences were not observed.

Based on the biomarker findings, abacavir may have proinflammatory properties. Abacavir causes hypersensitivity reactions in patients with HLA B*5701 and, as such, has already been demonstrated to have proinflammatory properties in genetically predisposed persons. However, because the abacavir-associated hypersensitivity reaction is observed within the first 6–8 weeks after the drug is started, and most patients in SMART had been on the drug for considerably longer periods at entry in the trial, it is unlikely that a hypersensitivity reaction, per se, can explain our findings. Consistent with this, the D:A:D study found a continuously elevated risk of MI associated with abacavir irrespective of duration of exposure. However, approximately one-third of patients with HLA B*5701 do not develop a hypersensitivity reaction after starting abacavir and it is possible that ongoing subclinical inflammatory reactions in these patients may contribute to our findings or that abacavir may stimulate inflammation by other mechanisms. How could elevated levels of IL-6 be linked with excess risk of CVD? Elevated levels of IL-6 are recognized to be associated with an increased risk of CVD. The mechanism may be that elevated IL-6 levels reflect an ongoing vascular inflammatory

reaction in the arterial wall, resulting in instability of existing plaques and thereby increasing the risk that preexisting subclinical atherosclerosis will manifest itself clinically as CVD. IL-6 may also directly exacerbate the aggregation potential of platelets, thereby increasing this risk. Of note, IL-6 may be elevated due to many different factors, and no prior studies have assessed what contribution drug-induced production may have to the circulating pool of IL-6, compromising the interpretation of further detailed comparisons of prior findings to our results. Based on the SMART and D:A:D results, we cannot exclude the possibility that women on abacavir had elevated hsCRP and IL-6 for reasons other than use of abacavir. Only prospective assessment of levels of these biomarkers before and after initiating abacavir will be able to clarify this association. In SMART, there is insufficient power to assess this. Additionally, comparisons of IL-6 levels between the two arms of the study are confounded by the fact that interruption of ART leads to loss of HIV control, which, by itself, induced IL-614. Rather, analyses of stored biobank material from studies designed to randomly compare virological outcomes of abacavir to other NRTIs are more suitable sources of this information. Using the biorepository of the WIHS cohorts, we would like to evaluate the longitudinal patterns of hsCRP and IL6 and d-dimer, a coagulation marker, in women initiating abacavir and non-abacavir-containing regimens. We would also like to evaluate the cardiovascular outcomes among women by abacavir treatment history. As a comparison group, we would like to evaluate these same factors in the MACS to determine the gender-specific differences that may or may not be present in abacavir response. Use of the MACS specimens will also increase the sample size and ensure that the study will be appropriately powered to study this relationship.

Title: **Gender Differences Among Women and Men Enrolled in China's National Free Antiretroviral Treatment**
P.I.: **Fujie Zhang**
Institution: **National Center for AIDS/STD Control and Prevention – Beijing, China**
Grant No.: **1 R03 TW008203-01**
Award: **$76,206**

The aims of this application are to (1) Evaluate gender differences in antiretroviral treatment outcomes; and (2) If gender differences are detected, examine factors associated with these differences. Specific Aim 1 will be accomplished by testing a set of hypotheses that women differ from men on the following measures of response to first-line antiretroviral therapy (ART), including a) all-cause and HIV-related mortality in the first 24 months after initiating therapy; b) immunologic response, as measured by changes in CD4+ cell count in the first 24 months; c) virologic response, as measured by the proportion of patients who reach the undetectable level of viral load in the first 24 months; d) ART-related side effects associated with different regimens, including symptoms and laboratory-based diagnoses within the first 24 months; and e) time to stopping first-line ART after initiating therapy. Specific Aim 2 will be accomplished by performing multivariable analysis for any outcome found to differ significantly between women and men. Covariates that might explain the treatment outcome differences will be examined to determine if they differ in proportion between women and men. Those that do will be inserted into the multivariate model to determine if any are statistically significant. All analyses will be conducted using a national ART database established by the China Center for Disease Control and Promotion. This large database collects demographic and clinical-care information on all patients participating in the free ART program, which provides a unique resource for examining gender-related differences in community-based HIV treatment outcomes. Determining whether these differences exist and understanding their causes will benefit HIV-infected individuals not only in China, but perhaps throughout the developing world. China has successfully implemented an ART program, but many challenges remain in managing the program. The proposed study is a secondary data analysis of the China National Antiretroviral Treatment Database. The findings from the proposed analysis will provide invaluable information for the understanding of treatment differences between HIV-infected women and men in community-based ART programs and will ensure the future success of the ART program in China. The analysis may also

provide much-needed information to guide the assessment of other community-based HIV treatment programs in developing countries.

Microbicides Innovation Program (MIP)

In collaboration with the NIH Office of AIDS Research (OAR), National Institute of Allergy and Infectious Diseases (NIAID), NICHD, and NIMH, ORWH has funded a number of R21/R33 innovation projects to support exploratory and developmental research on new microbicides and microbicide strategies and technologies with the goal of advancing promising strategies and technologies into the preclinical and clinical development of new agents. RFAs, all using the title "Microbicides Innovation Program (MIP)," have been issued in recent years to expand the research base in this area. The development of safe, effective, and acceptable topical microbicides to prevent the sexual transmission of HIV could play a major role in the worldwide reduction of new HIV infections. An effective and acceptable microbicide potentially could save millions of lives. Topical microbicides are agents that can result in inhibition of the transmission of HIV and/or other sexually transmitted infections, which may be cofactors in HIV transmission. The purpose of the MIP is to support novel and underexplored strategies in the field of topical microbicides.

Summaries for individual MIP awards

Title: **Improved Macaque Model for Topical Microbicides: Post-Coital Assessments**
P.I.: **Dorothy L. Patton**
Institution: **University of Washington – Seattle, WA**
Grant No.: **5 R21 AI071939-02**
Award: **$59,932**

Topical microbicides represent an emerging strategy for the prevention of transmission of HIV and other sexually transmitted infections (STIs). A successful topical microbicide product will be applied prior to intercourse, without necessitating partner consent, and will be active against a variety of STIs, including HIV. It will be acceptable to potential users in terms of physical characteristics, availability, ease of use, and safety and efficacy properties. We have utilized the macaque vaginal safety model (currently contracted by the NIH, N01-AI-95388) to provide standardized preclinical safety data for numerous topical microbicide products in development. In this model, measures of product safety include cervicovaginal colposcopy, vaginal microbiologic evaluation, and vaginal pH monitoring. This model characterizes the vaginal environment's response to repeated topical product applications in the absence of the exogenous factors of intercourse and potentially infectious ejaculate. While our preclinical evaluations of topical microbicide products have been well rounded in many respects, we have yet to investigate the effects of sexual intercourse on the cervicovaginal environment. Mucosal perturbation and potential microtrauma in the form of epithelial abrasions are likely to result from sexual activity. Additionally, the effects that seminal fluid may induce on the cervicovaginal environment, as well as its effects vis-a-vis topical microbicide product safety and efficacy, have not yet received their due attention. We propose to enhance our standardized vaginal safety evaluations conducted in the pigtailed macaque model to include evaluations after sexual activity and with the presence of seminal fluid. With continued R33 funding, we will collect baseline data from 24 female macaques, assessing the cervicovaginal environment before and after mating. In addition, we will collect parallel assessments when mating has occurred with a placebo gel (HEC universal placebo) in place. These studies will provide urgently needed data regarding topical microbicide use with coital activity.

Title: **Lactobacilli as a Source of Natural Microbicides Against HIV-1**
P.I.: **Ruth Ingrid Connor**
Institution: **Dartmouth College – Hanover, NH**
Grant No.: **5 R21 AI071948-02**
Award: **$10,000**

Topical microbicides formulated for vaginal use may help stem further spread of HIV-1 by reducing the number of new infections in women. One microbicide strategy under consideration is to strengthen the natural defenses in the vaginal mucosa where HIV-1 transmission takes place. Lactobacillus species are the predominant commensal bacteria found in genital tract secretions of healthy women. Under anaerobic conditions, these bacteria produce lactic acid and certain strains also produce hydrogen peroxide, a potent antimicrobial that has been shown to inactivate HIV-1 in vitro. Lactic acid bacteria also produce an array of antimicrobial molecules, termed bacteriocins, that are effective against competing organisms in the local milieu. Whether these natural antimicrobial factors can inhibit transmission and replication of HIV-1 in vaginal tissues is unknown. In preliminary studies, we have shown that conditioned media (CM) from cultures of *Lactobacillus rhamnosus GG* (LGG) inhibit replication of HIV-1 by 2 to 4 logs 10 in primary CD4+ T lymphocytes, and this antiviral activity is distinct from both lactic acid and hydrogen peroxide. We hypothesize that natural bacteriocin-like molecule(s) produced by commensal lactic acid bacteria can enhance innate immunity in the vaginal mucosa and can inhibit infection and/or replication of HIV-1 in these target tissues. The goal of the studies proposed in the exploratory (R21) phase is to purify and identify the low-molecular-weight active factor(s) produced by LGG bacteria and determine the extent to which the LGG-purified factors (LGG-PF) (1) inhibit replication of HIV-1 in vitro; (2) modulate cell activation, proliferation, and transcriptional regulation; and (3) affect the secretion of innate immune factors from primary epithelial cells from the human female reproductive tract. In the developmental (R33) phase, we will evaluate the effect of LGG-PF on HIV-1 infection and secretion of innate immune factors in primary explant cultures of human cervical and vaginal tissues and will further evaluate cervicovaginal toxicity and inflammation in a mouse model developed for preclinical evaluation of topical vaginal microbicides. If the purified factor(s) secreted by LGG bacteria are shown to inhibit HIV-1 replication in relevant target cells in vitro and modulate expression of innate immune factors in female genital tract tissue explants, this would provide evidence of a novel and beneficial effect that extends well beyond the established antimicrobial function of these bacteria. Moreover, these results would lay the foundation for application of lactobacilli-derived products as HIV microbicides either alone or in combination with targeted compounds that block HIV-1 infection and replication.

Title: **Peptide Deformylase Inhibitor LBM415 for Sexually Transmitted Infections**
P.I.: **Huizhou Fan**
Institution: **University of Medicine & Dentistry of New Jersey, Robert Wood Johnson Medical School – Piscataway, NJ**
Grant No.: **5 R21 AI071954-02**
Award: **$10,000**

This R21/R33 phased project will explore a novel strategy for combating sexually transmitted chlamydial and gonococcal infections. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most common sexually transmitted pathogens. In addition to acute urogenital inflammation, chlamydial and gonococcal infections frequently result in devastating complications, including infertility and chronic pelvic pain syndrome. Infection with these bacteria also increases the risk of HIV infection. Sexually transmitted chlamydial and gonococcal infections disproportionately affect the wellness of women. Therefore, there is an urgent need to develop effective self-administered topical antimicrobials to combat the transmission of these organisms and other sexually transmitted pathogens. We have discovered that *C. trachomatis* and *N. gonorrhoeae* are highly susceptible to inhibitors of peptide deformylase (PDF), an enzyme that catalyzes the removal of the formyl group from newly synthe-

sized proteins/peptides before they become biologically active. Lactobacilli and *Escherichia coli* are significantly resistant to PDF inhibitors. We hypothesize that PDF inhibitors may be used topically to prevent sexually transmitted chlamydial and gonococcal infections without disrupting normal microflora. The goal of the R21-phase research is to determine the feasibility of utilizing the lead PDF inhibitor, LBM415, topically for combating genital chlamydial and gonococcal infections. Thus, mice will be intravaginally exposed to a commercial gel containing LBM415 to determine whether LBM415 is free of acute and long-term toxicity and provides protection against vaginal chlamydial and/or gonococcal infections upon its topical application. In addition, the effects of LBM415 on vaginal probiotic lactobacilli and bacterial vaginosis-associated pathogens will be determined. Frequencies of resistance to LBM415 in *Chlamydia trachomatis* and *N. gonorrhoeae* will also be assessed. If the R21 research meets its defined milestones (i.e., meaningful protection against chlamydial and gonococcal infections in vivo, a lack of in vivo toxicity, significant toleration by probiotic lactobacilli, and acceptable resistance frequencies), additional studies will be carried out to further determine the value of LBM415 for combating chlamydial and gonococcal infections in the R33 phase. During the R33 phase, dose-response, inhibition of pathogen shedding from animals with preestablished infection, possibility of early application, and potential synergism with another promising broad-spectrum topical microbicide candidate will be studied.

Title: **Development of a Live Topical Microbicide for Women**
P.I.: **Qiang Xu**
Institution: **Osel, Inc. – Santa Clara, CA**
Grant No.: **5 R21 AI071978-02**
Award: **$10,000**

The company's lead product, LACTIN-V, is a naturally occurring human vaginal isolate of *Lactobacillus crispatus* presently undergoing Phase II clinical trials to examine its safety and efficacy in preventing recurrent urinary tract infections and bacterial vaginosis. Both of these infections are characterized by a depletion of hydrogen peroxide (H2O2)-producing lactobacilli that normally protect the vagina from infection by opportunistic pathogens. Epidemiological studies also suggest that loss of vaginal lactobacilli is associated with an increased risk of heterosexual HIV-1 transmission and other sexually transmitted infections. LACTIN-V represents an ecological approach to prevent vaginal infections by reestablishing the protective vaginal flora with a colonizing, H2O2-producing *Lactobacillus* strain. A second-generation *Lactobacillus* product, and the topic of this proposal, is a human vaginal isolate of H2O2-producing *L. jensenii* that has been genetically enhanced to constitutively secrete high levels of the potent HIV entry inhibitor cyanovirin-N (CV-N). This live, self-renewing microbicide may afford an efficacious yet inexpensive means to deliver a protein-based microbicide and addresses the urgent need for female-controlled approaches to block heterosexual transmission of HIV-1. In this R21 proposal, we will select a microbicide development candidate from a collection of bioengineered strains that contain optimized CV-N expression cassettes stably integrated into the *L. jensenii* chromosome. We will employ a Chinese rhesus macaque (*Macaca mulatta*) model that affords persistent vaginal colonization of *L. jensenii* to conduct preclinical safety and efficacy studies, including in situ CV-N expression, immunotoxicity, and efficacy against mucosal viral transmission. Furthermore, we propose to evaluate potential regulatory issues concerning the pharmaceutical development of a genetically modified organism and to optimize the formulation and manufacturing processes for this product. Following a pre-IND consultation with the FDA, we will file an exploratory IND application and then initiate two exploratory phase 0 studies in the R33 phase of the proposal to assess the effects of the recombinant *L. jensenii* strain on safety, tolerability, innate genital tract immune factors, vaginal colonization, and clearance of the organism after antibiotic administration in healthy female volunteers.

Title: Novel Stimulators of HIV-1 Integrase for Use in Combination Microbicide Regimens
P.I.: Michael Katzman
Institution: Pennsylvania State University, Milton S. Hershey Medical Center – Hershey, PA
Grant No.: 5 R21 AI075929-02
Award: $10,000

The long-term goal of this project is to develop ways to interfere with HIV replication and transmission, which would have major implications for preventing the spread of HIV/AIDS. Any successful preventive strategy must work before infection becomes established, and the hallmark of an established retroviral infection is integration. The viral integrase enzyme catalyzes at least two endonuclease reactions in vivo: specific nicking to prepare the ends of viral DNA for integration and nonspecific insertion of the viral DNA into cellular DNA. Integrase also has a potent nonspecific endonuclease activity that can nick any DNA sequence in vitro, and this activity is dramatically stimulated by certain small compounds. These facts suggest a novel (and ironic) antiviral strategy in which integrase is stimulated to destroy viral DNA before integration (with any damage to cellular DNA being limited to newly infected cells and also blocking infection). Thus, the objectives of this proposal are to identify potent stimulators of the nonspecific nicking activity of HIV-1 integrase and to bring at least one of these agents to the verge of clinical testing. The central hypothesis, based on known precedents and preliminary data, is that integrase's nonspecific endonuclease activity can be stimulated for a new antiviral strategy that can be part of a safe and effective combination microbicide regimen. In the R21 phase, Aim 1 will optimize a high-throughput assay for integrase-mediated nonspecific DNA nicking; Aim 2 will screen 50,000 chemicals in the Penn State Drug Development and Discovery Core for additional agents that stimulate HIV-1 integrase to nick DNA nonspecifically (with appropriate secondary assays to validate positive hits); and Aim 3 will use quantitative antiviral and cell toxicity studies to prioritize integrase stimulator (IS) compounds based on their therapeutic indices, all the while feeding back to organic chemists who will design and synthesize rational analogues of lead compounds for testing in an iterative fashion. In the R33 phase, Aim 4 will test the safety of each candidate IS compound in expanded toxicity studies, including a mouse model of cervicovaginal toxicity; and Aim 5 will test the range of antiviral activity against different subtypes of HIV-1 and in a NOD-SCID-hu mouse model of HIV-1 infection. These data will also feed back to the discovery pathway to make new derivatives of IS compounds. Finally, because the ideal microbicide regimen would combine agents that work outside cells to impede virus entry with agents that work inside cells to abort infection for any viruses that do gain entry, Aim 6 will evaluate microbicide combinations that include IS compounds for cooperative activity against HIV-1, in preparation for moving at least one drug candidate into future clinical trials.

Title: Mucosal Protection Against HIV Transmission by Combinations of Anti-HIV Antibody
P.I.: Lisa A. Cavacini
Institution: Beth Israel Deaconess Medical Center – Boston, MA
Grant No.: 5 R21 AI075932-02
Award: $10,000

There were approximately 5 million new infections with HIV-1 worldwide in 2005, with an increase in the prevalence of women becoming infected, especially in Africa, south and Southeast Asia, Eastern Europe, and central Asia, where social and cultural inequalities significantly impact on a women's ability to prevent infection. While prevention programs can be successful at reducing the incidence of transmission, assuming that they are long term and intensive, many individuals do not have access to prevention programs or are unaware of their partner's HIV status. Additional means of prevention must be developed to reduce the sexual transmission of HIV. A microbicide might be an effective means for women to use. It has been estimated that the regular use of a microbicide that is 60% efficacious by 20% of women in highly impacted countries would protect against hun-

dreds of thousands of infections. Passive administration or local application of human monoclonal antibodies has been shown to be effective in preventing mucosal infection in nonhuman primate models. We hypothesize that the structure of these monoclonal antibodies can be altered to improve in vivo efficacy at mucosal surfaces formulated as a microbicide that can provide long-lasting, convenient, reliable, and locally effective prevention. To study these hypotheses, we propose to (1) determine the relationship of IgA subclass and monomeric or polymeric structure to functional activity of anti-HIV antibodies and stability in the mucosal environment and (2) determine efficacy at preventing infection following vaginal challenge of nonhuman primates. Specific antibodies have been identified based on broad reactivity, structure–function relationships, epitope exposure, and availability and include F425A1g8, reactive with an epitope exposed by CD4 binding with neutralizing activity; b12, reactive with the CD4 binding site and neutralizes a broad range of isolates; F425B4e8, reactive with the V3 loop and neutralizes a broad range of isolates; and F240, reactive with gp41, binds to all clades of HIV, and neutralizes infection when expressed as an IgA antibody. F240 represents a prototype of a class of antibodies that may include other broadly reactive antibodies to well-conserved sites that may mediate local destruction or sequestration of virus away from target cells for destruction by innate immune mediators prevalent at the mucosal surface or neutralize infection under specific conditions. The studies proposed explore the hypothesis that local expression of a combination of broadly anti-HIV-1 antibodies at the mucosa represents an efficacious method to block entry of the virus into the body.

Title: **Inhibitors of HIV-Dendritic Cell Interactions as Microbicides**
P.I.: **Philippe Gallay**
Institution: **Scripps Research Institute – La Jolla, CA**
Grant No.: **5 R21 AI076005-02**
Award: **$10,000**

The development of a safe, effective, acceptable topical microbicide to prevent the sexual transmission of HIV could play a major role in worldwide reduction of the over 14,000 new HIV infections per day and potentially save millions of lives. Given that cell-free virus ineffectively crosses the genital epithelium in the absence of lesions, it is likely that HIV hijacks host cells as Trojan horses to cross the normally impermeable genital epithelium. It has been postulated that HIV exploits Langerhans cells (LC) and dendritic cells (DC) to facilitate its safe passage through the genital epithelium. In this application, we propose to develop compounds that prevent HIV-LC and HIV-DC interactions in vitro (R21 phase) and to test them as topical microbicides in vivo (R33 phase). We demonstrated that HIV uses three specific receptors to mediate its initial contact with vaginal LC and DC. We propose to generate reagents that target each of these receptors. These receptor antagonists will then be tested for their capacities to prevent HIV-LC and -DC interactions. The goal is to identify reagents that are the most potent at blocking in vitro HIV hijacking of vaginal LC and DC. These LC and DC receptor inhibitors will serve as microbicide candidates for subsequent in vivo studies proposed in the R33 phase. We demonstrated that gp120 mediates the contact between HIV and vaginal LC and DC. We propose to generate reagents that prevent gp120-LC and -DC interactions. Specifically, we propose to generate soluble reagents that mimic the receptors that HIV exploits to interact with LC and DC. These receptor mimics will serve as decoys to prevent gp120 contact with vaginal LC and DC. The goal is to identify receptor mimics that are the most potent at blocking in vitro HIV hijacking of vaginal LC and DC. These receptor mimics will serve as microbicide candidates for in vivo studies proposed in the R33 phase. One advantage of using compounds that prevent HIV-LC and -DC interactions is that many sexually transmitted pathogens also exploit LC and DC for host colonization, and thus the ability to block HIV-LC and -DC interactions may have the additional benefit of preventing other sexually transmitted pathogens. This approach may not only provide valuable novel microbicides, but it will also allow us to assess the contribution of LC and DC to HIV transmission.

Title: Models for Testing Candidate Topical Microbicides for Cytotoxicity and Activity A
P.I.: Mary F. Lampe
Institution: University of Washington – Seattle, WA
Grant No.: 5 R21 AI076020-02
Award: $10,000

Chlamydia trachomatis, an obligate intracellular parasite, is the most common sexually transmitted bacterial pathogen in the world. Infections are often asymptomatic and can cause serious complications, such as pelvic inflammatory disease, infertility, and ectopic pregnancy. In addition, chlamydial infections may increase the risk of HIV transmission. The development of topical microbicides to prevent sexually transmitted infections has recently gained attention. We have developed the in vitro minimal cidal concentration (MCC) assay to test the direct action of microbicides on the extracellular, infectious chlamydial EBs. We now propose to continue developing the MCC assay by studying the in vitro safety and efficacy of peptide and lipid topical microbicides and the effects of strain variation and the presence of human albumin, simulated vaginal fluid, or simulated semen. The MCC assay will further be employed to analyze the effect of novel antimicrobial agents, placed in formulation with universal placebo singly or in combination, for their activity against *C. trachomatis*. Finally, we will examine safe and active selected formulations of candidate topical microbicides in vivo in a nonhuman primate model for vaginal and rectal safety and efficacy. The mode of action of antichlamydial microbicides on the organism will be assessed as well as the possibility of *C. trachomatis* strains developing resistance to the selected microbicides. By providing these highly specialized laboratory tests and expertise not readily available in other laboratories, the chlamydia laboratory will contribute fundamentally to topical microbicide research that will ultimately help to prevent HIV and chlamydial infections around the world.

Title: High-Resolution Optical Imaging Assessment of Microbicide Toxicity
P.I.: Massoud Motamedi
Institution: University of Texas Medical Branch – Galveston, TX
Grant No.: 5 R21 AI076062-02
Award: $10,000

Evaluation of the safety and efficacy of microbicides requires an assessment of potential injury caused by microbicides in the epithelium of the cervicovaginal tract and rectum. The development of imaging technology and protocols that can be used for endoscopic, rapid, and quantitative assessment of tissue injury following topical application of microbicides could have a significant impact on the development and testing of microbicides in animal models and clinical studies. Unfortunately, current imaging technology, such as white-light colposcopy or colonoscopy, cannot provide high-resolution images of epithelial injury and cannot probe below the surface, where epithelial injury and inflammation may be evident. However, in recent years, new imaging technology has been developed where it is now possible to perform high-resolution imaging of epithelial tissue with microscopic resolution in vivo. Our overall goal is to develop an endoscopic image-based approach that can be used to (1) assess the degree of injury that may be induced by microbicides, and (2) correlate the results of imaging studies to susceptibility to genital infection in the mouse cervicovaginal tract and rectum caused by HSV-2. We will deploy emerging high-resolution imaging modalities, including confocal fluorescence microscopy and optical coherence tomography (OCT), to characterize the changes that occur in the architecture of cervical, vaginal, and rectal epithelium of untreated, sexually naive mice as well as mice treated with known irritative microbicides. These results will be correlated with susceptibility to infection using a well-characterized mouse model of HSV-2 infection. This will allow us to assess the predictive value of confocal fluorescence and OCT imaging for observed HSV-2 susceptibility based on microbicide-induced epithelial changes, with attention to the reproducibility/consistency of the findings. In Phase I of this project, we will demonstrate the capabilities of high-resolution optical imaging to quantitatively assess the response of cervicovaginal and rectal tissue to known microbicides and test the ability to predict the biological endpoint

of microbicide-induced changes in susceptibility in the cervicovaginal tract. In Phase II, the proposed image-based assessment of rectal response will be extended to establish correlation between image-based markers and rectal susceptibility following application of microbicides. Furthermore, instrumentation and imaging parameters will be optimized to make the imaging protocol suitable for imaging of cervicovaginal and rectal epithelial response in large animal models and humans. We also plan to use the developed imaging protocol to assess the performance of novel microbicides in small animal models as new products are developed.

Title: **Mucus-Penetrating Nanoparticles for Sustained Microbicide Delivery**
P.I.: **Richard A. Cone, Justin S. Hanes**
Institution: **Johns Hopkins University – Baltimore, MD**
Grant No.: **1 R21 AI079740-01**
Award: **$18,182**

We have developed mucus-penetrating nanoparticles (MPP) suitable for sustained delivery of small-molecule microbicides (Lai et al., *Proceedings of the National Academy of Sciences* 2007; 104(5):1487). Conventional particles (CP) are mucoadhesive and stick to the outer layers of mucus that are shed most rapidly out of the vagina. By densely coating MPP with low-molecular-weight polyethylene glycol, we found that unexpectedly large MPP 100–500 nm in diameter can be engineered to rapidly penetrate human cervicovaginal (CV) mucus and thereby reach the unstirred layer of mucus adhering to the epithelial surface. These MPP will likely significantly increase vaginal residence time and improve epithelial microbicide distribution. The aim of this R21/R33 project is to develop MPP for the sustained delivery of small-molecule microbicides to increase their protective efficacy, acceptability, and user reliability. "User failure" is the primary failure mode of barrier methods, and microbicides are likely to be used more reliably if applied daily on a coitally dissociated basis. Another failure mode that is well documented in animal models is inadequate microbicide distribution—the infectious inoculum reaches surfaces unprotected by the microbicide. MPP can provide a once-a-day, coitally dissociated method that is likely to achieve complete and essentially uniform epithelial distribution. MPP will not likely provide the month-long delivery of a vaginal ring, but MPP have advantages that are not immediately apparent: (1) The vaginal epithelium is highly permeable to small water-soluble molecules—thus, uniform epithelial distribution can best be achieved by uniform sustained delivery of small water-soluble microbicides directly to the entire epithelial surface, not just to the vicinity of a vaginal ring; (2) Uterine peristalsis exposes the upper reproductive tract to vaginally deposited pathogens, and reliable protection of the upper tract is more likely to be achieved by MPP that can transport, and then locally deliver, small water-soluble molecules to the epithelia surfaces of the upper tract. In the R21 phase, we propose to develop acyclovir-loaded MPP to evaluate in our mouse HSV models for efficacy, duration, vaginal distribution, and toxicity. The MPP will be composed of biodegradable copolymers that we have shown are capable of sustained delivery of a wide range of bioactive molecules. The key milestone for the R21 phase will be to develop acyclovir-MPP that provide at least 1 day of protection in the mouse. In the R33 phase, we will use the knowledge gained from the R21 phase to speed the development of an anti-HIV-MPP for sustained release of the best anti-HIV microbicide candidate then available (fall 2010), with tenofovir being a likely choice. The R33 anti-HIV-MPP will be optimized for drug delivery based on the R21 results and will be tested for toxicity in mouse models and for efficacy in the Hu-BLT-SCID mouse/HIV model by Dr. Victor Garcia at UT Southwestern. Worldwide, there is a great need for methods women can use to protect against AIDS and other sexually transmitted diseases. Several small-molecule vaginal microbicides are being developed that block HIV from infecting and/or replicating in target cells. The aim of this project is to enhance the protective efficacy of these small-molecule microbicides by developing mucus-penetrating nanoparticles that will improve coverage of susceptible tissues to increase the reliability of protection and to increase the duration of protection so that the microbicides can be applied regularly, on a daily basis, and not require coitally related applications.

Title: Novel Mucosal Models Predictive of Microbicide Safety
P.I.: Betsy Herold, Marla J. Keller
Institution: Yeshiva University – Bronx, NY
Grant No.: 1 R21 AI079763-01
Award: $18,181

The proposed Microbicide Innovation Program fosters the development of new model systems (dual chamber and murine) that have the potential to substantially advance microbicide science. This approach is designed to improve methods for assessment of microbicide safety. The optimal microbicide should protect against infection without disrupting the mucosal environment or its mediators of host defense. The clinical trial failures with nonoxynol-9 and cellulose sulfate highlight the challenges in microbicide research and the need to establish better markers predictive of microbicide safety. The proposed studies address this gap. The primary objective of the R21 component is to establish two synergistic models of microbicide safety: an in vitro dual-chamber model using primary human cervical epithelial cells and a murine model. Preliminary findings with these models demonstrate that the models would have predicted the increase in HIV acquisition observed in recently completed clinical trials. The microbicides disrupt the epithelium in vitro, as evidenced by a loss in transepithelial electrical resistance and in structural proteins, and these changes are associated with an increased migration of cell-free HIV across the epithelium. In parallel studies, the drugs also trigger substantial changes in genital tract tissue architecture in mice following repeated vaginal application and the observed changes are associated with an increased susceptibility to genital herpes infection. Establishment of these two complementary models will contribute to efficient assessment of microbicide safety. During the R33 phase, both models will be translated into the preclinical pipeline by evaluating leading microbicide candidates, singly and in combination. Candidate microbicides will be introduced in the presence of cervicovaginal secretions and challenged in vitro with virus introduced in semen. The migration of both cell-free and cell-associated HIV will be tested in the dual-chamber model system. In addition, during the R33 phase, the in vitro model will be expanded to assess the impact of microbicides on cells derived from women with human papillomavirus (HPV)-associated dysplasia. While it is critical to assess the effect of microbicides on healthy genital tract cells and mucosa, it is highly likely that many women who choose to use a microbicide will be infected with a sexually transmitted infection. HPV is the most common sexually transmitted infection worldwide and changes in genital tract epithelium in response to microbicides may differ in women with HPV. These results will provide critical new data on microbicide safety in women with a sexually transmitted infection. Biomarkers predictive of microbicide safety are urgently needed. Tissue and murine models may provide more efficient strategies to assess microbicide safety by expanding existing models to include testing of primary cells. Development of an effective dual-chamber and murine model may prove to be important in determining which candidate microbicides to move forward in the development pipeline. In addition, these models may provide a means to test the safety of microbicides in healthy women as well as those with underlying STIs.

Title: Novel Vaginal Microbicides Based on Stable AAV-Neutralizing Antibody Gene Transfer
P.I.: Wayne A. Marasco
Institution: Dana-Farber Cancer Institute - Boston, MA
Grant No.: 1 R21 AI079767-01
Award: $18,182

In the global AIDS pandemic, more than half of new HIV-1 infections are acquired by women through intravaginal HIV exposure. Although cervico-vaginal epithelial cells lining the mucosal surfaces of the female lower genital track provide the initial defense system against HIV-1 infection, the protection is often incomplete. Transport of HIV-1 across this mucosal barrier is absolutely critical for HIV-1 colonization and subsequent virus dissemination, and, thus, enhancing anti-HIV-1 humoral immunity at the mucosal cell surface by the local expression of anti-HIV-1-neutralizing an-

tibodies (nAbs) that block epithelial cell attachment and virus entry may provide an important new intervention that could slow the spread of HIV/AIDS. This R21/R33 project represents the combined efforts of the Marasco (antibody engineering, gene therapy), Anderson (mucosal immunity) and Mansfield (HIV/AIDS macaque model) laboratories to investigate whether stable adeno-associated virus (AAV)-nAb gene transfer to the cervico-vaginal epithelial stem cells can provide a strategy that will lead to durable protection against HIV-1. In the R21 phase, we will first determine which of nine AAV serotypes provides optimal gene transfer of GFP without toxicity to primary human (Hu) and rhesus macaque (Rh) primary genital epithelial cells (PGECs) comprising endocervical, ectocervical, and vaginal epithelial cells with special focus on stable gene transfer into p63+CK17+ epithelial stem cells, which are capable of renewing stratified epithelium. Persistence of AAV-GFP transduction; potential toxicities; and effects of proinflammatory cytokines, hormonal conditions, semen, and vaginal secretions on transduction efficiency and transgene persistence will be examined. We will construct a miniaturized version (minibody) of broadly neutralized human anti-gp120 Mab b12 in both the IgG1 and dimeric IgA2 format and assess b12 neutralizing activity against HIV-1/SHIV by both Ab treatment studies and AAV gene delivery to organotypic human vaginal and endocervical models and Hu and Rh PGECs. Upon successful demonstration of in vitro protection, the R33 phase will begin where we will first conduct an AAV-transduction dose escalation study in Rh (n=12) to evaluate depth, uniformity, and extent of p63+,CK17+ stem cell transduction, the PK of b12scFv-FcG1 and b12scFv-FcA2 secretion, and toxicity. This will be followed by a second intravaginal transduction study with the optimal dose of the two AAV-b12scFv vectors, each alone and together, followed by vaginal challenge with SHIV (Rh=15–16). Finally, we will evaluate enhanced SHIV protection through mixtures of gel-forming polymers and AAV to increase in vivo AAV transduction and b12scFv-Fc secretion (Rh=9). Overall, 13 hypotheses will be tested. These important studies fulfill a major objective of the R21/R33 program to support research that may be high risk/impact and have the potential to advance AIDS microbicide strategies. Given the safety profile, low immunogenicity, and rapid advancement of AAV-based gene therapy in numerous clinical trials, it is likely that the success of this novel approach could be quickly translated to human studies. HIV-1 infections are acquired most often through sexual contact and more than half of new infections are acquired by women through intravaginal HIV exposure. We propose to develop a genetic microbicide that, when delivered to the mucosal surface of the cervix and vagina, will allow the lining cells to stably produce a neutralizing human anti-HIV antibody that blocks HIV-1 attachment and infection. A protective genetic microbicide delivered to the female lower genital tract could dramatically slow the spread of HIV/AIDS.

Title: **HIV Integrase as a Target for Topical Microbicide Development**
P.I.: **Mary E. Klotman**
Institution: **Mount Sinai School of Medicine – New York, NY**
Grant No.: **1 R21 AI079776-01**
Award: **$18,182**

Over 4 million individuals were newly infected with HIV in 2006, with sexual transmission the predominant mode of infection worldwide, highlighting the need for effective prevention strategies. Unfortunately, clinical trials to date, with the first generation of candidate topical microbicides to block sexual transmission, have been disappointing, as both nonoxynol-9 (N-9) and, more recently, cellulose sulfate (CS) either did not block transmission or actually enhanced transmission. These results highlight the continued need for highly efficacious and safe microbicide candidates. This project will address the safety and efficacy of a new class of specific antiretrovirals as topical microbicide candidates, integrase inhibitors. The integrase inhibitor GS-9160 is a potent inhibitor of HIV that has been extensively studied in animals and most recently in a Phase I human trial and has had no significant toxicity. The potential of this drug as a candidate microbicide will be evaluated in two phases. In the R21 phase, a candidate gel formulation of GS-9160 will be generated in collaboration with Gilead Sciences and evaluated for in vitro drug loading and stability. The drug and candidate formulation with favorable loading will be evaluated in cervical and vaginal epithelial cell monolayers and cervi-

covaginal explants for release and uptake, cytotoxicity, and efficacy against primary and laboratory isolates. The parallel evaluation of gene expression induced by formulated GS-9160 in human and rhesus macaque (RM) cervicovaginal explants, along with a similar analysis of tissue and cervical vaginal lavage (CVL) fluid derived from in vivo RM studies in the R33 phase, will validate the cervicovaginal explant model as a screen for host responses in vivo. If the candidate formulation has an acceptable safety profile, as determined by the absence of a proinflammatory response (comparable to N-9), and inhibits HIV infection in the explant model, the R33 phase will be initiated with testing of local and systemic pharmacokinetics and toxicity associated with vaginal delivery of formulated GS-9160 in RM followed by an efficacy study in RM vaginally challenged with R5 SHIV. The proposed studies will directly address whether integrase inhibitors as a class should be added to the pipeline for microbicide development. In addition, the studies proposed will validate the genital explant model as a screen for host responses in vivo. Topical microbicides that could be applied by the user to protect against sexual transmission of HIV have, to date, been disappointing in clinical trials. This proposal examines the topical microbicide potential of a very potent antiretroviral drug that inhibits integration of the virus into host cells. If successful in these studies, it would be added to a new generation of topical microbicides in the pipeline that specifically target HIV.

Title: **Combinations of Entry Inhibitors as Anti HIV-1 Microbicides**
P.I.: **Patricia J. Liwang**
Institution: **University of California, Merced – Merced, CA**
Grant No.: **1 R21 AI079777-01**
Award: **$18,182**

Given the high rate of sexual transmission of HIV-1, particularly in the developing world, the need for a topical microbicide is critical. The long-term goal of this research is to develop an anti-HIV microbicide using HIV-1 fusion inhibitors. In particular, we have found that the combination of certain chemokine variants with gp41-binding proteins results in highly potent inhibition of HIV-1, both in fusion assays (IC50=1 pM) and in viral assays in PBMC (IC50=0.7 nM, R5 tropic strain Ba-L). The Aims of the proposal are as follows: Combinations of CCR5-binding proteins and gp41-binding peptides will be tested in both fusion assays and in viral assays with multiple clades of HIV as well as primary strains in order to determine which combinations provide the most potent protection. Then it will be determined if a higher level of inhibition efficiency can be obtained by combining both a variant chemokine and a gp41-binding protein on a single polypeptide chain. During the R33 phase of the project, it is proposed to carry out preclinical evaluation of the most potent inhibitors and combinations, including stability to pH and ionic strength, cell toxicity, and irritation in animal models. The most promising inhibitors will then be tested in two different ways. In Aim 4, they will be expressed by *Lactobacillus jensenii*, an organism that is naturally found in vaginal mucosa, and as such represents a method of delivery of protein microbicides having great potential. Finally, in Aim 5, the best entry inhibitors will be evaluated in a humanized mouse model that has been shown to be able to be infected with HIV. Anti-HIV microbicides are molecules that can be used topically to prevent the spread of the HIV-1 virus through sexual transmission. The proposed experiments will study the combination of CCR5-binding proteins and gp41-binding proteins to synergistically inhibit HIV and as components of a microbicide.

Title: **Scalable Production of Recombinant Protein Microbicides**
P.I.: **Julian Ma**
Institution: **St. George's Hospital Medical School – London, United Kingdom**
Grant No.: **1 R21 AI079785-01**
Award: **$18,182**

HIV microbicides are designed to be applied topically before sexual intercourse to inactivate the virus and prevent infection. Some of the most promising microbicide candidates have been proteins, but their clinical development and evaluation has been hampered by the lack of available

material and/or the prospect of having to manufacture vast quantities of recombinant protein very cheaply. Plant biotechnology offers some potential solutions. Whilst the production of microbicides at agricultural scale is a long-term aim, it is likely that the first-generation products will emerge from plants grown in containment, under conditions more recognizable as conventional medicine production systems. It has long been established that recombinant proteins can be expressed in all tissues of the plant, including roots. Indeed, some recombinant proteins produced by transgenic plants are actively secreted from the root system in a process known as rhizosecretion. This gives rise to the possibility that transgenic plants could be grown in greenhouses under hydroponic conditions, using a defined culture medium. Moreover, the microbicide product could be harvested from hydroponic culture medium, rather than plant tissue, which would greatly simplify purification and allow harvest over the lifetime of the plant. Hydroponic cultivation of plants is already a well-established technique in the horticultural industry and is also currently used for the production of natural medicinal compounds. The objective of this proposal is to establish a contained hydroponic tobacco plant culture approach for production of two microbicide protein candidates, cyanovirin-N and MAb 4E10, and to develop optimization strategies for growth and production that will deliver previously unavailable protein microbicides at a level to allow clinical evaluation. We will establish production at small commercial scale. In the first (R21) phase of the proposal, we intend to demonstrate feasibility of the approach and have established production-driven milestones for entry into the second (R33) phase, in which we will develop manufacturing and purification according to good practice regulatory requirements ultimately to deliver protein microbicides for clinical trials. Cyanovirin-N and MAb 4E10 are two of the most promising protein microbicide candidates currently available. However, the clinical development of both has been held back by production difficulties, and their efficacy and safety profiles are still to be determined. This project is aimed at developing a production platform for CV-N, MAb 4E10, and, ultimately, other recombinant protein microbicides, which will advance these products to human clinical trials.

Title: **Intravaginal Ring Microbicide Formulations Comprising Multiple Anti-HIV Agents**
P.I.: **Thomas J. Smith**
Institution: **Oak Crest Institute of Science – Pasadena, CA**
Grant No.: **1R21 AI079791-01**
Award: **$18,181**

The broad long-term goal of this project is to empower women to protect themselves from HIV infection through the development of improved microbicides based on our clinically proven sustained-release technology platform. Using this platform, drug delivery devices for a broad range of drugs have been approved by the FDA and are in current clinical use. The ganciclovir intraocular implant, the Vitrasert(r), approved for the treatment of AIDS-related CMV retinitis, releases the relatively soluble antiviral ganciclovir into the eye for a period of 8 months. The Retisert(r) releases the relatively insoluble steroid fluocinolone acetonide for up to 3 years. We propose to utilize this platform to develop sustained-release vaginal-ring microbicide formulations for the antiretroviral agents tenofovir and TMC 120. In the first 2 years of this project (R21), we will evaluate the hypothesis that, when incorporated into a ring formulation, the prodrug tenofovir disoproxil fumarate is superior to the parent drug tenofovir as a candidate microbicide. In the second phase of the project (R33), we will manufacture and test ring formulations containing multiple antiviral agents. We hypothesize that, using our unique drug-delivery platform, there will be no loss of elution characteristics with the incorporation of multiple drugs into our system. The successful completion of this project will result in the submission of an investigational new drug exemption leading to clinical trials for these formulations. Each day, 15,000 people are infected by HIV, the majority in sub-Saharan Africa, and a growing percentage of women are infected though heterosexual sex. The broad long-term goal of this project is to empower women to protect themselves from HIV infection through the development of improved vaginal ring formulations for microbicides based on the sustained-release drug delivery of antiviral agents. Our clinically proven sustained-release drug-delivery platform

uniquely allows us to deliver drug of both high and low aqueous solubility. We propose to utilize this platform technology to develop long-term vaginal-ring formulations for the potential microbicides tenofovir and TMC-120.

Title: **HIV Sexual Transmission in Mice: Study of Microbicide Efficacy**
P.I.: **Mary Jane Potash**
Institution: **St. Luke's–Roosevelt Institute for Health Sciences – New York, NY**
Grant No.: **1 R21 AI079792-01**
Award: **$18,182**

This application is submitted in response to RFA-AI-07-034. We have constructed a model of systemic infection of immunocompetent mice by chimeric HIV-1, EcoHIV. Our previous studies indicate that EcoHIV replicates in lymphocytes and macrophages in infected mice; infection in mice is sensitive to antiretroviral drugs; productive infection persists for months, inducing immune responses; and HIV-1 DNA vaccination can block infection in mice. Preliminary results reported here show that sexual transmission of EcoHIV in mice is rapid and efficient. Our overall goal in this application is to develop the mouse infection system to investigate the mechanisms of sexual transmission of HIV-1 as a platform to test the efficacy of candidate microbicides. The Specific Aims are: (1) To optimize conditions for sexual transmission of EcoHIV in mice and evaluation of interventions; (2) to identify the cell types involved in sexual transmission of EcoHIV; (3) to test the inhibition of sexual transmission of EcoHIV by antiretroviral-based microbicide; (4) To determine the HIV-1 subtype dependence of sexual transmission and efficacy of antiretroviral-based microbicides against different HIV-1 subtypes; and (5) to determine whether combination administration of an HIV-1 DNA vaccine followed by a microbicide can prevent sexual transmission of subtype B EcoHIV. Chimeric HIV-1 will be transmitted to conventional, immunocompetent female mice by mating with males infected through inoculation. Virus burden in multiple organs will be measured by real-time PCR and productively infected cells will be identified by flow cytometry and confocal microscopy. Accomplishment of Aims 1–3 will provide a firm foundation for and justification to extend the model to Aims 4–5 in studies directly relevant to the current HIV-1 epidemic and realistic means to control it. HIV-1 infection continues to spread worldwide, primarily by sexual transmission. The public health community responded to this pandemic by research into microbicides, compounds that women can apply to prevent transmission of HIV-1 during intercourse. Unfortunately, there is no simple way to determine which of many microbicides being developed actually blocks HIV-1 transmission before women begin their use. Some of the first to be tested by women in clinical trials actually increased HIV-1 transmission. This application is designed to develop a system for preclinical testing of microbicides in mice to determine their ability to reduce or prevent sexual transmission of HIV-1. We have shown that a form of HIV-1 that we genetically engineered to infect mice is very easily transmitted during mating. We propose to optimize this system to determine how well microbicides block sexual transmission of HIV-1. We shall also test in mice how the forms of HIV-1 that are widely distributed today can be controlled by microbicides. We have already shown that vaccination can reduce susceptibility to HIV-1 in mice. We also plan to both vaccinate mice and then treat them with microbicides to determine if it is possible to completely prevent sexual transmission of the virus. Our hope is that the model of sexual transmission of HIV-1 in mice can accelerate the development of safe and effective microbicides that can be used to control the AIDS pandemic.

Title: HIV Microbicides and the Vaginal Microbiome
P.I.: Claire M. Fraser-Liggett, Alison Motsinger-Reif, Steven L. Zeichner
Institution: Children's Research Institute – Washington, DC
Grant No.: 1 R21 AI079798-01
Award: $18,182

Vaginal HIV microbicides offer great promise to reduce HIV transmission, but Phase III microbicide trials have failed. In some studies, patients using the microbicides had higher HIV transmission rates than did subjects using placebos. There is no clear explanation for these failures, but one hypothesis holds that microbicides alter the vaginal microbial flora in ways that increase inflammation or activate potential HIV host cells, enhancing transmission. Studies examining the effects of microbicides on the vaginal flora found few significant effects on the microbiome, but they used conventional culture techniques. Recent studies using molecular, culture-independent techniques showed that the flora in many human microbial environments, including the vagina, is much more complex than previously appreciated and that conventional culture techniques only detect a small fraction of the microbes in the environment. We propose to use these new culture-independent techniques to explore the hypothesis that microbicides alter the vaginal microbiome in ways that can potentially enhance HIV transmission via these Specific Aims: (1) Examine the vaginal microbial flora before and after microbicide application in a CONRAD repeat Phase 1 study of nonoxynol-9, cellulose sulfate (CS), and placebo using Affymetrix Phylochip microarrays; (2) Examine the portfolio of expressed genes in the vaginal microbiome before and after microbicide application using microbial cDNA sequencing in the Phase 1 study; and (3) Examine the microbial species composition before and after microbicide application in the CONRAD CS Phase 3 study that failed using the Phylochip and direct 16S rRNA gene sequencing. The main milestone we propose to transition from the initial R21 phase of the project to the R33 phase is the demonstration that microbicide use leads to a significant alteration in the vaginal flora as assessed by the Phylochip. Determining whether microbicide application is associated with vaginal microbiome changes that could enhance HIV transmission would aid in the understanding of the failure of the previous Phase III trials and would help future microbicide development efforts because, if harmful changes in vaginal flora are associated with microbicide use, future microbicide development efforts would require careful measures to avoid inducing potentially harmful changes in the vaginal microbiome. Vaginal microbicides for the prevention of HIV sexual transmission offer great theoretical promise to reduce HIV sexual transmission and blunt the HIV pandemic, particularly in regions with the highest HIV prevalence rates. Unfortunately, several large late-phase trials of HIV microbicides have failed for unknown reasons, with the research subjects using the microbicides having rates of HIV transmission higher than subjects using placebos. We hypothesize that one factor contributing to the failure of the microbicides is that their use produces a harmful change in the microbial flora living in the vagina, which leads to inflammation or activation of the cells that HIV replicates in, increasing the risks of HIV transmission. In our study, we propose to use new molecular biological techniques to comprehensively catalog essentially all of the microbes living in the vagina and determine how the use of HIV microbicides alters the population of the microbes. Determining that the use of HIV microbicides lead to a significant, potentially harmful alteration in the population of vaginal flora would help explain the failure of the existing microbicides to prevent HIV transmission and may help enable the development of new, more effective HIV microbicides.

Title: Microbicide Properties of RT Inhibitor Combinations
P.I.: Michael A. Parniak
Institution: University of Pittsburgh – Pittsburgh, PA
Grant No.: 1 R21 AI079801-01
Award: $18,182

Topical microbicides are an important strategy to minimize heterosexual transmission of HIV. Several single-agent microbicides are in clinical trials, including one based on the nonnucleoside reverse-transcriptase inhibitor (NNRTI) UC781 that we discovered as a potential microbicidal agent. However, combination microbicides may be preferable, yet only a single combination microbicide is currently under evaluation. There is also an urgent need to identify new pipeline microbicidal agents. We have found that the nucleoside RT inhibitor (NRTI) 4′-ethynyl-2-fluoro-deoxyadenosine (4′E-2FdA) provides a potent and prolonged barrier to HIV-1 infection of cells in the subsequent absence of exogenous drug, a property previously only noted for NNRTIs such as UC781. The memory effect barrier is imparted by 4′E-2FdA at drug levels orders of magnitude less than those needed for protection by the nucleotide tenofovir, currently in clinical assessment for microbicide use. We hypothesize that microbicides comprising combinations of different classes of highly potent RT inhibitors, namely the NNRTI UC781 and an NRTI such as 4′E-2FdA, will provide an optimal barrier to HIV-1 transmission. We therefore propose these Specific Aims for this R21/R33 phased innovation application: R21 Aim (1) To evaluate the in vitro (cell-based) microbicidal properties of NRTI and UC781 alone and in combination. These studies include assessment of antiviral activity and memory effect protection imparted by NRTIs and UC781 alone and in combination using primary cells (PBMCs, CD4+ T-cells, and macrophages) and different HIV drug-sensitive and drug-resistant strains, isolates, and clades. R21 Aim (2) To elucidate the mechanism of 4′E-2FdA (and analogs) induced protective barrier or memory effect in HIV-susceptible cells. These studies include characterization of uptake, conversion to triphosphate, and intracellular stability of the NRTI-TPs, as well as detailed kinetic evaluations of the NRTI substrate activity with enzymes involved in metabolism of the NRTIs. R21 Deliverables: Identification of a lead NRTI and two backups for use with UC781 for development as a combination microbicide. R33 Aim (1) To formulate the NRTI/NNRTI combinations selected in the R21 phase into an appropriate delivery system for vaginal topical use. NRTIs and NNRTIs have different chemical properties; thus, appropriate delivery systems must be identified to enable incorporation and release of the active agents. We will prepare and evaluate both gel and rapidly dissolving film formulations for the combination microbicide. R33 Aim (2) To evaluate the anti-HIV microbicidal activity of formulated NRTI/NNRTI combinations in an ex vivo cervical explant tissue model. These studies will use a newly developed, physiologically relevant, polarized cervical tissue model to assess the impact of formulated microbicides alone and in combination on HIV transmission and infectivity. R33 Deliverables: Identification of an appropriate delivery formulation for the selected NRTI/NNRTI combination for entry into subsequent preclinical safety and efficacy studies. This project seeks to develop anti-HIV microbicides based on the nonnucleoside RT inhibitor UC781 in combination with novel 4′-substituted nucleosides, a combination found to provide profound and protracted protection of susceptible cells against HIV infection in vitro. Our studies will provide potent new formulations to the microbicide development pipeline for entry into clinical evaluation.

Title: New SHIV R5 env's (Based on all Subtypes) for Effective Microbicide Testing
P.I.: Eric J. Arts
Institution: Case Western Reserve University – Cleveland, OH
Grant No.: 1 R21 AI079852-01
Award: $18,182

SIV strains containing HIV-1 env genes (SHIVenv) have been successfully employed to infect macaques through intravenous and mucosal routes. These macaque models have been crucial for studies on HIV pathogenesis, vaccine, and microbicide testing. However, few SHIVenv strains can

maintain stable and prolonged infections. Several challenges are apparent in the testing of anti-HIV-1 microbicides and many of these stem from poor animal models to test efficacy. In the R21 proposal, we have outlined a system to construct and test the infectivity of SHIV based on the env and pol genes of subtypes A, B, C, and D from acute/early infections. In Aim 1, we will utilize a rapid yeast recombination cloning approach to shuttle approximately 400 HIV-1 env genes into an HIV-1NL4-3 or SIV backbones of mac239 and KB-9. The HIV-1 subtype A, C, and D env genes will be PCR amplified from the endocervix or blood of Ugandan and Zimbabwean women within 3 months or after 3 years of infection. Over 20 HIV-1 env chimeric viruses have already been constructed and tested using env genes from these patient samples. HIV and SIV env chimeric viruses will be included in subtype-specific pools if the clone is capable of replication on cell lines expressing human or rhesus CD4/CCR5 (respectively) and in human or rhesus PBMCs (respectively). In Aim 2, the pathogenicity of these pools will then be accessed (1) using vaginal explants and (2) through vaginal exposure in macaques. The clones that establish infection in both the explant tissue and macaques can then be reconstituted into the pathogenic subtype A, B, C, and D pools for the microbicide studies described in the R33 section of this proposal (Aim 3). First, we will determine if higher concentrations of cmpd167 or PSC- RANTES are required to inhibit the pathogenic subtype A, B, C, and D pools of HIV or SHIVs (as compared to the standard SHIVSF162-P3) in human or rhesus vaginal explant tissues. We will determine the identity of any HIV or SHIV clone(s) that are capable of infection even in the presence of the drug. These specific HIV-1 clones (produced from original DNA clones) can then be tested for sensitivity to CMPD167 and PSC-RANTES and to determine if infection was related to drug resistance. Finally and most importantly, microbicides CMPD167 and PSC-RANTES will be vaginally applied to rhesus macaques prior to exposure with the infectious subtype A, B, C, and D pools as well as the standard SHIVSF162-P3. We suspect that the majority of the treated macaques will be protected from SHIVSF162-P3 infection. In contrast, the protective effects of the microbicides may be reduced and in some animals, a slight delay in viremia (as compared to untreated animals) may be the result of infection by a specific clone in the SHIV pool with reduced sensitivity to CMPD167 and PSC-RANTES. Vaginal microbicides provide an excellent method to protect women from HIV-1 infection but testing these products prior to human use remains a challenge. A monkey species (e.g., rhesus macaques) and virus cousin of HIV-1 (SHIV) are used to test the level of protection by these compounds. In this proposal, we have designed new SHIVs that are more closely related to HIV-1 and provide more stringent testing of microbicides for future human use.

Immunity/Autoimmunity

Title: **Predictors of Pregnancy Outcome in SLE and APS**
P.I.: **Jane E. Salmon**
Institution: **Hospital for Special Surgery – New York, NY**
Grant No.: **2R01 AR049772-06**
Award: **$500,000**

Pregnancy complications in women with the antiphospholipid (aPL) syndrome (APS) and/or SLE include recurrent miscarriage, preeclampsia, placental insufficiency, and intrauterine growth restriction (IUGR). The mechanisms leading to placental and fetal injury in vivo are incompletely understood and treatment remains suboptimal. We have identified complement as an early effector in pregnancy loss and/or IUGR associated with placental inflammation in a mouse model of APS and shown that complement activation causes the release of antiangiogenic factors and abnormal placental development. The Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus (PROMISSE) study is a first-time effort to translate our novel findings in mice to humans and determine if elevations of complement split products predict pregnancy complications in patients with aPL antibodies and/or SLE. In the first 4 years of this prospective, observational study of pregnant patients grouped and analyzed according to the presence or absence of aPL antibodies and preexisting SLE, we have enrolled 342 pregnant patients

in seven centers; obtained detailed medical and obstetrical information monthly; and serially collected plasma, serum, DNA, RNA, and urine. Preliminary data suggest that elevated levels of complement activation products antecede and predict poor fetal outcome, consistent with our hypothesis that complement is a proximal mediator of fetal loss and IUGR. We propose to increase our target sample size from 400 to 700 pregnant patients to maintain study power given lower than expected outcome rates and to leverage the infrastructure and rich collection of patient data and samples by expanding the array of biomarkers and scope of adverse pregnancy outcomes. Specifically, in Aim 1, we will determine whether elevations of split products generated by activation of complement pathways predict poor fetal and/or maternal outcome in patients with aPL antibodies and/or SLE and, in Aim 2, whether the balance of circulating angiogenic and antiangiogenic factors predicts preeclampsia or delivery of IUGR infants. In Aim 3, a new direction, we will use the PROMISSE cohort to affirm in humans our recent findings in mice, that certain anti-DNA antibodies crossreact with N-methyl D-aspartate receptors (NMDAR) and cause neuronal death with ensuing cognitive and behavioral impairment. We propose to quantitate anti-NMDAR antibody levels throughout pregnancy in PROMISSE SLE patients and test the hypothesis that in utero exposure to maternal anti-NMDAR antibodies alters behavior and cognitive development in offspring by evaluating cortical function tasks in 12-month-old and 3.5-year-old children. This competitive renewal and extension of the PROMISSE study provides an outstanding opportunity to translate knowledge from mouse models to patients, define pathogenic mechanisms, identify predictors of poor pregnancy outcome in APL and/or SLE, and define novel therapeutic targets to prevent such outcomes. Patients with systemic lupus erythematosus and/or aPL antibodies are at increased risk for miscarriage, preeclampsia, and fetal growth restriction—major causes of maternal, fetal, and neonatal morbidity and mortality in the United States and worldwide—whose etiology and mechanism remain unknown and for which therapy is limited. In addition to causing placental dysfunction, maternal autoantibodies may also directly impair fetal brain development. Identification of biomarkers that predict poor pregnancy outcomes in these patients will elucidate mechanisms of disease, define targets for treating patients, and generate clinically applicable indicators to permit initiation of interventional trials in patients at greatest risk for pregnancy complications.

Title: **NARAC: The Genetics of Rheumatoid Arthritis**
P.I.: **Peter K. Gregersen**
Institution: **Feinstein Institute for Medical Research – Manhasset, NY**
Grant No.: **5 R01 AR044422-10**
Award: **$175,217**

This renewal application has the overall goal of identifying all of the major common genetic variants that underlie susceptibility to rheumatoid arthritis (RA) and to begin to identify rare susceptibility alleles, if they exist. In preliminary data, we have identified a number of candidate genes and regions on the basis of linkage analysis in multiplex RA families, as well as by whole-genome-association studies using approximately 550,000 SNPs on a panel of over 900 RA patients and matched controls. We now wish to identify the specific causal variants and understand their mode of action. In Specific Aim 1, we will identify the causal genetic variants within the common genes that confer risk for rheumatoid arthritis. We have already identified several genes and regions of interest, including STAT4 on chromosome 2q. In Specific Aim 1a, we will replicate these initial associations in case-control datasets totaling up to 5,000 patients. Various methods of genomic control for population stratification will be utilized for these replication studies. In Specific Aim 1b, we will carry out fine mapping of candidate regions. This will generally involve haplotypic analysis using custom sets of SNP markers. In Specific Aim 1c, we will utilize various approaches to identify the likely causative genetic variants in the gene under study. Examples of the approaches to be used in Specific Aim 1c are given for STAT4. In Specific Aim 2, we will apply a staged approach to identify gene–gene and gene–environment interactions that contribute to RA susceptibility. The top-performing markers in the univariate analyses of Specific Aims 1a and 1b will be examined for interactions using Classification and Regression Tree as well as traditional logistic regression methods. Top-performing models

will be tested in replication datasets of cases and controls. In Specific Aim 3, we will identify rare genetic variants that contributes to RA susceptibility. This specific aim is based on preliminary analysis indicating that slightly deleterious SNPs (sdSNPs) are a significant component of the genetic burden underlying complex disease. These sdSNPs are enriched in the low-frequency (MAF < 5%) component of the SNP population. We will initially investigate a limited number of candidate genes with high-throughput sequencing on the Solexa platform, along with followup analysis in large case-control datasets. Larger scale and more comprehensive approaches to this issue may be employed in the later years, depending on technical advances in the field.

Title: **International Research Registry Network for Sjögren's Syndrome**
P.I.: **Troy Daniels, John Greespan**
Institution: **University of California, San Francisco – San Francisco, CA**
Grant No.: **N01 DE-32636**
Award: **$300,000**

This contract focuses on the continuation of the International Research Registry Network for Sjögren's syndrome. As part of this registry, key elements being collected include using a set of standardized diagnostic criteria for the recruitment of Sjögren's syndrome patients, the collection, processing, storage, shipment, and analysis of clinical information and biological specimens (tissue, blood, saliva, and tears) from patients and families with Sjögren's syndrome and to disseminate to researchers clinical information and biological specimens from patients with Sjögren's syndrome. During this year, all research sites are focused on enrolling eligible study participants and have begun the process of 2-year recall evaluations of the pSSw and level 2 controls (called partial SS phenotype) groups. Enrollment of blood relatives and unrelated DNA control donors also is continuing. Currently, data analyses have begun to assess the progress toward developing a framework for the classification criteria.

Title: **OGT Overexpression in Women With Lupus**
P.I.: **Bruce C. Richardson**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **R21 AR056370-01**
Award: **$196,966**

Lupus afflicts women nine times more often than men. Estrogen contributes to lupus severity but does not completely explain the increased risk. Impaired DNA methylation, a repressive epigenetic modification, causes overexpression of T cell genes that contribute to lupus. DNA methylation also silences one X chromosome in women. CD40LG is an X-linked gene, known to be overexpressed in lupus and contribute to autoantibody production, on the inactive X demethylates and is overexpressed in women but not men with lupus, predisposing women to lupus. Other X-linked genes may also demethylate, predisposing to autoimmunity. The investigators surveyed methylation-sensitive T cell genes and identified O-linked N-acetylglucosamine transferase (OGT) as another X-linked gene overexpressed in demethylated female T cells. OGT couples N-acetylglucosamine (GlcNAc) to serines and threonines in a variety of proteins, including signaling molecules, modifying function in a manner analogous to phosphorylation and referred to as the hexosamine signaling pathway (HSP). HSP abnormalities are implicated in diabetes and neurodegeneration, but little is known regarding its role in T cells. The researchers hypothesize that demethylation of OGT on the inactive X results in overexpression in women, altering HSP signaling and contributing to pathogenic T cell function by modifying signaling. The investigators plan to test this hypothesis by: (1) Comparing OGT mRNA and protein levels in control and demethylated CD4+ and CD8+ T cells from healthy men and women with levels in CD4+ and CD8+ T cells from men and women with inactive lupus, active lupus, and disease/age controls, and confirming OGT demethylation by bisulfite sequencing; (2) Determining if OGT overexpression impairs T cell ERK, JNK, and/or p38 pathway signaling and modifies T cell gene expression patterns; and 3) Determining the functional significance of T cell OGT overexpression on

the development of autoimmunity using transgenic mice with a T cell-specific inducible OGT transgene. These studies will characterize a new pathway regulating T cell gene expression and characterize how abnormalities in the pathway may predispose women to autoimmunity.

Title: **Do Estrogen Receptors in B Cells and DC Mediate Sex Bias in Murine Lupus?**
P.I.: **Darise A. Farris, Susan Kovats**
Institution: **Oklahoma Medical Research Foundation – Oklahoma City, OK**
Grant No.: **1 R21 AI079616-01**
Award: **$198,750**

Systemic lupus erythematosus (SLE) is an autoimmune disease that preferentially affects women (9:1) in their reproductive years, indicating that sex-specific factors, including the sex hormone estradiol, play an important role in lupus pathogenesis. Murine models of lupus show natural earlier expression of disease and ensuing mortality in female mice. The Sle1 and Sle3 lupus susceptibility loci present in NZM2410 mice direct increased penetrance of disease in females, which is consistent with studies showing that elevation of systemic estradiol or exposure to estrogenic environmental compounds accelerate lupus development. An understanding of the mechanisms underlying the female preponderance of SLE requires that we precisely determine how endogenous estrogens and estrogen receptors (ER) regulate the function of immune cells such as B lymphocytes and dendritic cells (DC), which express ER and have been implicated in lupus pathogenesis. However, current models for the study of estrogen's effects on immune cells often have involved systemic exposure to supraphysiological levels of estradiol or global loss of ER, which creates hormonal imbalances. Elevated systemic levels of estradiol result in a profound depletion of hematopoietic progenitors, leading to alterations in numbers and phenotype of B cells and DC. To circumvent these effects of ER ligands on immune cell development, the study proposes to develop and use a novel model of murine lupus in which ER alpha expression may be specifically ablated in differentiated B cells or DC. The investigators will use lentiviral transgenesis to deliver Cre recombinase driven by the CD19 or CD11c promoters to lupus-prone B6.Sle13 bicongenic mice bearing a conditional ERalpha allele. This approach will determine whether aberrant DC or post-bone-marrow B cell phenotypes associated with the sex-sensitive Sle1 and Sle3 loci are mediated by direct effects of endogenous estrogens on B cells or DC. Aim 1 will determine if the elevated DC numbers or hyperactivated DC phenotypes leading to proinflammatory cytokine production in female B6.Sle13 bicongenic mice are a result of the direct action of endogenous estrogen on DC. Aim 2 will determine whether perturbations in transitional B cell subsets and subsequent enhanced loss of serologic tolerance in female B6.Sle13 bicongenic mice are a result of the direct action of endogenous estrogen on committed B cells and/or DC. The successful implementation of this lentiviral transgenesis strategy to delete ERalpha in specific cell types will establish a versatile model that could be used to study the role of ERalpha signaling in any cell type during the development of lupus nephritis. This knowledge will help to understand why autoimmune diseases preferentially afflict women.

Title: **Gender Bias in Lupus: Contribution of Sex Chromosomes**
P.I.: **Ram Raj Singh**
Institution: **University of California, Los Angeles – Los Angeles, CA**
Grant No.: **1 R01 AR056465-01**
Award: **$125,000**

Systemic lupus erythematosus (SLE) is an autoimmune disease that occurs more in females than males, at a ratio of 9:1. The female bias for the development of lupus is also seen in most genetically lupus-susceptible vertebrate animals. Sex hormones, sex chromosomes, or both may contribute to such sex difference. Extensive human and animal studies have investigated the role of gonadal hormones in the development of SLE. It has been difficult to dissect the role of sex chromosome X and Y genes, independent of sex hormones. The goal of the current proposal is to investigate the contribution of sex chromosomes in the gender bias in autoimmune diseases, such as systemic lu-

pus erythematosus, which affect women much more frequently than men, with a ratio of 9:1. The proposed studies will examine the influence of sex chromosomes and the female-biased episode of systemic lupus erythematosus and other autoimmune diseases. The significance of the experiments described in this application stems from better insights into a previously less investigated area of sex chromosomal contribution to the pathogenesis of SLE, as well as the potential for identification of novel targets for therapeutic intervention. The results of the proposed study will not only aid our understanding of lupus, but will also potentially lead to identification of newer targets of treatment.

Title: **Genetic Control of Renal Disease in Lupus-Prone Mice**
P.I.: **Marcia McDuffie**
Institution: **University of Virginia – Charlottesville, VA**
Grant No.: **1 R01 DK063005-01A1**
Award: **$125,000**

The purpose of this study is to understand the genetic basis associated with the expression of chronic glomerulonephritis in systemic lupus erythematosus. Protection from renal disease is associated with a complex immunological phenotype previously seen only in mice homozygous for inactivating mutations in Runx3, a gene that maps to the congenic interval. Runx3 is a master transcriptional integrator of transforming growth factor 2 signaling and multiple other cell type-specific signaling pathways in hematopoietic lineages. In addition to regulating survival and expansion of CD8+ T cells after activation, it plays a critical role in the development and activity of both macrophages and dendritic cells. The purpose is to determine whether any additional loci within the congenic interval encoding Runx3 contribute to the development of renal disease in this model and to test directly whether Runx3 expression from the NZM allele is specifically associated with susceptibility to chronic nephritis in lupus-prone NZM mice. For these studies, the investigators will engineer selective replacement of the interval encoding wild-type NZM Runx3 expression in vivo using both introgression and transgenic approaches. This project will identify specific genes that play a role in the progression of kidney damage once inflammation has been initiated by deposition of proinflammatory antigen-antibody complexes in the renal glomeruli and these studies will lead to improved understanding of the process and possibly will lead to novel therapeutic strategies for prevention of this devastating complication.

Title: **Complement Genetics and Clinical Variability of Systemic Lupus Erythematosus**
P.I.: **Chack Y. Yu**
Institution: **Research Institute at Nationwide Children's Hospital – Columbus, OH**
Grant No.: **1 R01 AR054459-01A2**
Award: **$125,000**

Comparative genomic hybridization (CGH) and molecular genetic experiments in the past few years have revealed an important phenomenon that has escaped the attention of most human geneticists: many genes in our genomes exhibit an inborn, interindividual variation in copy numbers. Many of those copy-number variation (CNV) loci include genes engaged in host–environment interactions, including those for immune responses and sensory functions. This discovery provides a new and exciting opportunity to examine the genetic basis of quantitative traits and complex diseases. The investigators hypothesize that gene CNVs and their associated polymorphisms create qualitative and quantitative diversities of their gene products. Such diversities can lead to differences in the intrinsic strengths of the immune system and result in varying susceptibilities to autoimmune diseases. This proposal seeks to investigate the roles of gene CNVs as genetic risk factors and disease modifiers for human SLE and patients with antiphospholipid antibodies. It will examine large cohorts of patients with SLE from different ethnic groups, female and male patients and their first-degree relatives, and unrelated race-matched controls. The significance of this study is that it is directed to two areas of the genome, the class III region of the MHC and FcR-HSP on ch 1 that are of considerable importance and interest in lupus, not only because they are involved in determining disease susceptibility,

but because their products are directly involved in innate immune effector functions in the tissue damage of lupus. Complement is implicated in lupus in several ways, including as an effector of immune complex injury, in the physiologic clearance of apoptotic cells, and as a gene in the MHC haplotypes that govern susceptibility. The knowledge to be gained can be highly relevant for more effective disease diagnosis and management of human SLE.

Title: **Innate Immunity and Allergy: Modulation by CTLA4**
P.I.: **Patricia W. Finn**
Institution: **University of California, San Diego – San Diego, CA**
Grant No.: **5 R01 HL081663-05**
Award: **$19,600**

The immune responses, including those modulated by Toll-like receptor (TLR) 4, set the stage for the adaptive allergic immune response. Our preliminary data have uncovered a potential novel immune pathway in the lung by linking TLR4 activation with upregulation of cytotoxic T lymphocyte antigen 4 (CTLA4). We demonstrate that CTLA4 signals can inhibit allergic responses in experimental asthma. Specifically, we show that blocking CTLA4 increases allergic inflammation, whereas overexpression of CTLA4 suppresses allergic inflammation. Two pathways extend these findings. First, innate TLR4 ligands upregulate CTLA4 both in vitro and in vivo and inhibit experimental asthma; and consistent with this observation, TLR4 mutant mice, which have deficient TLR4 responses, have enhanced allergic responses. Second, increased CTLA4, by CD45RB signals, decreases allergic responses. Because all three molecules (CTLA4, TLR4, and CD45RB) are expressed on T regulatory (Treg) cells, we will investigate the function of Tregs in the TLR4- and CD45RB-mediated inhibition of experimental asthma. Interestingly, our preliminary data also show that the endotoxin component lipid A, which is a TLR4 ligand, ameliorates experimental asthma. Consistent with our murine results, epidemiological studies show that exposure to an endotoxin-rich environment decreases the risk of childhood asthma. Furthermore, in our model, the depletion of Treg cells in vivo enhances allergic responses and blocks TLR4 ligand mediated inhibition of experimental asthma. These observations indicate that TLR4-mediated suppression of asthma is mediated by CTLA4-expressing Tregs. Thus, our hypothesis is that TLR4 attenuates the adaptive immune response by modulating upregulation of CTLA4, a critical pathway in the suppression of allergic inflammation. Aim 1 will characterize the role of CTLA4 in the suppression of allergic inflammation by determining how inhibition of CTLA4 (using anti-CTLA4 antibody or deficient mice) promotes allergic inflammation and how increased CTLA4 expression decreases allergic inflammation (using CTLA4 transgenics that overexpress CTLA4 or CD45RB antibody). Aim 2 will investigate whether TLR4 signals modulate CTLA4 expression in vivo. Aim 3 will determine the mechanisms by which TLR4 signals suppress allergic inflammation, including the cellular components (APC and T cells) and whether CTLA4 signals enhance TLR4-induced suppressor activity in allergic inflammation. Aim 4 will determine the molecular mechanisms by which TLR4 and CD45RB regulate CTLA4 expression in T cells by analysis of the CTLA4 promoter region. The objective of this project is to identify novel pathways and potential therapeutic targets by which innate immunity modulates allergic asthma.

Menopause

Title: **Study of Women's Health Across the Nation III**
P.I.: **Kim Sutton Tyrrell**
Institution: **University of Pittsburgh – Pittsburgh, PA**
Grant No.: **5 U01 AG012553-14**
Award: **$232,304**

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 followup examinations during which 895 (48%) women will have transitioned to postmenopause. This application requests funding to complete four additional followup 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 and urinary incontinence) and chronic diseases (e.g., fractures, diabetes, and hypertension). Specimens from the additional followup visits will continue to contribute to the SWAN biological specimen repository (annual blood and urine samples as well as DNA and immortalized cells). This is a separately funded component that broadens the opportunities to address future hypotheses about health and disease in aging women. As women reach the end of early postmenopause (2 years following the final menstrual period), we will shift from an annual to a biannual followup examination schedule with mail and telephone contact in the alternating years. This will permit cost-effective and less intensive followup. SWAN's organization and operations have been modified to enhance productivity and we are poised to publish important biological, symptom, and behavioral results pertaining to the menopause transition. With SWAN III, many of the original goals of SWAN will be brought to fruition. We will build upon the rich foundation developed during SWAN I and II and link these data to important menopause-related and health outcomes in SWAN II.

Title: **Neurobiology of the Menopausal Transition**
P.I.: **Yolanda R. Smith**
Institution: **University of Michigan at Ann Arbor – Ann Arbor, MI**
Grant No.: **5 R01 AG027675-03**
Award: **$47,579**

This project is part of an RFA jointly funded by NIA and ORWH on the biology of the perimenopause and its impact on health and aging in nonreproductive somatic and neuronal tissues. This and other projects funded under this RFA focus on increasing our understanding of the 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 is on how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within nonreproductive somatic and neuronal target tissues, the role of steroid hormone biosynthesis and/or metabolism within nonreproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across the perimenopause, and the role of aging on these pathophysiologic processes.

Title: **Biological Mechanisms of Arterial Stiffening with Age and Estrogen Deficiency**
P.I.: **Kerrie Moreau**
Institution: **University of Colorado – Denver, CO**
Grant No.: **5 R01 AG027678-03**
Award: **$47,579**

The purpose of this project is to determine the key functional mechanisms by which the loss of female sex hormones, particularly estradiol (E2), contribute to the age-related decrease in large-artery compliance. The overall hypothesis is that basal large-artery compliance will decrease in response to acute sex hormone suppression in pre- and perimenopausal women due in part to a decrease in vascular endothelial-dependent vasodilatory tone mediated, in part, to the development of vascular oxidative stress. However, E2 administration during sex hormone suppression will decrease vascular

oxidative stress, improve endothelial vasodilatory tone, and restore arterial compliance to basal levels. Secondary and tertiary hypotheses are that the changes in arterial compliance and vasodilatory function with sex hormone suppression and E2 will be related to unfavorable and favorable, respectively, changes in vascular endothelial cell protein expression, including oxidant (e.g., NADPH) and antioxidant (e.g., glutathione peroxidase) enzymes, vasoconstrictors (endothelin- 1), and estrogen receptor alpha (ERalpha). To test these hypotheses, healthy pre-, peri-, and postmenopausal women will be studied before and following acute sex hormone suppression (gonadotropin-releasing hormone antagonist [GnRHant]) with or without E2 add-back therapy. The GnRHant intervention will enable us to study the direct mechanisms associated with sex hormone deficiency and the E2 add-back intervention will enable us to isolate the independent effects of E2. Insight into the molecular mechanisms mediating the decrease in large-artery compliance will be obtained using a novel translational research technique to determine changes in vascular endothelial cell protein expression of genes involved in the regulation of cellular and systemic adaptations to aging and sex hormone deficiency, including oxidative stress, nitric oxide bioavailability, and the potent transcription factor ERalpha proteins. The results should provide new insight into the integrative biological mechanisms by which sex hormone deficiency modulates the age-related reduction in large-artery compliance in women as they transition through menopause.

Title: **Impact of Endocrine Aging on Brain and Immune Responses**
P.I.: **Farida Sohrabji**
Institution: **Texas A&M University Health Science Center – College Station, TX**
Grant No.: **5 R01 AG027684-03**
Award: **$47,579**

This project seeks to determine the mechanisms by which reproductive aging and estrogen replacement alter the inflammatory response and consequently the neuronal environment. In a series of studies, we have established that estrogen replacement in young adult animals increases trophic support in the forebrain and attenuates inflammation following neural injury. However, estrogen replacement at reproductive senescence, which is physiologically akin to menopause, fails to increase trophic factors and, paradoxically, increases inflammatory mediators following neural injury. Collectively, these data suggest that the timing of estrogen replacement in relation to reproductive aging may critically determine whether estrogen has a benign or deleterious outcome. Our central hypothesis is that the age-related decline in endogenous hormones triggers compensatory changes in estrogen receptor systems in specific immune cells, thus increasing the central and peripheral inflammatory response. This hypothesis will be tested in three Specific Aims, using animal and human tissue models that span the reproductive spectrum, namely, normally cycling (premenopause), irregularly cycling (perimenopause), and reproductive senescent (postmenopause). In Specific Aim 1, we will test the hypothesis that permissive changes in the blood–brain barrier will cause a more rapid and robust neural inflammation in reproductive senescent animals compared to normally cycling or irregularly cycling animals. Animals will be injected systemically with the bacterial pathogen lipopolysaccharide (LPS) and inflammatory mediators will be measured in peripheral organs and the brain. Additionally, we will examine endothelial cells of the blood–brain barrier for reproductive age-related changes in this barrier. In Specific Aim 2, we will determine if the inflammatory response of peripheral blood mononuclear cells (PBMC) is affected by clinically relevant variables, namely, the route of hormone administration (oral versus transdermal) and diet (regular versus high cholesterol). The response quotient, derived from an ex vivo LPS challenge assay, will be measured in rat and human blood samples to determine if salient lifestyle variables increase the risks associated with reproductive aging. Finally, in Specific Aim 3, we will test the hypothesis that compensatory alterations of the estrogen receptor system resulting from ovarian decline are a principal mechanism underlying estrogen's deleterious effects in reproductive senescence. Changes in the pattern and levels of estrogen receptor-alpha will be evaluated by immunohistochemistry and western blots, while functional changes will be evaluated using signaling arrays. Human and rodent PBMCs and rodent cerebral endothelial cells from each reproductive stage will be studied. Collectively, these studies will

test the hypothesis that in order for estrogen replacement to be beneficial, therapy must be initiated before compensatory responses to ovarian decline.

Title: **Effects of Chronic Estrogen on TIDA Neurons: Role of Cytokines and NO**
P.I.: **Puliyur S. Mohankumar**
Institution: **Michigan State University – East Lansing, MI**
Grant No.: **5 R01 AG027697-03**
Award: **$47,579**

This project is part of an RFA jointly funded by NIA and ORWH on the biology of perimenopause and its impact on health and aging in nonreproductive somatic and neuronal tissues. This and other projects funded under this RFA focus on increasing our understanding of the 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 is on how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within nonreproductive somatic and neuronal target tissues, the role of steroid hormone biosynthesis and/or metabolism within nonreproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across perimenopause, and the role of aging on these pathophysiologic processes.

Title: **Estrogen: Neuroprotection in the Perimenopause**
P.I.: **Anne M. Etgen**
Institution: **Yeshiva University – Bronx, NY**
Grant No.: **5 R01 AG027702-03**
Award: **$47,579**

Alterations in the hypothalamic-pituitary-ovarian axis in perimenopausal women are associated with multiorgan risk factors for disease, yet the biological mechanisms underlying this increased disease risk are largely unknown. This proposal addresses unanswered questions regarding the vulnerability of the middle-aged brain to global ischemia. In young female rats, the presence of physiological levels of estradiol before and after global ischemia, as might occur during cardiac arrest, reduces hippocampal CA1 neuron loss and associated cognitive impairments. Whether estradiol retains its neuroprotective actions in middle-aged females and whether the age-related decline in insulin-like growth factor-l (IGF-I) increases vulnerability to ischemia-induced neurodegeneration and cognitive impairment are unknown. This proposal aims to examine the roles of age, estrogen, and IGF-I in the survival and function of hippocampal neurons in a rat model of global ischemia. The underlying hypotheses are (1) that the middle-aged brain retains its responsiveness to the neuroprotective actions of estradiol if the duration of estrogen withdrawal is brief (critical period hypothesis) or circulating levels of IGF-I are maintained, and (2) that estrogen acts in the middle-aged brain to activate specific cell survival pathways and thereby intervenes in apoptotic cascades to prevent death of neurons otherwise destined to die. Specific Aim 1 uses stereological cell counting and behavioral tests to evaluate the outcome of global ischemia in middle-aged female rats that are intact, ovariectomized at various intervals prior to insult, or ovariectomized and treated with estradiol at various intervals after ovariectomy. If estradiol does not preserve neurons and cognitive function in older hormone-deprived animals, we will also determine if IGF-I can reinstate estrogen protection. Specific Aim 2 examines the apoptotic death cascades triggered by global ischemia and identifies the site at which estrogen intervenes in these cascades. We will examine (1) mitogen-activated protein kinase and cAMP response element binding protein at early times after ischemia, (2) the antiapoptotic gene Bcl-2 and activation of caspase 3 at later times after ischemia, (3) inactivation of Akt and subsequent activation of the forkhead transcription factor FKHRL1 at early times after ischemia. These experiments will provide new information on the potential for hormone therapy instituted during the perimenopausal transition to protect the brain from damage due to global ischemia.

Title: Menopause: Decreased Response to Increasing Inflammation
P.I.: Adriana Caterina Maggi
Institution: University of Milan – Milan, Italy
Grant No.: 5 R01 AG027713-03
Award: $46,199

The long-term goal of our research is to find treatments for the prevention of the disorders associated with menopause that are safer and more efficacious than present hormone replacement therapy (HRT). The failure of present HRT to fulfill medical and women's needs has to be ascribed to insufficient knowledge of the biology of menopause. The aim of our research is focused on understanding the consequences of cessation of ovarian function on the physiology of nonreproductive organs such as bone, brain, arteries, and fat. In particular, our studies and the studies proposed in the present project will focus on the effects of decreased estrogen production at menopause transition and after in nonreproductive organs. Given recent results demonstrating that in nonreproductive organs of fertile female mice, estrogen receptors (ERs) are activated by factors other than estrogens, our Specific Aim 1 will focus on assessing the extent to which ERs are transcriptionally active during the menopause transition and after. We will then try to identify the factor(s) involved in ER activation. This part of the project relates to questions that, so far, can be addressed only partially with current technology. The generation of a novel model reporter system, the ERE-Luc mouse, will enable us to precisely quantify ER activity in the organs of interest and facilitate the search for factors involved in ER unliganded activation. Specific Aim 2 will give us the opportunity to test an original hypothesis that would explain the widespread protective effects provided by the estrogen–ER system. This hypothesis is based on numerous very recent observations made in our group and several other groups showing that estrogens and cognate receptors may exert a strong anti-inflammatory action by inhibiting the immune response of cells of the monocyte lineage. We propose here that menopause consists of a decreased response to increased inflammation. We will test this hypothesis by direct assessment of ER relevance to macrophage activity through the generation of a novel conditional ERalpha KO mouse. Furthermore, using brain as a paradigmatic nonreproductive organ, we will measure basal and induced activity of brain inflammatory cells. Finally, the specific involvement of ER anti-inflammatory activity in the development of menopause-associated diseases will be tested with the study of the activity in menopause of another class of intracellular receptors devoted to the control of inflammation, the PPARs.

Title: Genetics of Reproductive Life Period and Health Outcomes
P.I.: Joanne M. Murabito
Institution: Boston University Medical School – Boston, MA
Grant No.: 1 R21 AG032598-01
Award: $213,900

The onset and conclusion of the reproductive life period are central factors influencing women's health later in life. Age at menarche and menopausal age affect risk for adverse health outcomes, including osteoporosis, cardiovascular disease, and breast cancer. Further scientific study is needed to elucidate the contribution of menopause and reproductive factors versus aging per se to health conditions common in women in later life. More than half the variation in age at menarche and menopause is attributable to genetic factors, yet the genes regulating these traits remain largely unknown. Data from longitudinal studies, such as the Framingham Heart Study (FHS), provide a wealth of data across adulthood, including reproductive factors, disease occurrence, and health behaviors in both women and men. The FHS is multigenerational and includes an extensive genetics database with extant genotyping from a 550K genome-wide scan obtained through the NHLBI's SNP Health Association Resource (SHARe) project. We postulate that novel genetic variants influencing the age at menarche and natural menopause can be identified using a dense genome-wide association study (GWAS). This proposal has the following Specific Aims: Aim (1) To identify genetic variants that influence age at menarche and age at natural menopause through a GWAS using extant 550K geno-

typing data and to perform in silico replication of significant associations in independent samples;, Aim (2) To examine the associations between genetic variants identified in Aim 1 and osteoporosis-related traits obtained using dual x-ray absorptiometry (DXA) and hand radiogrammetry in women as well as in men, and Aim (3) To perform a phenome scan using the genotypes associated with reproductive aging to identify other associated phenotypes that may provide additional insights into underlying biological mechanisms mediating the associations in women. The phenome scan will also be performed in men to explore sex-specific associations. The use of the 550K genotyping will be resource effective and our work will be publicly available through the FHS SHARe project located at the NCBI, permitting investigators around the world to embark on this research. Insights from this project may lead to the discovery of genes related to female reproductive aging and associated health outcomes and in turn lead to innovative diagnostic and therapeutic interventions to improve the overall health of women and possibly of men. Public health relevance: This project may lead to the discovery of genes related to female reproductive aging (menarche and menopause) and, in turn, provide insights into the pathophysiologic mechanisms leading to important health conditions later in life in women. The knowledge gained may lead to innovative diagnostic and therapeutic interventions to improve the overall health of women and possibly of men.

Mental Health

Title: **Antimanic Use During Pregnancy**
P.I.: **Katherine L. Wisner**
Institution: **University of Pittsburgh – Pittsburgh, PA**
Grant No.: **5 R01 MH075921-03**
Award: **$190,316**

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 postbirth. 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 have 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 nonexistent in women with either 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 decisionmaking to a new level of sophistication. This is a prospective, observational study of women with BP during pregnancy and the mother–infant pairs in the first postpartum year. We 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; and (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.

Title: **Sex Stress Emotional Disorders: Uniting Preclinical and Epidemiologic Research**
P.I.: **Elizabeth J. Costello**
Institution: **Duke University – Durham, NC**
Grant No.: **1 R21 MH083964-01**
Award: **$241,800**

The overall research objectives of this grant are to (1) bring together researchers who have made important advances in preclinical, experimental, and epidemiological research on stress responsitivity and psychopathology; (2) integrate their findings across disciplines and identify key questions related to gender disparities; and (3) plan a new program of research that takes a developmental approach to sex differences in stress responsivity as they affect depression and anxiety disorders in young people. The program of work has three aspects: (1) Two annual meetings of the workgroup members to identify key questions and plan a program of analysis of existing datasets. Meetings will be designed so that participants will learn as well as teach. At the second meeting, each workgroup member to commit to be first author on one or more specific papers. (2) A program of data analysis to be carried out at the Center for Developmental Epidemiology, Duke University. Analyses will be reported to the group by e-mail; group members can request additional followup analyses. Monthly conference calls between meetings will discuss output of analyses and plan further work. (3) An application for an Interdisciplinary Developmental Science Center for Mental Health (IDSC) or similar mechanism, to be submitted in October 2010. Questions to be addressed include the following: (1) What has been learned from animal research about sex differences in the effects of early adversity on neurobiological parameters, such as the HPA axis, the autonomic nervous system, and neural systems implicated in psychopathology? (2) What has been learned from laboratory and epidemiological research with humans about sex differences in the effects of early adversity on neurobiological parameters, such as the HPA axis, the autonomic nervous system, and neural systems implicated in anxiety and depression in the first decades of life? (3) Where do these bodies of work agree, where do they conflict, and where are they most important gaps? We expect that the answers to questions 1 to 3 will lead to the planning of a center application to focus on such questions as: (4) How does gender moderate the effects of childhood stress on mental health and neurobiological function, that is, what are the interactions between stress response systems and sex steroids? (5) What are the sex-specific effects of stress and life events in different developmental stages or during transitions between stages (e.g., puberty) on risk for anxiety and depression? (6) How does the timing of differences in onset of anxiety and depression in males and females relate to sex differences in psychological and neurobiological functioning?

Title: **Sex Differences in the Entorhinal Cortex**
P.I.: **Helen E. Scharfman**
Institution: **Nathan S. Kline Institute for Psychiatric Research – Orangeburg, NY**
Grant No.: **1 R21 MH084215-01**
Award: **$230,085**

There are many differences between females and males in the brain, behavior, and disease. One of these is established in rodents as well as man: spatial memory. What could be the underlying basis? In this project, we test the hypothesis that there are robust sex differences in the rodent medial entorhinal cortex that could explain sex differences in spatial memory. The medial entorhinal cortex seems a logical candidate, given that it is critical to spatial representation in the rat and lies in an ideal anatomical position because it is situated between hippocampus and cortex. Our preliminary data, using slices of entorhinal cortex, show a sex difference in evoked responses to afferent input in entorhinal cortex; in slices from females, responses are repetitive or prolonged relative to males,

a sex difference that is blocked by the NMDA receptor antagonist D-APV. When estrogen levels are high, these events are most robust, and when estrogen is low or a prepubertal animal is evaluated, they are relatively rare. We hypothesize that the responses of entorhinal neurons to afferent input are increased in the female rat relative to males, and this disrupts information processing and synaptic plasticity, that is, long-term potentiation (LTP). Because the difference appears to be localized to superficial layers, the perforant path projection to hippocampus may be selectively influenced, and this is important because the perforant path is the major afferent system to hippocampus from entorhinal cortex. In this proposal, we will establish the cellular physiology in slices of entorhinal cortex of female and male rats, test sex differences in LTP in the entorhinal cortex and hippocampus, and address whether puberty and estrogen are key factors, as preliminary data suggest. Together, the results will shed light on an area of the brain where sex differences are relatively unexplored and could have important implications for understanding cognitive function, as well as treating learning disorders. Public health relevance: This project will evaluate whether sex differences exist in a part of the brain where they have not previously been recognized, the entorhinal cortex, and address their implications. We hypothesize that there is increased neuronal activity in the female medial entorhinal cortex and this disrupts processing of new information, particularly spatial information. Based on preliminary findings, estrogen appears to play a key role by facilitating NMDA receptor-mediated activation of entorhinal neurons. The implications are important because they could help address sex differences in cognitive function and lead to new considerations for treatment of learning disorders.

Title: **Emotions Are Emergent Events Constrained by Affective and Conceptual Processes**
P.I.: **Lisa Barrett**
Institution: **Boston College – Boston, MA**
Grant No.: **5 DP OD003312-02**
Award: **$390,000**

Emotional states are central to mental and physical health. NIH invests tremendous resources in research on emotion, much of it devoted to animal models. Ironically, this research is guided by a scientific paradigm that is grounded in human experience. People experience fear and see it in others, so scientists assume there must be a literal (modular) neural circuit for fear in the mammalian brain. Rats freeze when they hear a tone paired with a foot shock, so they are presumed to be in a state of fear (versus surprise, anger, or even a general state of alarm) and undergoing "fear learning." Scientists also presume that a map of the neural circuitry of freezing behavior will yield a neural mechanism for fear that is largely preserved in humans, and a decade of neuroimaging studies have focused on locating a homologous neural circuit in the human brain. In the past 5 years, I have traced the roots of this "natural kind" model, conducted a comprehensive review of the literature to examine its veracity, and found it wanting (Barrett, 2006a). In response, I have fashioned a new systems-level model, called the Conceptual Act Model, grounded in the neuroanatomy of the human brain. My model parsimoniously incorporates neuroscience findings from rats, primates, and humans and explains the mechanisms that produce the range and variety of behavioral and introspective instances that we call "emotion" (Barrett 2006, b, c; Barrett, Mesquita, Ochsner, & Gross, 2007; Barrett, Ochsner, & Gross, 2007; Duncan & Barrett, 2007). The Conceptual Act Model asks different—and perhaps better—questions about what emotions are and how they function in mental and physical health. The NIH Director's Pioneer Award will allow me the intellectual freedom and resources to continue building evidence for the Conceptual Act Model of emotion, thereby shaping a new paradigm to guide the scientific study of emotion.

Title: Oral Self-Dosing/Behavioral Assessment
P.I.: Michael R. Weed
Institution: Johns Hopkins University - Baltimore, MD
Grant No.: 5 U01 MH075378-04
Award: $20,000

Approximately 3–5% of children ages 3–17 in the United States are diagnosed with attention deficit/hyperactivity disorder (ADHD), and 4 million children are medicated chronically to treat ADHD. Methylphenidate (MPD) and amphetamine (Amph) control ADHD in the majority of those treated. However, there are concerns over long-lasting developmental changes in behavior, neurochemistry, growth rates, and potential for substance abuse in children treated with MPD or Amph. The proposed research will test the hypothesis that chronic MPD or Amph results in long-term behavioral, physiologic, and neurochemical alterations in preadolescent rhesus monkeys. Oral self-dosing techniques will provide nonstressful administration of MPD or Amph in doses within the therapeutic window for treatment of ADHD in children. Specific Aim 1 will determine if chronic MPD or Amph alters physiological development of preadolescent monkeys, including circadian rhythms, body weights, food intake, and body growth rate. After 18 months of MPD or Amph administration, tests for behavioral sensitization to amphetamine will also be performed. Specific Aim 2 will test the hypothesis that chronic MPD or Amph alters the developing central nervous system, including chronic activation of microglia and long-lasting alterations in dopaminergic function in preadolescent monkeys. Measures of dopaminergic function will include levels of dopamine transporters, dopamine D2 receptors, and amphetamine-stimulated dopamine release. Specific Aim 3 will determine the effects of chronic MPD or Amph on development of executive function, including inhibitory control and attentional set shifting. Specific Aim 4 will test the hypothesis that monkeys previously exposed to MPD or Amph have a higher propensity to self-administer cocaine. The proposed studies provide a comprehensive interdisciplinary evaluation of the chronic effects of therapeutic doses of MPD and Amph in preadolescent nonhuman primates. These studies will advance understanding of the long-term neurochemical, behavioral, and physiologic effects of chronic low-dose stimulant treatments and have direct translational application to the medication of children with ADHD.

Musculoskeletal Systems

Title: A Study of Reduced Bone Quality as a Cause of Fractures
P.I.: Creighton University – Omaha, NE
Institution: Robert R. Recker
Grant No.: 1 R01 AR054496-01A2
Award: $125,000

Bone quality factors other than bone density determine more than half of the propensity to fracture in patients suffering from osteoporosis. A number of candidate bone quality defects have been described, but their relative importance in patients who are suffering from fractures has not yet been explored. The purpose of this study is to characterize these defects in bone quality that contribute to low-trauma fractures in postmenopausal women. In postmenopausal women with osteopenia, measured values of bone quality factors differentiate those who sustain low-trauma fractures from those who do not. Postmenopausal women with osteopenia who sustain low trauma fractures have (1) increased bone remodeling, (2) reduced trabecular connectivity, and (3) defective intrinsic material properties of bone tissue. Moreover, postmenopausal women with low-trauma fractures have reduced bone quality, as indicated by a battery of clinical measures, compared to those that have not fractured. The purpose of this human study is to characterize defects in bone quality, independent of bone mass, that contribute to low-trauma fractures in postmenopausal women. Whatever the outcome, this project will feed information to investigators on future directions of basic research on the defects in bone quality that weaken the skeleton in humans. This project will point the direction for research on the cause of fractures and the development of diagnostic methods to predict risk of frac-

tures before they occur and on development of surrogate measures for fracture that could be used in human treatment trials.

Title: **Estrogen Effects on Atrophic Skeletal Muscle**
P.I.: **Marybeth Brown**
Institution: **University of Missouri–Columbia – Columbia, MO**
Grant No.: **1 R21 HD058834-01**
Award: **$125,000**

In the physical rehabilitation setting, women typically demonstrate less return to function than men. Estrogen (E2) deficiency might contribute to the gender discrepancy, as low E2 levels have been linked to a decrease in lean-muscle mass. Of the more than 2 million women receiving postoperative or rehabilitation care each year, approximately half of them are "estrogen deficient" due to natural menopause, surgical menopause, and normal hormonal rhythms disrupted by illness or trauma. The purpose is to study whether E2 therapy, rehabilitation exercise, and combined E2 therapy + exercise promote regrowth of atrophied skeletal muscle in estrogen-deficient rats; it also will examine if E2 effectiveness is mediated through the alpha or beta estrogen receptor. The overall goal of this translational research project is to use animal models to determine if exogenous E2 should be considered as an adjunct to standard physical rehabilitation for E2-deficient women.

Title: **Bone-Sparing Effects of Soy Phytoestrogens in Menopause**
P.I.: **Silvina Levis**
Institution: **University of Miami School of Medicine – Coral Gables, FL**
Grant No.: **5 R01 AR048932-05**
Award: **$97,100**

Women will live a third of their lives in 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. We propose to conduct the 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. Our 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: **Osteoarthritis Initiative (OAI), Public–Private Partnership with NIAMS, NIA, ORWH, NCCAM**
Award: **$800,000**

Network update: The OAI is now in the second half of what has been a highly successful project in terms of enrollment of the cohort, data collection, retention, and followup and distribution of public use datasets. Subject recruitment was completed, with close to 5,000 participants, aged 50 and older, who have a high risk of developing symptomatic knee osteoarthritis. Numerous releases of data have occurred and continue to occur at 3–6-month intervals. First-year followup visits are

completed. Second- and third-year followup visits are well underway. Completion of this study is anticipated in late 2010. Four clinical centers enrolled subjects, with 58% women and 21% minority participants (predominantly African-American). The progression cohort (those with existing osteoarthritis) make up 29% of the cohort and the incidence (those at risk of osteoarthritis) 69% and a "nonexposed" control group make up the remaining 2%. Currently, the followup exams at 24 months are on track to exceed by several percentage points the 85.5% projected. The 36-month visits are underway and the 48-month visits have also begun. By achieving these basic operational objectives, the OAI is on course to achieve its primary scientific goals by providing longitudinal imaging, biochemical, and clinical data and endpoints to investigators. There have been several data releases to the OAI Online web site (www.oai.ucsf.edu) over the past 2 years. As of fall 2007, there are over 800 registered users of the OAI online, and OAI clinical datasets have been obtained by 110 investigators worldwide. Hard drives containing knee image sets from 200 to 5,372 patient visits have been delivered to 63 investigators.

Neurology/Neurosciences

Title: **Pathophysiology of MeCP2 Spectrum Disorders**
P.I.: **Melissa B. Ramocki**
Institution: **Baylor College of Medicine – Houston, TX**
Grant No.: **1 K08 NS062711-01**
Award: **$125,000**

MeCP2 spectrum disorders include classic Rett syndrome, females with Rett syndrome variants, Angelman-like phenotypes, autism, mental retardation, learning disabilities, attention disorders, as well as males with Rett syndrome, fatal infantile encephalopathy, mental retardation with tremors/movement disorders and/or seizures, or early-onset psychosis in the form of bipolar disorder or schizophrenia. The mechanism by which alterations in the MeCP2 protein itself, or the dosage of MeCP2 protein, result in the various disease phenotypes is unclear. There are three Specific Aims; the first two are to identify changes in gene expression patterns between wild-type and MeCP2 knockout, mutant, or overexpressing mice, while the last Aim is to use HDAC inhibitors as potential treatments for the MeCP2 mice.

Title: **Sex Differences in Episodic Neurologic Disease**
P.I.: **Hyder A. Jinnah**
Institution: **Johns Hopkins University – Baltimore, MD**
Grant No.: **1 R21 NS061349-01A2**
Award: **$125,000**

This proposal examines the hormonal mechanisms that underlie sex differences in neurological disorders. The rocker mouse model of paroxysmal dystonia is employed where adult females, but not males, display dystonia. The anticipated results may provide significant insights into the origin of sex differences in the occurrence of movement disorders in humans. Sex influences the clinical manifestations of many human diseases. Sex may affect prevalence, severity, or even specific clinical manifestations. At present, specific mechanisms responsible for these sex differences in so many different diseases are not well understood. One reason for the limited understanding is that the types of experimental manipulations most helpful for definitively delineating the responsible mechanisms cannot be conducted in affected human populations. In this setting, animal models can be valuable for preliminary identification of mechanisms that subsequently can be verified in humans. Gender influences the clinical manifestations of many human diseases. In humans, different mutations in the same gene are responsible for a variety of neurological disorders, including episodic ataxia, familial hemiplegic migraine, spinocerebellar ataxia 6, epilepsy, benign paroxysmal torticollis of infancy, and focal or segmental dystonias. In humans, several such disorders demonstrate sex differences in expression. In the rocker mutants, transient attacks of disabling motor dysfunction resembling hu-

man paroxysmal dystonia occur frequently in female rockers, but are absent in males. Ovariectomy eliminates attacks in females, suggesting an ovarian influence. The goal of the current project is to begin to dissect the hormonal influences that could be responsible for the sex differences in these mice. Gender may affect prevalence, severity, or even specific clinical manifestations. The proposed studies are devoted to the development of a novel monogenic mouse model for elucidating the contributions of sex steroid hormones to the differences seen in so many human neurological diseases.

Obesity/Overweight

Title: DHA, Inflammation, and Insulin Sensitivity in Obese Pregnant Women
P.I.: Debra Ann Krummel, Theresa L. Powell
Institution: University of Cincinnati – Cincinatti, OH
Grant No.: 1 R21 HL093532-01
Award: $234,000

Obesity prevalence is increasing worldwide and with the difficulty of treating this condition, the need for early intervention is urgent. Obesity in pregnancy is rapidly becoming a major obstetric complication, because it increases the risk of gestational diabetes and preeclampsia and predisposes the mother to later metabolic and cardiovascular disease. A common problem for the baby is fetal overgrowth, which is associated with traumatic birth injuries and the development of the metabolic syndrome in childhood or later in life. The obese, pregnant woman has increased serum levels of proinflammatory cytokines and low circulating levels of adiponectin, leading to decreased insulin sensitivity, which has been suggested to link obesity in pregnancy to metabolic and cardiovascular disease later in life. Fetal growth is determined by placental nutrient supply and our preliminary data show that placental nutrient transport is increased in obesity. Upregulation of placental nutrient transporters in obesity may be caused by the abnormal maternal metabolic profile, because high insulin and proinflammatory cytokines and low adiponectin have been shown to stimulate placental nutrient transport. Approximately one-third of all women enter pregnancy obese, and despite the serious adverse consequences for the health of the woman and her child, no specific treatment is currently available. The aim of the study is to supplement the diet of obese pregnant women with docosahexaenoic acid (DHA), a safe, low-cost, readily available dietary component that we have shown is extremely low in the diet of our midwestern urban population (10% of recommended levels for pregnancy). This omega-3 fatty acid has been shown to have a significant impact on improving insulin sensitivity and circulating levels of proinflammatory cytokines and adiponectin in nonpregnant obese women. DHA has been studied extensively as a dietary supplement in pregnancy as a potential mechanism to improve cognitive function in children. However, the effect of DHA maternal metabolic status and placental function has not been previously reported. The study hypothesizes that DHA supplementation will improve maternal insulin sensitivity, reduce proinflammatory cytokines, increase circulating adiponectin, downregulate placental nutrient transport, and reduce fetal growth. The approach for this pilot study will be to recruit 90 obese (BMI 30–45), pregnant women in midgestation and randomize these subjects into placebo or DHA treatment (800 mg/day) groups. Subjects will be studied again in late gestation after 12 weeks of supplementation. Aim 1 will determine the effect of DHA supplementation on maternal inflammatory status and insulin sensitivity. Aim 2 will establish the impact of DHA supplementation in obese pregnant women on placental nutrient transport and fetal growth.

Title: Histaminergic Pathways and Energy Intake in Obese Women
P.I.: J. Yanovski
Institution: Sackler School of Medicine – Tel Aviv, Israel
Award: $80,000

Pain

Title: Using fMRI To Evaluate CBT Treatment Response for Patients with Chronic Pain
P.I.: Magdalena R. Naylor
Institution: University of Vermont and State Agricultural College – Burlington, VT
Grant No.: 1 R21 AR055716-01A1
Award: $150,000

The primary goal of this revised R21 application is to investigate whether a psychotherapeutic approach, group cognitive behavioral therapy (CBT), modifies the dysfunctional emotional and sensory neural circuitry associated with chronic pain, as examined by functional magnetic resonance imaging (fMRI). We propose to apply previously tested and accepted paradigms for symptom provocation (acute pain and negative emotional stimuli) to investigate CBT effects on neural correlates of chronic pain. Because chronic pain is not just an isolated sensory event, but rather a complex sensory and emotional experience, it is reasonable to expect that an intervention that improves chronic pain, such as CBT, will alter responses to both painful and emotionally provocative stimuli and thus the underlying neural circuitry. The efficacy of a group CBT treatment modality for chronic pain patients has been well established. In addition, our fMRI pilot study results revealed that the exaggerated amygdala response to negative emotional stimuli in chronic-pain patients was normalized after 12 weeks of group CBT, suggesting that CBT may affect at least the emotional component of the pain process. Forty subjects who meet inclusion and exclusion criteria for the fMRI study will be randomly assigned to two study conditions: 12-week group CBT treatment condition and attention control condition. Each participant will undergo two fMRI examinations (before and after group interventions) to explore two study goals: (1) whether CBT treatment changes the function of brain neural circuitry in response to application of acute noxious stimuli and emotional (fearful) stimuli and (2) whether there is a relationship between altered activation in brain areas associated with the attentional, affective, and sensory aspects of chronic pain and quantifiable improvement in clinical measures reported at the conclusion of group CBT. Our approach is novel as there are no published studies that explore the neurobiological effects of psychotherapeutic approaches in chronic pain. By combining a noxious pain stimulation paradigm, an emotional stimulation paradigm, and brain imaging, and putting this approach into a clinical framework, we will open important new avenues of research on chronic pain. Our approach may represent a valuable strategy for advancing our understanding of the neurobiology of emotional control related to pain and the effects of cognitive–behavioral therapy in the group setting. Measuring directly the effects of CBT on brain function could ultimately improve clinical decisionmaking and contribute to development of the individualized treatment of patients with chronic pain. Public health relevance: This proposed study will test the hypothesis that CBT can modify the dysfunctional neural circuitry associated with chronic pain. Because chronic pain is considered a complex sensory and emotional experience, we expect that an intervention such as CBT could alter patients' responses to both painful and emotionally provocative stimuli and, thus, the underlying neural circuitry tested by fMRI. We believe that our paradigm represents a valuable strategy for advancing our understanding of the neurobiology of emotional control related to pain and the effects of CBT in the group setting.

Physical Activity

Title: Sustained Skeletal Benefits of Adolescent Exercise
P.I.: Tamara A. Scerpella
Institution: Upstate Medical University – Syracuse, NY
Grant No.: 1 R01 AR054145-01A2
Award: $125,000

Exercise and physical activities play important roles in bone growth and development. The optimal timing and type of exercise for bone density and quality still remain to be investigated. Whether exercise in earlier life has a lasting effect on bone health in adulthood is a very important question and needs to be addressed. Therefore, this research uses an extreme-exercise model to longitudinally investigate efficacies of high-impact exercise on bone mass and bone quality at different puberty stages and in young adulthood. The study results may help form evidence-based recommendations for improving bone health in young girls and women. A 6–10-year longitudinal study of approximately 60 late-adolescent female gymnasts and nongymnasts will be extended and supplemented by the addition of 80 early-adolescent girls (gymnasts and nongymnasts). Annual dual-energy x-ray absorptiometry scans of the forearm, proximal femur, lumbar spine, and total body, with concurrent peripheral quantitative computed tomography scans of the forearm, will evaluate skeletal geometry, density, and strength. Diet, gymnastics and other physical activity, anthropometry, and Tanner self-stage will be assessed semiannually; muscle strength will be measured annually to coincide with skeletal scans.

Title: Young Adult Environmental and Physical Activity Dynamics
P.I.: Barry M. Popkin
Institution: University of North Carolina, Chapel Hill – Chapel Hill, NC
Grant No.: 5 R01 CA109831-05
Award: $97,100

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. We will use 4 study years (1985, 1992, 1995, and 2001) of the Coronary Artery Risk Development in Young Adults Study (CARDIA), a longitudinal study of the antecedents of 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. We will use complex longitudinal and spatial analytical models 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. We will model physical activity as a function of covariates, some of which may be endogenous choices made by the individual. We will examine race/ethnic differentials in these effects and the impact of the environment shifts over time and through the lifecycle. The focus will be on examining how modifiable environmental factors will affect physical-activity patterns among underserved communities and, consequently, will reduce ethnic and socioeconomic differentials in health status. The longitudinal analysis and the vast array of environmental measures used, coupled with the very high-quality physical activity measures of CARDIA, allow us to capture the effects of the environment (and changes in location) on physical-activity shifts. No study heretofore has had large-scale groupings and in-depth environmental measures over time to examine these issues in a dynamic manner.

Title: Mediators and Moderators of Exercise Behavior Change
P.I.: Sara Anne Tompkins
Institution: University of Colorado at Boulder – Boulder, CO
Grant No.: 5 R01 CA109858-05
Award: $92,977

Rates of cancer and cardiovascular disease have shown very little improvement over the past two decades, and the incidence of type 2 diabetes mellitus is increasing at an alarming rate. Recent reports estimate that approximately 30% 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 (Booth et al., 2002). 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 (CDC, 2001), and 40% of the population is completely sedentary (USDHHS, 1996). 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 (c.f., Marcus et al., 1998) is successful at helping sedentary individuals initiate and maintain a moderate-intensity physical-activity regimen, compared to a health and wellness control intervention; (2) Increases in positive attitudes, perceived normative support, self-efficacy, and intentions to exercise will mediate the effectiveness of the intervention; (3) Increased positive mood and better temperature, stress, and lactate regulation immediately after exercise challenge (assessed in the laboratory) will moderate the effectiveness of the intervention; and (4) Secondarily, we 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: Social Cognitive Theory and PA After Endometrial Cancer
P.I.: Karen M. Basen-Engquist
Institution: University of Texas M.D. Anderson Cancer Center – Houston, TX
Grant No.: 5 R01 CA109919-05
Award: $95,215

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 survivor 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 and sixty-seven sedentary Stage I–IIIa endometrial-cancer survivors will be recruited to participate in this 6-month study. Participants will complete fitness tests, questionnaires, and cognitive tests every 2 months to assess functional capacity and efficiency, physical activity, and social cognitive theory-related variables. All participants will receive an intervention to increase their physical activity consisting of a customized exercise prescription, telephone counseling, and written materials. Results of the study will provide a rigorous test of social cognitive theory as it is applied to physical activity and will inform the development of effective interventions for cancer survivors.

Reproductive Health/Developmental Biology

(Please see Menopause section for additional projects)

Title: **Genetics of Reproductive Life Period and Health Outcomes**
P.I.: **Joanne M. Murabito**
Institution: **Boston University Medical Campus – Boston, MA**
Grant No.: **1 R21 AG032598-01**
Award: **$216,900**

The overall research objective of this grant is to elucidate the contribution of menopause and reproductive factors versus aging per se to health conditions common in women in later life. More than half the variation in age at menarche and menopause is attributable to genetic factors, yet the genes regulating these traits remain largely unknown. Data from longitudinal studies, such as the Framingham Heart Study (FHS), provide a wealth of data across adulthood, including reproductive factors, disease occurrence, and health behaviors in both women and men. The FHS is multigenerational and includes an extensive genetics database with extant genotyping from a 550K genome-wide scan obtained through the NHLBI's SNP Health Association Resource (SHARe) project. We postulate that novel genetic variants influencing the age of menarche and natural menopause can be identified using a dense genome-wide association study (GWAS). This proposal aims to identify genetic variants that influence age at menarche and age at natural menopause through a GWAS using extant 550K genotyping data, to perform in silico replication of significant associations in independent samples, to examine the associations between genetic variants and osteoporosis-related traits obtained using dual x-ray absorptiometry (DXA) and hand radiogrammetry in women as well as in men, and to perform a phenome scan using the genotypes associated with reproductive aging to identify other associated phenotypes that may provide additional insights into underlying biological mechanisms mediating the associations in women. The phenome scan will also be performed in men to explore sex-specific associations. The use of the 550K genotyping will be resource effective and our work will be publicly available through the FHS SHARe project located at the NCBI, permitting investigators around the world to embark on this research. Insights from this project may lead to the discovery of genes related to female reproductive aging and associated health outcomes and, in turn, lead to innovative diagnostic and therapeutic interventions to improve the overall health of women and possibly of men.

Title: **The Role of GPR54 Signaling in Pubertal Disorders**
P.I.: **Suzy Bianco, Drumond Carvalho**
Institution: **University of Miami School of Medicine – Coral Gables, FL**
Grant No.: **1 R21 HD059015-01**
Award: **$191,249**

The long-term goal of this project is to identify factors that regulate the timing of pubertal onset and reproductive maturation. The identification of GPR54, a G-protein-coupled receptor, and its ligand, kisspeptin, as upstream regulators of GnRH secretion has led to intense research to elucidate their roles in the regulation of the reproductive axis. Inactivating mutations in GPR54 cause failure to undergo puberty and infertility. In contrast, early stimulation of this receptor triggers precocious puberty in mice. Preliminary results indicate that GPR54 is desensitized and internalized in response to continuous kisspeptin stimulation and that a GPR54 amino acid substitution identified in a female patient with central precocious puberty (a disorder with disproportionately high female incidence) increases GPR54 responsiveness by delaying the desensitization of the receptor. The hypothesis is that the timing of signaling and desensitization of GPR54 is critical for its role in controlling puberty and reproduction and that amino acid substitutions in GPR54 may affect its responsiveness by interfering with signaling or desensitization, thereby contributing to the clinical presentation. Although G-protein-coupled receptor desensitization is generally strongly regulated, no data have been published on GPR54 desensitization. The short-term goal of this project is to define the mechanisms

underlying GPR54 desensitization in order to understand how genetic mutations of this receptor affect these mechanisms and, hence, the timing of pubertal onset and sexual maturation. A thorough understanding of the mechanisms underlying GPR54 signaling may uncover the basis of gender differences in normal and abnormal pubertal development, as well as reveal a new array of potential targets of pharmacological manipulation for the treatment and prevention of abnormal pubertal development and possibly other reproductive disorders.

Title: **Thyroid Function and Pregnancy**
P.I.: **Menachem Miodovnik**
Institution: **Georgetown University – Washington, DC**
Grant No.: **5 U10 HD047890-05**
Award: **$135,000**

Thyroid hormones are required for homeostasis of all cells. They represent the major metabolic hormones, because they target virtually every tissue, as well as modulating protein, lipid, and carbohydrate metabolism and influencing cell differentiation, growth, and development. Hypothyroidism has been reported to occur in up to 15% of adults, with severe forms of hypothyroidism observed in about 2%. Hypothyroidism complicates pregnancy; thyroid-stimulating hormone (TSH) concentrations below 6 early in pregnancy are associated with less than 1% of fetal deaths; in contrast, the fetal death rate is ~4% if TSH concentrations are above 6. Maternal hypothyroidism can have a significant impact on fetal growth and development, most importantly producing an adverse impact on fetal central nervous system development. Consequently, maternal hypothyroidism represents a public health problem in the United States as well as in developing countries. Despite the public health impact of maternal hypothyroidism, essentially nothing is known about the pharmacokinetics and pharmacodynamics of thyroid hormones during pregnancy. Pilot work among the Obstetrical Pharmacology Network sites over the past year has begun to describe some aspects of the pharmacokinetics and pharmacodynamics of levothyroxin during pregnancy using a molecule with a stable label. The study is designed to determine the pharmacokinetics of levothyroxin, as represented by area under the concentration vs. time curve (AUC), after oral ingestion of carbon-13-labeled levothyroxin by hypothyroid women during pregnancy. The women will serve as their own controls and will be studied in the nonpregnant state.

Title: **Washington Obstetric–Fetal Pharmacology Research Unit**
P.I.: **Menachem Miodovnik**
Institution: **Georgetown University – Washington, DC**
Grant No.: **5 U10 HD047890-05**
Award: **$49,000**

The Washington Obstetric Pharmacology Research Unit (WOPRU) represents a collaboration among two universities and four medical centers in the Nation's capital that is uniquely positioned to use population pharmacokinetic, pharmacokinetic-pharmacodynamic, clinical trials simulation, cutting-edge in vivo and in vitro techniques to assess the clinical pharmacology of important therapeutic agents and their effects in pregnant women and their offspring. Specifically, the WOPRU combines the basic research resources of Georgetown University (lead agency) and George Washington University (GWU) with the clinical strengths of MedStar Health (Washington Hospital Center and Georgetown University Hospital), GWU Hospital, and Children's National Medical Center. Our 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 our diverse community. The faculty of the WOPRU represents a team of highly motivated basic scientists and clinical investigators who are enthusiastically approaching the prospect of becoming a new center

for OPRU. They are experienced investigators in a multitude of basic science and clinical disciplines with a unique combination of strengths in pharmacometrics, pharmacodynamics, pharmacogenetics, drug metabolism, therapeutic drug monitoring, proteomics, genomics, and biostatistics in conjunction with significant experience in multicenter clinical trials. The administration and the basic science and clinical investigators of the WOPRU institutions are unanimous in their eagerness to support and participate in the future OPRU network.

Title: **Obstetric–Fetal Pharmacology Research Units Network**
P.I.: **Gary D. Hankins**
Institution: **University of Texas Medical Branch – Galveston, TX**
Grant No.: **5 U10 HD047891-05**
Award: **$47,579**

The University of Texas Medical Branch (UTMB) has the capability to participate actively as a member of the Obstetric-Fetal Pharmacology Research Units (OPRU) network. Gary Hankins, M.D., as PI, is responsible for the proposed clinical trial on the use of hypoglycemic drugs in the treatment of diabetes during pregnancy. He has extensive experience within several NIH multicenter trials, e.g., First and Second Trimester Evaluation of Risk of Aneuploidy (FASTER), Beneficial Effects of Antenatal Magnesium Sulfate Study (BEAM), and the Vaginal Ultrasound Cerclage Trial. Dr. Hankins has achieved successful patient recruitment and retention by involvement with UTMB's Regional Maternal and Child Health Program (RMCHP). All RMCHP clinics follow protocols established by the Maternal-Fetal Medicine Division, headed by Dr. Hankins. Over 12,000 pregnant women are cared for annually within the RMCHP clinic system, approximately 7,000 of whom deliver at UTMB. The pharmacology/pharmacokinetics (PK) coinvestigator, Mahmoud S. Ahmed, Ph.D., has over 25 years of expertise in utilizing human placenta and derived preparations in his investigations. Dr. Ahmed is a laboratory-pioneering investigator in placental receptors, their natural ligands, and mediated responses, as well as the mechanism of hCG release from trophoblast tissue. They 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. Kenneth D. Carey, D.V.M., Ph.D., as animal model coinvestigator, 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. Dr. Hankins is an adjunct investigator at the SNPRC and has had extensive involvement with the primate research staff. The Department of Ob/Gyn has well-funded scientists with expertise in areas relevant to this RFA, including infection, vascular physiology, and placental functions. Clinical PK co-investigators Susan Abdel-Rahman, Pharm. D., and Wayne Snodgrass, M.D., Ph.D., have over 30 years of combined experience in the development of protocols for PK studies, evaluation of data obtained, and PK/PD modeling. The Division of Neonatology, the GCRC, and other departments at UTMB will provide support for this project.

Title: **UW Obstetric–Fetal Pharmacology Research Unit**
P.I.: **Mary F. Hebert**
Institution: **University of Washington – Seattle, WA**
Grant No.: **5 U10 HD047892-05**
Award: **$49,000**

The overall objective of this grant proposal 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. This proposal describes the available en-

vironment and resources at the University of Washington for establishing a successful and productive Obstetric–Fetal Pharmacology Research Unit. As a demonstration of our research interests and capabilities, the following translational research studies that integrate our strengths in clinical and basic sciences are proposed to evaluate the following study aims: (1) We aim 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) We aim 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: **Pregnancy and Drug Metabolizing Enzymes and Transporters**
P.I.: **Steve N. Caritis**
Institution: **Magee–Women's Research Institute and Foundation – Pittsburgh, PA**
Grant No.: **5 U10 HD047905-05**
Award: **$44,835**

The purpose of this proposal is to establish an Obstetric–Fetal Pharmacology Research Unit (OPRU) at the University of Pittsburgh and to summarize the components of the applicants' 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. They provide three protocols for assessment by the network for future exploration. The Pittsburgh OPRU is composed of a large clinical facility (Magee-Women's Hospital) with more than 8,000 deliveries and a wide array of women with medical or obstetric complications. A CRC satellite at Magee provides an optimal site for recruitment and study of pregnant women. These clinical facilities are linked to the Center for Clinical Pharmacology (CCP), which provides a core laboratory for classical pharmacology analyses and a pharmacogenetic laboratory for genotyping, mRNA expression, and sequencing endpoint measurements. A proteomics laboratory is also linked to the CCP. In addition to these clinical and analytical resources is a breeding rhesus monkey colony housed at Magee-Women's Hospital. A basic science component completes the Pittsburgh OPRU. A diverse group of basic scientists and clinical researchers has been interacting through the CCP and will add considerable breadth and depth to their OPRU. The leadership of the Pittsburgh OPRU provides a diverse and experienced group of researchers with a long history of collaboration and investigation in the area of maternal–fetal pharmacology. The leadership has experience in collaborative endeavors and is prepared to cooperate with other OPRUs to conduct collaborative research.

Title: **The History of Emergency Contraception**
P.I.: **Heather Munro Prescott**
Institution: **Central Connecticut State University – New Britain, CT**
Grant No.: **1 G13 LM009242-01A2**
Award: **$75,530**

The National Library of Medicine Grant for Scholarly Works in Biomedicine and Health will be used to research and write a book-length project on the history of emergency contraception from the 1960s until the present. Postcoital methods of contraception were first developed in the early 1960s as part of a larger movement to provide reproductive health care to adolescent and young adult women. This project will explore the multiple constituencies involved in the development and marketing of emergency contraceptives since the 1960s. It will draw upon the personal papers of major reproductive scientists, gynecologists, population groups, and feminist activists. This study will emulate the method used by social historians of medicine, which views the history of medicine as a ne-

gotiated process between experts and clients. Therefore, a major focus of the project will be the role women patients played in the dissemination of this technology. This project will show women not only as test subjects for this new method of birth control, but also as active healthcare consumers.

Title: **ORWH–NICHD Leiomyoma Tissue Bank**
P.I.: **James Segars**
Institution: **NICHD Intramural Program**
Grant No.: **Z01 HD008737**
Award: **$85,000**

The health of 30–50% of women in the United States 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, because 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- 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 tissue established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

Title: **Pelvic Floor Disorders Network**
P.I.: **Anthony G. Visco**
Institution: **Duke University – Durham, NC**
Grant No.: **5 U01 HD041267-09**
Award: **$24,500**

Women's health research at the University of North Carolina (UNC) is sophisticated and widespread, with many committed investigators addressing issues of fundamental importance to women. UNC has a tradition of excellence in clinical care, training, and research in pelvic floor disorders and includes one of the Nation's first accredited fellowship programs in the Division of Urogynecology and Reconstructive Pelvic Surgery. UNC offers comprehensive evaluation and treatment options in a high-volume care setting that serves as a tertiary referral center for women from across the State. Women sought consultation or treatment for more than 2,700 pelvic floor disorders by urogynecologists at UNC in the previous 2 years. Seventy-eight percent of the women were Caucasian and 15% were African-American, predominantly from rural and suburban communities, with stable care and followup patterns. Approximately 427 women had multichannel urodynamic studies annually. UNC providers have extensive expertise in both surgical and nonsurgical management of urinary incontinence, pelvic organ prolapse, and defecatory dysfunction.

The Division of Urogynecology performs an average of 106 surgical procedures for the primary indication of urinary incontinence and 300 for prolapse, and provides medical management for over 1,464 women with these conditions each year. The UNC Pelvic Floor Disorders Research Collaborative, led by the Division of Urogynecology, is a multidisciplinary team of outstanding investigators in urogynecology, urology, gastroenterology, radiology, maternal–fetal medicine, and clinical research methodology. They have a history of strong clinical ties and dedication to interdisciplinary research. Diagnostic resources include multichannel urodynamic testing, cystoscopy, defecography, pelvic MRI, 360-degree endoanal ultrasound, anal manometry, and needle electromyography. Clinical services include surgical treatment of complex pelvic floor disorders and a wide range of nonsurgical options. As an active Pelvic Floor Disorders Network (PFDN) clinical network site, UNC has an established research infrastructure with the proven ability to support large-scale, multicentered clinical research. The collaborative is well equipped and uniquely qualified to continue as a valuable member of the PFDN. Given the exceptional quality of the research opportunities and resources

available at UNC, the stable and diverse patient population, the strength of the investigator pool, the proven high-level recruitment, and the commitment of the institution to the stated goals of this RFA, the PIs look forward to continuing to make substantial contributions to advancing women's health related to pelvic floor disorders.

Title: **Pelvic Floor Disorders Network**
P.I.: **Joseph I. Schaffer**
Institution: **University of Texas Southwestern Medical Center – Dallas, TX**
Grant No.: **5 U01 HD054241-03**
Award: **$23,790**

In 2004, there were more than 2,100 women with pelvic floor disorders seen in our clinics and 617 women underwent surgical procedures for correction of pelvic floor disorders. The Departments of Obstetrics and Gynecology and Urology have increasingly collaborated since 1997 to offer comprehensive care of women with pelvic floor disorders. In addition to urogynecology and urology, collaboration includes faculty from colorectal surgery, radiology, physical therapy, and maternal–fetal medicine. The clinical research teams from the urogynecology and urology faculty and research teams at the University of Texas Southwestern Medical Center and Parkland Hospital and the facilities described in this application have successful prior as well as ongoing experience in NIH-sponsored national multicenter trials. Centerpieces in this application are two existing research clinics, one targeted at private patients (operated by the Urology Department) and the other focused on medically indigent patients (operated by the Obstetrics and Gynecology Department). Also included in this application is a concept application for a randomized trial designed to assess the efficacy of end-to-end versus overlapping repair of the external anal sphincter lacerated during childbirth. The primary outcome is anal incontinence, which is a significant consequence of such lacerations. This trial would permit accurate evaluation of the outcome of specific surgical procedures, which is one of the prime areas of interest leading to creation of the Pelvic Floor Disorders Network. The PIs are of the view that along with strategies for prevention of anal sphincter laceration during childbirth, optimal management of the torn sphincter should also be studied because more than 200,000 women sustain such pelvic floor injuries each year in the United States.

Title: **Pelvic Floor Disorders Network**
P.I.: **Matthew Barber**
Institution: **The Cleveland Clinic – Cleveland, OH**
Grant No.: **5 U01 HD054215-03**
Award: **$23,790**

Pelvic floor disorders (PFDs), including urinary incontinence, pelvic organ prolapse (POP), and fecal incontinence, affect a substantial proportion of women in the United States. PFDs result in significant psychosocial costs to an individual and their aggregate social and economic costs to society are enormous. Despite their substantial health impact, the quality of the evidence supporting most of the commonly used treatments, especially surgical interventions, is limited by the lack of standardization of diagnostic and therapeutic interventions, use of nonstandardized and nonvalidated outcome measures, poor-quality research designs, and inadequate power to detect clinically meaningful differences. The long-term objective of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with PFD using the highest quality research methods available. The specific aims of this application are (1) To demonstrate that the Cleveland Clinic Foundation possesses the personnel, patient, clinical, and administrative resources needed for successful participation as a clinical site in the PFDN and that the applicants' participation would be advantageous to the successful attainment of the network's scientific goals; and 2) To present a concept application for potential conduct by the PFDN. The broad, long-term objectives of the concept application are (1) to compare sacrospinous ligament fixation (SSLF) to uterosacral vaginal vault fixation (USWS) and (2) to assess the role of perioperative pelvic floor physiotherapy

(PFPT) in women undergoing transvaginal surgery for apical or uterine POP. Specific aims are to (1) Compare the anatomic outcomes of SSLF to USWS in women undergoing transvaginal surgery for Stage 2–4 POP involving the vaginal apex or uterus 3 years after surgery; (2) Compare functional, sexual, and health-related quality of life (HRQOL) outcomes of SSLF to USWS in the same women 3 years after surgery; (3) Assess whether short-term functional, sexual, and HRQOL outcomes improve in women receiving PFPT perioperatively compared to those who receive surgery alone; (4) Assess whether perioperative PFPT improves anatomic, functional, sexual, and HRQOL outcomes 3 years after surgery (long-term) compared to surgery alone; and (5) Determine the incremental cost-effectiveness of perioperative PFPT at the time of transvaginal surgery for POP. The PI presents a collaborative multicentered randomized trial comparing SSLF to USSVS with or without perioperative PFPT using a 2x2 factorial study design. A standardized common protocol for enrollment, treatment, and data collection will be employed by six to eight clinical sites within the PFDN coordinated by the data coordinating center.

Title: **The Pelvic Floor Disorders Network**
P.I.: **Linda Brubaker**
Institution: **Loyola University Chicago – Chicago, IL**
Grant No.: **5 U01 HD041250-08**
Award: **$23,790**

Loyola is a productive, innovative clinical research institution that has contributed to the first cycle of the Pelvic Floor Disorders Network (PFDN) and is eager to build on the PFDN's excellent start. Our application documents the following: (1) The qualifications and commitment of institution and key personnel at Loyola, a qualified and committed institution with a multidisciplinary faculty with experience in clinical trials design and conduct, along with a highly qualified and committed research team led by the same PI, Dr. Brubaker. This research team also employs urogynecologists and urologists. Two of the faculty members received master's degrees in clinical research design and statistical analysis and one is currently in this degree program. A cadre of study coordinators are crosstrained to meet the needs of the PFDN study roster. The team has an excellent collaborations within the Loyola faculty. (2) Loyola's participation in PFDN protocols and procedures: High-quality participation in PFDN protocols with excellent and consistent recruitment. We also demonstrate our consistent contributions in PFDN work, including dissemination of PFDN scientific findings. Loyola has been productive and has worked well with the PFDN team. Our first cycle application proposed the essence of the CARE trial, which was completed ahead of schedule and is under consideration for publication. (3) A feasible, scientifically relevant concept protocol (randomized surgical trial): We believe that we have demonstrated our ability to design and conduct high-quality clinical trials. This application also describes a randomized surgical trial for women who select vaginal apical reconstruction. A comparison of the two most common techniques may inform a future study that seeks to determine which route of surgery (abdominal vs. vaginal) is best suited for an individual woman. This trial is a feasible, scientifically relevant, randomized surgical trial. The draft protocol is suitable for PFDN Steering Committee discussion and revision prior to implementation.

Title: **Pelvic Floor Disorders Network**
P.I.: **Holly E. Richter**
Institution: **University of Alabama at Birmingham – Birmingham, AL**
Grant No.: **5 U01 HD041261-08**
Award: **$24,500**

Surgical techniques for the treatment of stress incontinence (SUI) have significantly evolved over the last 100 years. The gold standard Burch urethropexy and pubovaginal sling procedures are now being performed less frequently, with the increased use of the newer minimally invasive midurethral sling procedures, the most common being the tension-free vaginal tape procedure (TVT). The TVT procedure is comparable in efficacy to the open Burch procedure, with low morbidity and fewer

complications. Because the sling is placed at the level of the midurethra under no tension, it was thought that the TVT would yield fewer postoperative lower urinary tract symptoms. However, a review of the literature has not borne this out, with postoperative storage symptoms reported in up to 42% of women. The primary purpose of the proposed randomized clinical trial is to test whether a perioperative behavioral/pelvic-floor muscle-training program can reduce the occurrence of these postoperative storage symptoms and voiding dysfunction in women undergoing a TVT procedure for SUI. Behavioral interventions are known to be effective for treating urge incontinence and voiding dysfunction unrelated to surgery, but have not been tested as a preventive adjunctive strategy. Approximately 400 subjects will be randomized to a perioperative behavioral program or usual care. The intervention will be implemented 2 weeks preoperatively and reinforced before leaving the hospital and 2 weeks postoperatively. The primary outcome will be complaints of urgency, frequency, nocturia, and urge incontinence using the overactive bladder questionnaire (OABq). Evaluations will be performed at 2 and 6 weeks and at 3, 6, and 12 months postoperatively and will include the OABq, questionnaire for urinary diagnosis (QUID), urogenital distress inventory (UDI), pelvic-organ prolapse/urinary incontinence sexual-function questionnaire (PISQ), patient global impression of severity (PGI-S), and SF-36. Subjects will also complete a 7-day bladder diary to assess frequency of storage symptoms. Secondary aims are to determine whether this intervention reduces time to voiding and symptoms of voiding dysfunction, whether it impacts on patient satisfaction and quality of life, and to identify predictors of postoperative storage symptoms and voiding dysfunction symptoms. This type of information will allow physicians to more effectively counsel and treat their incontinent female patients to further enhance long-term quality of life.

Title: **Pelvic Floor Disorders Network (PFDN)**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah – Salt Lake City, UT**
Grant No.: **5 U01 HD054136-03**
Award: **$24,500**

Pelvic floor disorders are common, bothersome, and inadequately treated. The overarching aim of the investigators from the proposed University of Utah Pelvic Floor Disorders Clinical Site is to improve women's health in the area of pelvic-floor dysfunction. To this end, site-specific aims include (1) Identifying priority areas of research, (2) Developing assessment tools, (3) Developing and implementing PFDN protocols, (4) Recruiting and enrolling subjects in PFDN protocols, (5) Achieving on-target recruitment goals and high subject retention, (6) Ensuring high-quality data, (7) Transmitting data accurately to the Data Coordinating Center, (8) Participating in data analysis, (9) Disseminating results to the research community, and (10) Producing high-quality publications. The broad scientific aim for the randomized clinical trial outlined in this proposal is to evaluate whether postoperative pelvic floor muscle training following surgery for pelvic organ prolapse and/or stress urinary incontinence improves postoperative outcomes (anatomic, symptomatic, and quality-of-life outcomes) at 3 months, 1 year, and 2 years postoperatively.

Title: **Pelvic Floor Disorders Network**
P.I.: **Charles W. Nager**
Institution: **University of California, San Diego – San Diego, CA**
Grant No.: **5 U01 HD054214-03**
Award: **$23,790**

The objectives and aims of this application are for San Diego to become the first Western U.S. clinical site in the Pelvic Floor Disorders Network (PFDN). The San Diego Clinical Site is a collaboration of three medical centers: (1) the University of California, San Diego (UCSD); (2) Kaiser Permanente, San Diego (Kaiser); and (3) the Naval Medical Center, San Diego. This same collaboration in the Urinary Incontinence Treatment Network (UITN) led all sites in patient recruitment for the UITN Stress Incontinence Surgery Treatment Efficacy (SISTEr) trial. The efficiency of the San Diego

Clinical Site's efforts was recognized by the PFDN and we were asked to become a subcontract site for the University of Alabama for the Colpopexy and Reduction Efforts (CARE) study. In the brief 9 months available before the CARE study ended, San Diego (UCSD and Kaiser only) recruited 19 patients to CARE. This total was more than all but one center during those 9 months. We were the third UITN site to reach recruitment goals in the UITN's Behavior Enhances Drug Reduction Incontinence (BE-DRI) study. Additionally, in the UITN, our site has led efforts in the design, protocol development, and workgroup leadership for the UITN's current study, Trial Of Mid-Urethral Slings (TOMUS). Urodynamic studies are commonly performed in the United States at an annual cost of approximately $400 million. These urodynamic studies are routine preoperative investigations in most centers that have urodynamic capability, yet we do not have evidence that these tests improve outcomes. Our concept proposal is a randomized trial of preoperative urodynamic studies in women with predominant stress urinary incontinence. The primary aim is to determine if preoperative urodynamic studies improve treatment success rates in all women considered candidates for SUI surgery after an office evaluation. We believe that this proposed urodynamics study requires a multicenter, randomized clinical trial and has significant relevance to the appropriate evaluation and care of women with pelvic floor disorders, namely, urinary incontinence. The proposed study also has potentially significant importance for national health care resource allocation and expenditures. The work that the San Diego investigators have done for the UITN in the past 5 years to develop standardized, quality urodynamic studies makes them the ideal investigators to lead this effort. We believe that the PFDN will benefit greatly by the proven ability of the San Diego Clinical Site's demonstrated energy, skills, and leadership.

Title: **MsFLASH: Relative Efficacy of Hormonal and Nonhormonal Interventions for VMS**
P.I.: **Lee S. Cohen, Hadine Joffe**
Institution: **Massachusetts General Hospital – Boston, MA**
Grant No.: **1 U01 AG032700-01**
Award: **$130,000**

The purpose of this proposal is to enable the MsFLASH clinical trials network to establish a core fund to be used for laboratory testing to measure reproductive hormone levels with a specific aim to obtain core hormone assays in order to understand the mechanisms underlying the onset and treatment of vasomotor symptoms. The biological basis of vasomotor symptoms (VMS) is poorly understood. Higher levels of the pituitary hormone follicle stimulating hormone (FSH), lower levels of estradiol, and fluctuations in estradiol have all been shown to correlate with the occurrence of VMS in peri- and postmenopausal women. In addition, while estrogen therapy treats hot flashes and preliminary evidence suggests that some nonhormonal medications, complementary therapies, and behavioral interventions suppress VMS, the specific physiological pathways through which these treatments work are not known. The study proposes to obtain serum estradiol and FSH levels in participants involved in the network's clinical trials before and after treatment interventions. By obtaining levels of these reproductive hormones in the network participants, who will have well-characterized VMS, the study will advance our understanding of the mechanisms of VMS and their treatment.

Title: **SGI Annual Meeting: Fostering a Multidisciplinary Approach to Research in Women**
P.I.: **Kelle H. Moley**
Institution: **Society for Gynecologic Investigation – Washington, DC**
Grant No.: **5 U13 HD044185-05**
Award: **$5,000**

Physicians and other health professionals face new challenges in obstetrics, gynecology, developmental biology, and reproductive biology and medicine. A multidisciplinary approach to translational research in women's health is needed to make significant advances in the subspecialties of

gynecologic oncology, maternal–fetal medicine, and reproductive endocrinology, as well as reproductive and developmental biology. While the need for professionals devoted to women's health escalates, we are simultaneously confronted with a steadily growing shortage of academic physicians and scientists who work in the fields of translational reproductive biology and medicine. The shortfall is due both to fewer physicians and scientists entering these fields and to the attrition of trained researchers from earlier generations. As the preeminent national and international professional organization for clinicians and researchers involved in reproductive biology and medicine, the Society for Gynecologic Investigation (SGI) must play a major role in addressing these issues and providing a forum for the exchange of ideas, presentation of the best science, networking, and mentoring. The SGI is the only organization in this field that represents the breadth of clinicians and scientific investigators in all areas of women's health dedicated to translational reproductive medicine. Specific Aims: (1) To provide support to young investigators in all aspects of reproductive sciences and encourage them to attend the SGI annual scientific meeting by educational, collegial, and meritorious incentives; and (2) To provide outstanding speakers at the annual SGI meeting whose research exemplifies cutting-edge science in the collective fields of reproductive biology, genomics, and genetics, in an attempt to introduce trainees to the high quality of science conducted in these areas. The 54th annual SGI scientific meeting is entitled "Multidisciplinary Approach to Translational Research in Reproduction, Development, and Women's Health," and this theme prevails throughout the 4-day meeting. The objective of this proposal is to continue support for the outstanding scientific content of the meeting and to attract young investigators to attend and join this unique society. Throughout the meeting, the contributions of trainees to research is emphasized; there is a plenary session at which the top-ranked trainee abstracts will be presented and awards granted to authors of top-ranked abstracts. A new ad hoc trainee committee has been created by the SGI Council for supportive infrastructure for trainees within the SGI membership. The rationale for these efforts is that by presenting interdisciplinary research in women's health to young investigators in the community of the society, more trainees will be encouraged to pursue these areas and translational reproductive science will advance. The rationale for this proposal is to support the annual meeting of the SGI in order to present interdisciplinary research in women's health to young investigators as a means to attract more young physician-scientists to these biomedical research areas. The SGI is the premier organization in this field and is the only one that represents the breadth of clinicians and scientific investigators in all areas of women's health dedicated to translational reproductive medicine. Our goal is to make a significant impact on the training of young investigators in order to advance reproductive science.

Title: Stillbirth Collaborative Research Network (SCRN) Ancillary Followup Study
P.I.: Carol R. Hogue
Institution: Emory University School of Medicine – Atlanta, GA
Grant No.: HD 045925-05S2
Award: $472,912

Title: Stillbirth Collaborative Research Network Followup Ancillary Study
P.I.: George R. Saade
Institution: University of Texas Medical Branch at Galveston – Galveston, TX
Grant No.: HD 045952-05S1

Title: Stillbirth Collaborative Research Network Followup Ancillary Study
P.I.: Donald J. Dudley
Institution: University of Texas Health Sciences Center – San Antonio, TX
Grant No.: HD 045955-05S1

Title: Stillbirth Collaborative Research Network Followup Ancillary Study
P.I.: Robert M. Silver
Institution: University of Utah Health Sciences Center – Salt Lake City, UT
Grant No.: HD 045944-05S1

Title: Stillbirth Collaborative Research Network Followup Ancillary Study
P.I.: Donald Coustan
Institution: Brown University – Providence, RI
Grant No.: HD 045953-05S1

Background: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) established the Stillbirth Collaborative Research Network (SCRN) to study the extent and causes of stillbirth in the United States. It is hoped that the information gained will benefit families who have experienced a stillbirth, women who are pregnant or who are considering pregnancy, and their physicians. In addition, the knowledge gained by the investigators is expected to support future research aimed at improving preventive and therapeutic interventions and at understanding the pathological mechanisms that lead to fetal death. The specific aims of the SCRN are to—

1. Determine the causes of stillbirth using a standardized stillbirth postmortem protocol, to include review of clinical history, protocols for autopsies, and pathologic examinations of the fetus and placenta, as well as other postmortem tests to illuminate genetic, maternal, and other environmental influences;

2. Obtain a geographic, population-based determination of the incidence of stillbirth, defined as fetal death at 20 weeks gestation or greater; and

3. Elucidate risk factors for stillbirth.

Five clinical sites are collaborating with a coordinating center and NICHD, as well as local hospitals, to design and carry out the study objectives. A variety of specialists, from obstetricians to grief counselors, are participating in the research initiative to support the mothers and their families and to develop guidelines for studying and reporting stillbirths.

ORWH, in FY 2008, agreed to fund the SCRN Ancillary Followup Study for the development of a telephone interview, including CATI programming, and analysis of the potential 1,800 women who consented to be followed in the parent SCRN study. The 45-minute interview will include determi-

nation of pregnancy attempts and outcomes since the index pregnancy, a brief history of the grief experience for women with perinatal loss, and a series of psychosocial instruments that will assess childhood traumatic events (as risk factors for stillbirth), current psychological status, and the woman's assessment of her grief and growth processes. It is estimated that 800 of the potential 1,800 women will be difficult to find. These women are more likely to be poor, highly mobile, and possibly represent a higher proportion of minority populations. They would likely be at greater risk of subsequent poor pregnancy outcomes and psychological sequelae. Their mobility requires that additional staff be hired in order to track these women down and administer the interview as described above to include them in the analyses.

Title: Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH Network)
P.I.: Andrea Z. LaCroix, Garnet Anderson
Institution: Fred Hutchinson Cancer Research Center – Seattle, WA
Grant No.: 1 U01 AG032699-01
Award: $300,000

MsFLASH Centers:

Title: MSI-FLASH: Relative Efficacy of Hormonal and Nonhormonal Interventions for VMS
P.I.: Lee Cohen, Hadine Joffe
Institution: Massachusetts General Hospital – Boston, MA
Grant No.: 1 U01 AG032700-01

Title: MSI-FLASH: Paced Respiration for Breast Cancer Survivors
P.I.: Janet S. Carpenter
Institution: Indiana University–Purdue University at Indianapolis – Indianapolis, IN
Grant No.: 1 U01 AG032659-01

Title: MSI-FLASH: An Excercise Intervention for Women with Menopausal Symptons
P.I.: Barbara Sternfeld, Bette Caan
Institution: Indiana University School of Medicine – Indianapolis, IN; Kaiser Permanente, Northern California – Oakland, CA
Grant No.: 1 U01 AG032669-01

Title: MSI-FLASH: Efficacy of an SSRI for Menopausal Symptoms in Perimenopausal Women
P.I.: Ellen Freeman
Institution: University of Pennsylvania School of Medicine – Philadelphia, PA
Grant No.: 1 U01 AG032656-01

Title: MSI-FLASH: An RCT of Yoga and Ultra Low-Dose Estrogen Gel for Vasomotor
P.I.: Katherine Newton, Susan Reed
Institutions: Group Health Center for Health Studies – Seattle, WA; University of Washington School of Medicine – Seattle, WA
Grant No.: 1 U01 AG032682-01

Women going through the menopause transition may experience a variety of symptoms, ranging from vasomotor symptoms (hot flashes and night sweats) to sleep disturbance, mood disorders, loss of sexual desire, and vaginal dryness. As many as two-thirds of all women report vasomo-

tor symptoms, and over 85% report at least one menopausal symptom as they transition through menopause. For the 25% of women whose symptoms are severe, the resulting discomfort greatly diminishes their quality of life. For many decades, menopausal hormone therapy (MHT) using estrogen (or, in a woman with a uterus, a combination of estrogen and a progestin) has been the therapy of choice for relieving menopause-related symptoms. But recently, several large clinical trials and, in particular, the Women's Health Initiative, have found an increased risk of serious health problems, such as blood clots, stroke, heart disease, breast cancer, and cognitive impairment, in women using estrogen–progestin regimens. Not surprisingly, women are reluctant to use MHT for menopausal symptoms and in search of alternative strategies to improve their quality of life.

The primary goal of the MsFLASH Network is to conduct multiple collaborative clinical protocols to evaluate a variety of strategies (e.g., pharmacological, botanical, behavioral, etc.) to alleviate vasomotor symptoms (VMS) and to assess the role of these strategies and changes in the burden of VMS on menopause-related sleep disturbance, mood disorders, and vaginal dryness. Secondary objectives of the network are the following:

- Provide necessary multidisciplinary scientific input in reproductive endocrinology, gynecology, oncology, behavioral medicine, psychiatry, sleep, physiology, biostatistics, psychometrics, pharmacology, complementary and alternative medicine, and clinical trials methodology;
- Implement the rapid identification/development of standard definitions and terminology, data collection instruments, and needed new methodologies for assessment and analysis of participant outcomes;
- Ensure the success of recruitment by providing access to a broad base of populations of interest (of different race/ethnicities, types of menopause [spontaneous or induced by surgeries, treatments, and conditions that propel women of reproductive age into the menopause transition]);
- Establish a knowledge base that will advance therapeutic decisionmaking through a better conceptualization of menopausal symptoms, testing of promising strategies, and advancement of strategies shown to be efficacious and safe;
- Establish collaborations between the practice community and the clinical field sites; and
- Disseminate validated findings to the medical and scientific communities.

A number of different treatment strategies are under consideration. Possible treatments to be studied during the 5-year project period include the following:

- Antidepressants such as paroxetine (Paxil) or escitalopram (Lexapro);
- Paced respiration (slow deep breathing also known as relaxation breathing);
- Yoga;
- Low-dose estradiol patch and low-dose estradiol gel; and
- Exercise programs, both moderate and vigorous.

Appendix D

ORWH-Cofunded Research Conferences and Workshops, FY 2007 and FY 2008

Parental Brain Conference

This conference was held in June 2007 and was cosponsored by the Office of Research on Women's Health (ORWH) and the National Institute of Mental Health (NIMH) to bring together basic and clinical researchers using state-of-the-art scientific approaches to examine the role of the central nervous system in both maternal and paternal care. Normal parental behavior and maladaptive responses during the critical periods associated with raising offspring will be explored.

Basic underlying mechanisms that regulate the adaptations of the maternal and paternal brain toward parenting will be one central focus of the meeting. Translational aspects of the conference will constitute a second key component of the program. Issues related to postpartum mood disorders, such as postpartum depression, anxiety, and aggression in women, and inadequate parental bonding to infants, will be discussed in an effort to bridge the gap between the basic and clinical sciences on these crucial topics and to advance our understanding of women's and men's health issues.

Reproductive Medicine and the Law Workshop

With the National Institute on Deafness and Other Communication Disorders (NICHD), ORWH cosponsored this joint workshop of the American Society for Reproductive Medicine (ASRM) and the Association of American Law Schools (AALS). The topic of the workshop was "Reproductive Medicine and the Law." This unique educational activity brought together legal and medical scholars to develop guidance for the legal and medical professions dealing with legal issues that have arisen with the advent of assisted reproductive technologies (ART). The workshop took take place in two parts, at the Midyear Meeting of the AALS in June 2007, and at the Annual Meeting of the ASRM in October 2007. The workshop was open to legal and medical scholars and professionals.

16th Ovarian Workshop, "The Ovary: Signaling Mechanisms Regulating Development and Dysfunction"

This workshop, organized by NICHD and cosponsored by ORWH, was held in July 2007. The goal of the Workshop was to advance understanding of ovarian function so that this basic knowledge could be translated to clinical applications to enhance or control fertility and treat, reduce, and/or eliminate ovarian dysfunction and cancer. Conditions related to ovarian dysfunction under consideration at the workshop included sex reversal; metabolic disease; and steroid excess, including hyper-androgenic states leading to hirsutism, acne, and alopecia. Also considered at the meeting were other topics such as infertility treatments for women with ovarian dysfunction; preservation of fertility for women with cancer; the prevention and treatment of gynecological cancers related to ovarian dysfunction, including endometrial and ovarian cancer; and environmental threats to reproductive function. Another goal of the meeting was to provide participants with the ethical framework to understand the varying positions of the many constituents who weigh in on these issues.

Grantsmanship Workshop for Research on Chronic Fatigue Syndrome

The Trans-National Institutes of Health (NIH) Chronic Fatigue Syndrome (CFS) Working Group held a 1-day grantsmanship workshop in September 2007 to provide CFS researchers with an enhanced understanding of the NIH funding process, an overview of the diverse funding opportunities available through the NIH Office of Extramural Research, and the opportunity to meet with and query Program Officers from the Institutes, Centers, and Offices represented on the Working Group. Emphasis was placed on the need to move to interdisciplinary, crosscutting research approaches. An afternoon session was devoted to explaining mechanisms appropriate for seeking research and training funding for CFS, even when the term itself is not included in the title. The 43 workshop registrants were a diverse group, both geographically and in terms of their scientific areas of interest. There was ample time for meaningful exchange and participant ratings were uniformly excellent. For more information, see http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html.

Uterine Fibroid Workshops

With NICHD, ORWH cosponsored two sequentially held scientific workshops on uterine fibroids in September 2007. The first workshop focused on updating the science base. The second workshop, which followed immediately, considered a classification system for uterine fibroids that would better guide clinical treatment decisions and advance research in this area.

The Menstrual Cycle and Adolescent Health Conference

NICHD, the American Society for Reproductive Medicine, ORWH, the NIH Office of Rare Diseases, the Food and Drug Administration Office of Women's Health, and the U.S. Department of Health and Human Services Office of Women's Health cosponsored a Menstrual Cycle and Adolescent Health Conference in October 2007. A major meeting objective was to build a community of investigators, clinicians, patient advocacy groups, and governmental agencies committed to the long-term goal of focusing attention on the menstrual cycle as a marker of general health in adolescent girls. The meeting sought to define the scientific basis for the public health message that the menstrual cycle is a marker of general health in adolescent girls and to develop a related research agenda for the 21st century.

Annual Interdisciplinary Symposium on Research on Women's Health

The Interdisciplinary Symposium on Research on Women's Health is held annually in November in conjunction with the annual Specialized Centers of Research (SCOR) and the Building Interdisciplinary Research Centers in Women's Health (BIRCWH) Principal Investigator meetings and the BIRCWH scholar meeting in order to showcase scientific research from ORWH interdisciplinary research and career development programs.

At the Fourth Annual Interdisciplinary Women's Health Research Symposium in November 2007, Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA), gave a keynote address entitled "Women and Substance Abuse: What Do We Know?" Platform presentations included studies of female-specific factors in stress responses, sex differences in pelvic floor conditions and urinary tract infections, health disparities research and epidemiological studies of diverse populations of women, and studies investigating sex-specific factors in relation to risk for cardiovascular diseases. A poster session provided BIRCWH scholars with an opportunity to present their ongoing research.

The Fifth Annual Interdisciplinary Women's Health Research Symposium, held in November 2008, included a keynote address by Dr. Steven Katz, Director, National Institute of Arthritis and Musculoskeletal Disease, entitled, "Translating Science Into Improved Patient Care." As in 2007, the 2008 Symposium had presentations of research from BIRCWH and SCOR programs and a poster session for BIRCWH scholars. Presentations included research on a wide range of topics related to women's health and sex/gender factors, including substance abuse, pain, psychiatric comorbidity with perinatal depression, irritable bowel syndrome, cardiovascular disease risk factor control, urinary incontinence, and Human Papillomavirus vaccines.

George Washington University—BIRCWH Scholars' "Day on the Hill" Training Program in Health Policy for NIH Fellows

Each year, ORWH provides support for an educational program to provide the ORWH BIRCWH scholars with a solid understanding of the health policy legislative process in Washington, DC. This Fellows Training Program is designed to educate them on the structure and processes of health policymaking. In November 2007, this unique program focused upon the development of health, health care, and medical research policy, with a particular focus on women's health. This was accomplished via a day-long event on Capitol Hill. The program was conducted by faculty of the George Washington University Department of Health Policy (including Dr. Carolyn Mazure, who now serves as a Professorial Lecturer, and Dr. Marsha Simon, former Staff Director for the Senate Committee on Appropriations, Subcommittee on Health). The session also included guest speakers involved with the daily workings of the legislative process.

In 2008, ORWH once again held the BIRCWH Scholars "Day on the Hill" training program, which was focused on the impact of the 2008 Presidential Election on biomedical research, with particular attention to women's health research and health policy.

The Status and Future of Acupuncture Research

In November 2007, the Society for Acupuncture Research (SAR) hosted an international conference, cosponsored by ORWH and the National Center for Complementary and Alternative Medicine (NCCAM), to mark the 10th anniversary of the landmark NIH Consensus Development Conference on Acupuncture. More than 300 acupuncture researchers, practitioners, students, funding agency personnel, and health policy analysts from 20 countries attended the SAR meeting held at the University of Maryland School of Medicine, Baltimore, MD. Invited lectures covered topics such as the scientific assessment of acupuncture points and meridians, the neural mechanisms of cardiovascular regulation by acupuncture, mechanisms for electroacupuncture applied to persistent inflammation and pain, basic and translational research on acupuncture in gynecologic applications, the application of functional neuroimaging to acupuncture research with specific application to carpal-tunnel syndrome and fibromyalgia, and the association of the connective tissue system to acupuncture research.

Joint NIH-HHS-DOJ Scientific Workshop on Teen Dating Violence

In response to the 2005 reauthorization of the *Violence Against Women Act* (P.L. 109-162) and the charge to the National Advisory Committee on Violence Against Women, ORWH cosponsored a 2-day meeting in December 2007 on teen dating violence along with the HHS and the Department of Justice's National Institute of Justice. The goals of this workshop included the following: (1) build a consensus research and practical definition of teen dating violence; (2) discuss and review methods, measurements, and outcomes used for quantifying and defining teen dating violence, both in research and in practice; and (3) examine the research, both basic and applied, on teen, disabled youth, and particular cultural subgroups. A summary of the workshop is available at: http://www.ojp.usdoj.gov/nij/topics/crime/violence-against-women/workshops/teen-dating-violence-agenda.htm.

Preconception Care Research: Improving Birth Outcomes and Reproductive Health Workshop

Because many events before and around fertility may affect pregnancy outcomes, the workshop focused on women's health long before pregnancy begins. The purpose of this April 2008 workshop, which ORWH cosponsored with NICHD, was to bring together a broad spectrum of experts, including clinicians and basic and behavioral scientists to define a multidisciplinary framework for developing an agenda in preconception care research. The meeting covered a broad range of biological determinants that directly and indirectly influence preconception care. The diverse components of preconception care research and its specific impact on the reproductive system leading to improved birth and long-term health outcomes were explored.

Women and Smoking: Understanding Socioeconomic Influences Workshop

ORWH cosponsored a workshop with NIDA in April 2008 on "Women and Smoking: Understanding Socioeconomic Influences." Health disparities in women's smoking behavior exist, and there is ample sociological and epidemiological research to indicate that education moderates risk of smoking. The workshop aimed to enhance recognition of the urgency of the problem, embed the problem in a broader context with regard to other types of substance abuse as well as other non-substance-related public health problems, and foster interdisciplinary research efforts.

First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators

In June 2008, ORWH sponsored the First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators. The meeting brought together seven individuals who had received funding under an RFA specific to understanding the relationship of neuroimmune mechanisms and CFS. The investigators presented their results to date in the first half of the meeting and then participated in a team building exercise designed to encourage innovative collaborations. Discussions centered on how their work could be applied to understanding infection as a prototypical initial insult. Their work was seen as potentially providing insights into how systems become dysregulated and interact with one another to upset health. Other discussions focused on identifying methods that would be necessary for the investigators to function as an interdisciplinary team.

The Eighth Add Health Users' Conference

This biennial conference, held in July 2008 and cosponsored with NICHD, provided an opportunity for investigators using the Add Health data to share research findings, discuss issues in the analysis of this complex dataset, and to learn about specialized aspects of the data and its use. This year, a greater emphasis was placed on identifying and highlighting outstanding research that has been conducted using the dataset. With the third wave of data having been available since mid-2003, researchers have had ample time to undertake complex longitudinal analyses of all three waves for presentation in 2008. Special didactic sessions on use of the high school transcript, relationship, and contextual data were held. The research team provided a status report and preview of the next phase of the study, and the opportunities it affords for research involving biological (including genetic), behavioral, and contextual data.

The Add Health Users Conference provides graduate students and early career investigators with an opportunity to learn about the study, hone their skills in using the data, share and receive feedback on their research, and, perhaps most importantly, network with other junior investigators and senior scientists.

Trauma Spectrum Disorders: The Role of Gender, Race, and Other Socioeconomic Factors Conference

The goal of this conference, which was held in October 2008, was to provide a forum at which existing evidence-based science on sex, gender, race, and health disparities could be examined in the context of clinical management and care of traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD). The conference provided a unique opportunity to showcase what science could offer to the military and civilian practice and caregiver worlds. The three NIH Institutes represented—NIMH, NINDS, and NICHD—provided their perspectives on the science base. Civilian and military scientists and caregivers also provided their perspectives. Potential cross-disciplinary partnerships were seen as having the potential to influence the care provided to those suffering from PTSD and TBI, as well as their family members. ORWH coordinated NIH involvement in this effort by working closely with the Defense Centers of Excellence on Psychological Health and Traumatic Brain Injury (DCoE), and the Department of Veterans Affairs. Proceedings of the conference will be published and posted on both the DCoE and ORWH Web sites.

APPENDIX E

Ad Hoc Trans-NIH Working Group for Research on Chronic Fatigue Syndrome, FY 2007 and FY 2008

Eleanor Z. Hanna, Ph.D. *Chair*	ORWH
Rebecca B. 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
Susanna Serrate-Sztein, Ph.D.	NIAMS
Michael Twery, Ph.D.	NHLBI

APPENDIX F

Ad Hoc Tracking and Inclusion Committee, FY 2007 and FY 2008

Office of the Director

Office of Research on Women's Health
Vivian W. Pinn (Co-Chair), Angela Bates, Janine Smith

Office of Extramural Research
Robin Wagner,* Israel Lederhendler, Katrina Pearson, Maria Koshy, Svetlana Diggs, Lakshmi Kompella

Office of Acquisition, Management, and Procurement
Rosemary Hamill, David Redd

National Cancer Institute
Gail Blaufarb,* Kim Witherspoon, Clarissa Douglass

National Eye Institute
Donald Everett,* William Darby

National Heart, Lung, and Blood Institute
Carl Roth (Co-Chair),* Sharry Palagi, Barbara Marzetta

National Human Genome Research Institute
Joy Boyer*

National Institute on Aging
Robin Barr,* Karen Bashir, Nina Silverberg, Marilyn Miller

National Institute on Alcohol Abuse and Alcoholism
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
Shahnaz Khan,* Frank Cromwell, Ann Nicholson

***Eunice Kennedy Shriver* 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
Trenita Davis*

National Institute of Diabetes, Digestive, and Kidney Diseases
Karl Malik,* Michelle Johnson, Lauren Meskill, Garman Williams, Karen Salomon

* Indicates the IC Lead Representative to the Tracking and Inclusion Committee

National Institute on Drug Abuse
Christie Espinoza*

National Institute of Environmental Health Sciences
Martha Barnes*

National Institute of General Medical Sciences
Justin Rosenzweig,* Lori Burge, Alison Cole

National Institute of Mental Health
Kathleen O'Leary,* Dawn Corbett

National Institute of Neurological Disorders and Stroke
Lynn Morin,* Kristy Woolbert, Aricia Ajose

National Institute of Nursing Research
Paul Cotton,* Angela Marshall

National Library of Medicine
Hua-Chuan Sim,* Valerie Florence

Warren G. Magnuson Clinical Center
Kim Jarema,* Theresa Doged

National Center for Complementary and Alternative Medicine
April Bower*

National Center for Research Resources
Sheila McClure,* Delores Lee, Patricia Newman, Stephen Seidel, Louise Ramm

Fogarty International Center
Aron Primack,* Francine Hill

Center for Scientific Review
Joy Gibson*

National Center on Minority Health and Health Disparities
Nathaniel Stinson,* Derrick Tabor, Francisco Sy

National Institute of Biomedical Imaging and Bioengineering
Valery Gordon,* Anthony Dempsey

APPENDIX G

NIH Working Group on Women in Biomedical Careers Members, FY 2007 and FY 2008

Members of the NIH Working Group on Women in Biomedical Careers, FY 2007

Co-Chairs

Elias A. Zerhouni, M.D., Director, NIH
Vivian W. Pinn, M.D., Director, Office of Research on Women's Health;
Associate Director for Research on Women's Health, NIH

Institute and Center Directors

Barbara Alving, M.D., Director, NCRR
Jeremy Berg, Ph.D., Director, NIGMS
Story Landis, Ph.D., Director, NINDS
Donald Lindberg, M.D., Director, NLM
Lawrence Tabak, D.D.S., Ph.D., Director, NIDCR
Patricia Grady, Ph.D., RN, FAAN, Director, NINR

Office of the Director

Raynard S. Kington, M.D., Ph.D., Deputy Director, NIH
Ruth L. Kirschstein, M.D., Senior Advisor to the Director, NIH
Catherine Manzi, J.D., Attorney Advisor, Public Health Division, DHHS, OGC
Joyce Rudick, Director, Programs and Management, ORWH
Ex-Officio: Lawrence Self, Director, OEODM

Intramural Research

Michael Gottesman, M.D., Deputy Director for Intramural Research, OIR
Joan Schwartz, Ph.D., Assistant Director, Office of Intramural Research, OIR
Ira Pastan, M.D., Chief, Laboratory of Molecular Biology, NCI
Janine Smith, M.D., Deputy Clinical Director, NEI
Kathryn Zoon, Ph.D., Scientific Director, NIAID
Edward Giniger, Ph.D., Investigator, NINDS
Elaine Ostrander, Ph.D., Chief and Senior Investigator, Cancer Genetics Branch, NHGRI
Catherine Kuo, Ph.D., Postdoctoral Fellow Cartilage Biology and Orthopedics Branch, NIAMS

Extramural Research

Norka Ruiz Bravo, Ph.D., Deputy Director for Extramural Research, OER
Walter Schaffer, Ph.D., Senior Scientific Advisor for Extramural Research, OER
J. Taylor Harden, Ph.D., Assistant to the Director for Special Populations, NIA
Pamela Marino, Ph.D., Program Director, Pharmacology, Physiology, and Biological Chemistry Division; Co-Director, Pharmacology Research Associate Program, NIGMS
Belinda Seto, Ph.D., Deputy Director, NIBIB

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Amy Bany Adams, Ph.D., Special Assistant to the Director, NIH
Jennifer Reineke Pohlhaus, Ph.D., AAAS Science & Technology Policy Fellow, ORWH

Members of the NIH Working Group on Women in Biomedical Careers, FY 2008

Co-Chairs

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

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Story Landis, Ph.D., Director, NINDS
Donald Lindberg, M.D., Director, NLM
Lawrence Tabak, D.D.S., Ph.D., Director, NIDCR
Patricia Grady, Ph.D., RN, FAAN, Director, NINR

Office of the Director

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Ruth L. Kirschstein, M.D., Senior Advisor to the Director, NIH
Janine Austin Clayton, M.D., Deputy Director, ORWH
Catherine Manzi, J.D., Attorney Advisor, Public Health Division, DHHS, OGC
Joyce Rudick, Director, Programs and Management, ORWH
Ex-Officio: Lawrence Self, Director, OEODM

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Kathryn Zoon, Ph.D., Scientific Director, NIAID
Edward Giniger, Ph.D., Investigator, NINDS
Elaine Ostrander, Ph.D., Chief and Senior Investigator, Cancer Genetics Branch, NHGRI

Extramural Research

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J. Taylor Harden, Ph.D., Assistant to the Director for Special Populations, NIA
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Staff to Working Group

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Joslyn Yudenfreund Kravitz, Ph.D., AAAS Science & Technology Policy Fellow, ORWH
Jennifer Reineke Pohlhaus, Ph.D., AAAS Science & Technology Policy Fellow, ORWH

APPENDIX H

Intramural Program on Research on Women's Health Steering Committee, FY 2007 and FY 2008

Principal Steering Committee Members	IC
Esther Sternberg, M.D., Co-Chair	NIMH
Barbara Vonderhaar, Ph.D., Co-Chair	NCI
Rosemarie Filart, M.D., WHSIG Coordinator 2008	NCRR
Joan Schwartz, Ph.D.	OD, OIR
Janine Smith, M.D., WHSIG Coordinator 2007	OD, ORWH
Vicki Malick	OD, OIR
Joyce Rudick	OD, ORWH
Jennifer Pohlhaus, Ph.D. (AAAS Fellow)	ORWH

Current Members	
Lawrence Brody, M.D.	NHGRI
Giovanni Cizza, M.D., Ph.D.	NIDDK
Wendy Fibison, Ph.D.	NIAID
Kenneth Korach, M.D.	NIEHS
Joslyn Kravitz, Ph.D. (AAAS fellow)	OD, ORWH
James Lacey, Ph.D.	NCI
Maria Morasso. Ph.D.	NIAMS
Lawrence Nelson, M.D.	NICHD
Pamela Robey, Ph.D.	NIDCR
Anne Rothfeld	NLM
Norman Salem, M.D.	NIAAA
Monica Skarulis, M.D.	NIDDK
Jeffrey Struewing, M.D.	NCI
Cathy Wolkow, Ph.D.	NIA
Marian Young, Ph.D.	NIDCR

Intramural Program on Research on Women's Health Fellows	
Shannon Laughlin, M.D. NIEHS (2006 Women's Health Fellow)	OD
Suzanne O'Neill, Ph.D. NHGRI (2006 Women's Health Fellow)	OD

Ex-Officio Members	
Michael Gottesman, M.D.	OD, OIR
Vivian Pinn, M.D.	ORWH, OD
Richard Wyatt, M.D.	OD, OIR

Former Members	
Marc Blackman, M.D.	NCCAM
Deborah Carper. Ph.D.	NEI (2002-2003 WSA representative)
Jennifer Eng-Wong, M.D.	NCI
Lynn Gerber, M.D.	CC
Hynda Kleinman, Ph.D.	NIDCR
Suzanne O'Neill, Ph.D.	NHGRI
Manon Parry, Ph.D.	NLM
Susan Pierce, Ph.D.	NIAID (2003-2004 WSA representative)
Mindy Tinkle, Ph.D.	NINR
Susan Wray, Ph.D.	NINDS
Jo Anne Zujewski, M.D.	NCI

APPENDIX I

Vulvodynia Awareness Campaign Partners, FY 2008

Office of Research on Women's Health
Vulvodynia
http://orwh.od.nih.gov/health/vulvodynia.html

***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
Vulvodynia
http://www.nichd.nih.gov/health/topics/Vulvodynia.cfm

National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov

The NIH Pain Consortium
http://painconsortium.nih.gov

National Library of Medicine
Vaginal Diseases
http://sis.nlm.nih.gov/outreach/whrhome.html

Additional HHS Resources

Agency for Healthcare Research and Quality
http://www.ahrq.gov

Centers for Disease Control and Prevention
http://www.cdc.gov

Health Resources and Services Administration
http://www.hrsa.gov

Office of Disease Prevention and Health Promotion
http://odphp.osophs.dhhs.gov

Office of Minority Health
http://www.omhrc.gov

Office of Women's Health, U.S. Department of Health and Human Services
http://www.womenshealth.gov
Tel: 1-800-884-9662 for an information specialist in English and Spanish

U.S. Food and Drug Administration
http://www.fda.gov

Non-Federal Resources and Partners

American College of Nurse-Midwives
8403 Colesville Road, Suite 1550
Silver Spring, MD 20910-6374
http://www.midwife.org

American College of Obstetricians and Gynecologists
409 12th Street, SW, P.O. Box 96920
Washington, DC 20090-6920
http://www.acog.org

American Medical Women's Association
100 North 20th Street, Fourth Floor
Philadelphia, PA 19103
http://www.amwa-doc.org

American Society for Colposcopy & Cervical Pathology
152 West Washington Street
Hagerstown, MD 21740
http://www.asccp.org

Association of American Indian Physicians
1225 Sovereign Row, Suite 103
Oklahoma City, OK 73108
http://www.aaip.org

Black Women's Health Imperative
1420 K Street, NW, Suite 1000
Washington, DC 20005
http://www.blackwomenshealth.org

International Society for the Study of Vulvovaginal Disease
8814 Peppergrass Lane
Waxhaw, NC 28173
http://www.issvd.org

National Alliance for Hispanic Health
1501 16th Street, NW
Washington, DC 20036-1401
http://www.hispanichealth.org

National Black Nurses Association
8630 Fenton Street, Suite 330
Silver Spring, MD 20910
http://www.nbna.org

National Hispanic Medical Association
1411 K Street, NW, Suite 1100
Washington, DC 20005
http://www.nhmamd.org

National Medical Association
1012 Tenth Street, NW
Washington, DC 20001
http://www.nmanet.org

National Research Center for Women & Families
1701 K Street, NW, Suite 700
Washington, DC 20006
http://www.center4research.org

National Vulvodynia Association
P.O. Box 4491
Silver Spring, MD 20914-4491
http://www.nva.org

National Women's Health Network
514 Tenth Street, NW, Suite 400
Washington, DC 20004
http://www.nwhn.org

National Women's Health Resource Center
157 Broad Street, Suite 106
Red Bank, NJ 07701
http://www.healthywomen.org

North American Menopause Society
5900 Landerbrook Drive, Suite 390
Mayfield Heights, OH 44124
http://www.menopause.org

Our Bodies Ourselves
34 Plympton Street
Boston, MA 02118
http://www.ourbodiesourselves.org

Society for Women's Health Research
1025 Connecticut Avenue, NW, Suite 701
Washington, DC 20036
http://www.womenshealthresearch.org

The Women's Sexual Health Foundation
http://www.twshf.org/

University of Medicine and Dentistry of New Jersey
Women's Health Institute
Clinical Academic Building, 6th Floor
125 Paterson Street
New Brunswick, NJ 08901
http://rwjms.umdnj.edu/whi

University of Michigan Center for Vulvar Diseases
A. Alfred Taubman Health Care Center
1500 East Medical Center Drive
Floor 1, Room 1342, Reception: E
Ann Arbor, MI 48109-5384
http://www.med.umich.edu/obgyn/

University of Minnesota Division of Epidemiology and Community Health
West Bank Office Building
1300 S. Second Street, Suite 300
Minneapolis, MN 55454-1015
http://www.epi.umn.edu

WebMD
1175 Peachtree Street, NE, Suite 2400
Atlanta, GA 30361
http://www.webmd.com

Women's Health Institute at Howard University
2041 Georgia Avenue, NW, Towers Suite 6000
Washington, DC 20060
http://www.howard.edu/whi/

Women's Health Specialists
7800 Wolf Trail Cove
Germantown, TN 38138
http://www.whsobgyn.com

Acronyms

Acronyms Used in This Report

AALS	Association of American Law Schools
AAPIs	Asian Americans and Pacific Islanders
ACL	Anterior Cruciate Ligament
ACRWH	Advisory Committee on Research on Women's Health
ACVR2B	Activin A Receptor IIB
ADHD	Attention Deficit Hyperactivity Disorder
AEDS	Anti-Epileptic Drugs
AgPEM	Agentic Positive Emotionality
AHA	American Heart Association
AHEAD	Action for Health in Diabetes
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immune Deficiency Syndrome
AITRP	AIDS International Training and Research Program
AMA	American Medical Association
AMD	Age-Related Macular Degeneration
AMI	Acute Myocardial Infarction
AN	Anorexia Nervosa
ANS	Autonomic Nervous System
ANSWHR	Advancing Novel Science in Women's Health Research
AP	Attention Placebo
APA	American Psychological Association
APLS	Antiphospholipid Antibodies
APM	Association of Professors of Medicine
ART	Assisted Reproductive Technologies
ASA	American Stroke Association
ASCB	American Society for Cell Biology
ASRM	American Society of Reproductive Medicine
AWIS	Association for Women in Science
BAA	Broad Agency Announcement
BBB	Blood–Brain Barrier
BCERC	Breast Cancer and the Environment Research Centers
BCPT	Breast Cancer Prevention Trial
BCRAT	Breast Cancer Risk Assessment Tool
BCSC	Breast Cancer Surveillance Consortium
BDNF	Brain-Derived Neurotrophic Factor
BIRCWH	Building Interdisciplinary Research Centers in Women's Health
BMD	Bone Mineral Density
BMI	Body Mass Index

BRCA1/2	Breast Cancer-Gene Mutation
BU	Boston University
CAD	Computer-Aided Diagnosis
CAM	Complementary and Alternative Medicine
CARE	Women's Contraceptive and Reproductive Experience Study
CAREDS	Carotenoids and Age-Related Eye Disease Study
CBPR	Community-Based Participatory Research Program
CBT	Cognitive Behavioral Therapy
CC	Clinical Center
CCCT	Coordinating Center for Clinical Trials
CCHD	Comprehensive Centers on Health Disparities
CCR	Center for Cancer Research
CCRWH	Coordinating Committee on Research on Women's Health
CDC	Centers for Disease Control and Prevention
CECCR	Centers of Excellence in Cancer Communication Research
CF	Common Fund
CFS	Chronic Fatigue Syndrome
CFSWG	Chronic Fatigue Syndrome Working Group
CGEMS	Cancer Genetic Markers of Susceptibility
CHD	Coronary Heart Disease
CIDR	Center for Infectious Disease Research
CIS	Cancer Information Service
CISNET	Cancer Intervention and Surveillance Modeling Network
CJCEST	Criminal Justice Client Evaluation of Self and Treatment
CJ-DATS	Criminal Justice Drug Abuse Treatment Studies
CLEK	Collaborative Longitudinal Evaluation of Keratoconus
CME	Continuing Medical Education
CMV	Common Virus
CMV	Cytomegalovirus
CNRU	Clinical Nutrition Research Units
CNS	Central Nervous System
CNSWH	Center for Neurovisceral Sciences and Women's Health
COBRE	Centers of Biomedical Research Excellence
COE	Center of Excellence
COMT	Catechol-O-Methyltransferase
COPE	Creating Opportunities for Parental Empowerment
COTC	Community-Based Outreach and Translation Core
CPAP	Continuous Positive Airway Pressure
COPD	Chronic Obstructive Pulmonary Disease
CR	Cardiac Rehabilitation
CR	Computed Radiography
CRD	Colorectal Distention

CRECD	Clinical Research Education and Career Development
CREST	Carotid Revascularization Endarterectomy vs. Stenting Trial
CREST	Clinical Research/Reproductive Scientist Training
CRF	Corticotropin-Releasing Factor
CRH	Corticotropin-Releasing Hormone
CROI	Conference on Retroviruses and Opportunistic Infections
CSR	Center for Scientific Review
CT	Computed Tomography
CVD	Cardiovascular Disease
CWSEM	Committee on Women in Science, Engineering, and Medicine
CYC	Cyclophosphamide
dbGaP	NIH Database of Genotypes and Phenotypes
DCB	Division of Cancer Biology
DCCPS	Division of Cancer Control and Population Sciences
DCCT	Diabetes Control and Complications Trial
DCEG	Division of Cancer Epidemiology and Genetics
DCE-MRI	Dynamic Contrast-Enhanced MRI
DCIS	Ductal Carcinomas in Situ
DCoE	Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DDRCCs	Digestive Diseases Research Core Centers
DED	Dry Eye Disease
DES	Diethylstilbestrol
DHHS	Department of Health and Human Services
DIBA	Disulfide Benzamide
DoD	Department of Defense
DOE	Department of Education
DOT	Diffuse Optical Tomography
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcome Study
DRG	Dorsal Root Ganglion
DSPP	Dentin Sialophosphorotein
DT	Drive for Thinness
DVT	Deep Vein Thrombosis
DW-MRI	Diffusion-Weighted MRI
EAGLE	Environment and Genetics in Lung Cancer Etiology
ECG	Electrocardiogram
EDIC	Epidemiology of Diabetes Interventions and Complications
EFA	Essential Fatty Acids
EFGR	Epidermal Growth Factor Receptor
EH	Endometrial Hyperplasia

EPA	Environmental Protection Agency
ER	Estrogen Receptor
FAES	Foundation for Advanced Education in the Sciences
FAQs	Frequently Asked Questions
FARE	Fellows Award for Research Excellence Program
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FDRs	First-Degree Relatives
FEPP	Fall Evaluation and Prevention Program
FHS	Framingham Heart Study
FIC	Fogarty International Center
FICA	Faith, Importance, Community, and Address
FICRS	The Fogarty International Clinical Research Scholars Program
FMS	Fibromyalgia Syndrome
FORE	Facilities of Research Excellence
FSH	Follicle-Stimulating Hormone
FY	Fiscal Year
GAIT	Glucosamine/Chondroitin Arthritis Intervention Trial
GCRC	General Clinical Research Centers
GDM	Gestational Diabetes
GEI	Genes, Environment, and Health Initiative
GEMS	Gene Expression Meta Signatures
GEMS	Ginkgo Evaluation of Memory Study
GEMS	Girls Health Enrichment Multisite Studies
GFWC	General Federation of Women's Clubs
GPP	Graduate Partnerships Program
GRIP	Global Research Initiative Program
GWAS	Genome-Wide Association Studies
HAART	Highly Active Antiretroviral Therapy
HBCUs	Historically Black Colleges and Universities
HBOC	Hereditary Breast Ovarian Cancer
HDL	High-Density Lipoprotein
HF	Heart Failure
HISS	High Spectral and Spatial Resolution
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
HPA	Hypothalamic-Pituitary-Adrenal Axis
HPV	Human Papillomavirus
HRQOL	Health-Related Quality of Life
HSIs	Hispanic-Serving Institutions
HHS	Health and Human Services
HT	Hormone Therapy

HUMC	Human Umbilical Cord Matrix
HWI	Hauptman Woodward Medical Research Institute
IBS	Irritable Bowel Syndrome
IC	Interstitial Cystitis
ICAM	Intracellular Adhesion Molecule
ICD	Implantable Cardioverter Defibrillator
ICs	Institutes and Centers of the National Institutes of Health
ITCUs	Indian Tribal Colleges or Universities
IHGP	International Human Genome Project
IIH	Idiopathic Intracranial Hypertension
IMRT	Intensity-Modulated Radiation Therapy
IOM	Institute of Medicine
IPV	Intimate Partner Violence
IRPWH	Intramural Research Program in Women's Health
IRWG	Institute for Research on Women and Gender
ITREOH	International Training and Research in Environmental and Occupational Health
IUGR	Intrauterine Growth Restriction
IWHR	Interdisciplinary Women's Health Research
KSIC	Know Stroke in the Community
LAM	Lymphangioleiomyomatosis
LBW	Low Birthweight
LDL	Low-Density Lipoprotein
LMICs	Low- and Middle-Income Countries
LONS	Longitudinal Optic Neuritis Study
LRP	Loan Repayment Program
LTB	Leiomyoma Tissue Bank
LUPUSDAI	Lupus Disease Activity Index
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MATE	Multidrug and Toxin Extrusion
MBS	Metabolic Syndrome
MCID	Minimum Clinically Important Difference
MDD	Major Depressive Disorder
MDSCs	Muscle-Derived Stem Cells
MEG	Magnetoencephalography
MFMU	Maternal Fetal Medicine Units
MFSP	Minority Faculty Student Partnership Program
MHIRT	Minority Health and Health Disparities International Research Training Program
MILES	Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus
MIP	Microbicides Innovation Program
MiRNA	Single-Stranded RNA Molecules
MMG	Magnetomyographic

MMHCC	Mouse Models of Human Cancers Consortium
MOTOR	Maternal Oral Therapy to Reduce Obstetric Risk Trial
MRCN	Maryland Regional Community Network
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSCs	Mesenchymal Stem Cells
MsFLASH	Menopause Strategies: Finding Lasting Answers for Symptoms and Health
MSNA	Muscle Sympathetic Nerve Activity
MSTP	Medical Scientist Training Program
MSU-PHP CAMRTP	Morgan State University-Public Health Program's Complementary and Alternative Medicine Research Training Program
MTCT	Mother-to-Child Transmission
M-TMJD	Myofascial Temporomandibular Joint Disorder
MTX	Methotrexate
MUSC	Medical University of South Carolina
NAEC	National Advisory Eye Council
NAHH	National Alliance for Hispanic Health
NARAC	North American Rheumatoid Arthritis Consortium
NAS	Neonatal Abstinence Syndrome
NCCAM	National Center for Complementary and Alternative Medicine
NCCU	North Carolina Central University
NCDD	National Commission on Digestive Diseases
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCLR	National Council of La Raza
NCMHD	National Center on Minority Health and Health Disparities
NCNW	National Council of Negro Women
NCRR	National Center for Research Resources
NDEP	National Diabetes Education Program
NDRI	National Disease Research Interchange
NEI	National Eye Institute
NETT	National Emphysema Treatment Trial
NHANES	National Health and Nutrition Examination Survey
NSDUH	National Survey on Drug Use and Health
NHGRI	National Human Genome Research Institute
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NHW	Non-Hispanic White
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	*Eunice Kennedy Shriver* 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 for Occupational Safety and Health
NKCC	National Killer Cell Cytoxicity
NKDEP	National Kidney Disease Education Program
NKUDIC	National Kidney and Urologic Diseases Information Clearinghouse
NLAAS	National Latino and Asian American Study
NLM	National Library of Medicine
NMDA	Nmethyld Aspartate
NMRI	Network of Minority Research Investigators
NO	Nitrous Oxide
NOD	Non-Obese Diabetes
NORDIC	Neuro-Ophthalmology Research Disease Investigator Consortium
NPY	Neuropeptide
NR	Nuclear Receptor
NRSA	Ruth L. Kirchstein National Research Service Award
NSA	National Stroke Association
NSCLC	Non-Small Cell Lung Cancer
NT	Neurotensin
NURSA	Nuclear Receptor Signaling Atlas
OAI	Osteoarthritis Initiative
OAR	Office of AIDS Research, NIH
OB/GYN	Obstetrics and Gynecology
OBSSR	Office of Behavioral and Social Sciences Research, NIH
OBT	Operant-Behavioral Therapy
OC	Office of Communications, NIH
OCA	Ovarian Cancer
OCAIDHD	Oklahoma Center for American Indian Diabetes Health Disparities
OCL	Office of Community Liaison, NIH
OCPL	Office of Communications & Public Liaison, NIH
OD	Office of the Director, NIH

ODS	Office of Dietary Supplements, NIH
OEODM	Office of Equal Opportunity and Diversity Management, NIH
OER	Office of Extramural Research, NIH
OFC	Orbitofrontal Cortex
OHAM	Office of HIV and AIDS Malignancy, NCI
OHSU	Oregon Health and Science University
OIR	Office of Intramural Research, NIH
OITE	Office of Intramural Training and Education, NIH
OLPA	Office of Legislative Policy and Analysis, NIH
OMAR	Office of Medical Applications Research, NIH
OMB	U.S. Office of Management and Budget
ONRC	Obesity/Nutrition Research Centers
ONTT	Optic Neuritis Treatment Trial
OPASI	Office of Portfolio Analysis and Strategic Initiatives, NIH
OPPERA	Orofacial Pain Prospective Evaluation and Risk Assessment
OPRU	Obstetric–Fetal Pharmacology Research Unit
ORs	Odds ratios
ORSC	Obesity Research Strategic Core
ORWH	Office of Research on Women's Health, NIH
OS	Opposite Sex
OSA	Obstructive Sleep Apnea
OSAT	Outpatient Substance Abuse Treatment
OSE	Office of Scientific Education, NIH
OSHA	Occupational Safety and Health Administration
OSM	Oncostatin
OSP	Office of Science Policy, NIH
OTC	Over the Counter
OWH	Office on Women's Health, HHS
PA	Program Announcement
PACE	Promoting Activity and Change in Eating
PAHs	Polycyclic Aromatic Hydrocarbons
PBS	Painful Bladder Syndrome
PCE	Prenatal Cocaine Exposure
PCOS	Polycystic Ovary Syndrome
PTSD	Posttraumatic Stress Disorder
PET/CT	Positron Emission Tomography/X-Ray Computed Tomography
PH	Pulmonary Hypertension
Ph.D.	Doctor of Philosophy
PHS II	Physicians' Health Study II
PI	Principal Investigator
PI	Protease Inhibitor
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

POF	Premature Ovarian Failure
POP	Pelvic Organ Prolapse
POTS	Postural Tachycardia
POWER	Evaluating Weight Loss Programs for Obese People at Risk for Heart Disease
POWER	Premenopausal, Osteoporosis Women, Alendronate, Depression
PPD	Postpartum Depression
PPRU	Pediatric Pharmacology Research Unit
PRIDE	Program to Reduce Incontinence by Diet and Exercise
PR	Progesterone Receptor
PTH	Parathyroid Hormone
PVN	Paraventricular Nucleus
QIRs	Quiescent Intracellular Reservoirs
QOL	Quality of Life
QD	Quantum Dots
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
rCBF	Regional Cerebral Blood Flow
REAP	Research Enhancement Awards Program
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RF	Rheumatoid Factor
RFA	Radiofrequency Ablation
RFA	Requests for Applications
RFP	Request for Proposals
RRISK	Reproductive Risks of Incontinence Study at Kaiser
ROC	Receive Operating Characteristics
RTT	Rett Syndrome
SBP	Systolic Blood Pressure
SCCOR	Specialized Centers of Clinically Oriented Research
SCCPIR	Specialized Cooperative Centers Program in Reproduction and Infertility Research
SCOR	Specialized Centers of Research
SCRN	Stillbirth Collaborative Research Network
SD	Spasmodic Dysphonia
SERMs	Selective Estrogen Receptor Modulators
SGI	Society of Gynecological Investigation
SGs	Salivary Glands
SHARe	SNP-Health Association Resource
SIDS	Sudden Infant Death Syndrome
SISTEr	Stress Incontinence Surgical Treatment Efficacy Trial
SLE	Systemic Lupus Erythematosus
SNHL	Sensorineural Hearing Loss
SNPs	Single Nucleotide Polymorphisms

SoS	State of the Science
SPORE	Specialized Program of Research Excellence
SPYWS	Stroke Prevention in Young Women Study
SS	Same Sex
SS	Sjögren's Syndrome
SSRIs	Selective Serotonin Reuptake Inhibitors
STAR	Study of Tamoxifen and Raloxifene
SUCCEED	Study to Understand Cervical Cancer Early Endpoints and Determinants
SUD	Substance Use Disorders
SUI	Stress Urinary Incontinence
SUNY	The State University of New York
SWAN	Study of Women's Health Across the Nation
T2D	Type 2 Diabetes Mellitus
TAAG	Trial of Activity for Adolescent Girls
TANF	Temporary Assistance for Needy Families
TAU	Tel Aviv University
TBI	Traumatic Brain Injury
T-CBSM	Telephone-Based Cognitive Behavioral Stress Management
TEAM	Training and Education to Advance Multidisciplinary and Clinical Research Program
TG	Triglycerides
TGFbeta	Transforming Growth Factor Beta
THC	Tetrahydrocannabinol
THP	Telephone Health Promotion
TKR	Total Knee Replacement
TMD	Temporomandibular Disorders
TMJMDs	Temporomandibular Joint and Muscle Disorders
TNF	Tumor Necrosis Factor
TOMUS	Trial of Mid-Urethral Slings
TRIAD	Translating Research Into Action for Diabetes
UCDHSC	University of Colorado at Denver and Health Sciences Center
UIC	University of Illinois at Chicago
UM	University Michigan
UMB	University of Maryland, Baltimore
UMSOM	University of Maryland School of Medicine
UNC	University of North Carolina
UPEC	Uropathogenic *Escherechia Coli*
US	Ultrasound
USLs	Uterosacral Ligaments
USU	Uniform Services University
UTI	Urinary Tract Infection
UTMB	University of Texas Medicine Branch

UW	University of Wisconsin, Madison
VAC	Vulvodynia Awareness Campaign
VCU	Virginia Commonwealth University
VEGF	Vascular Endothelial Growth Factor
VWD	Von Willebrand Disease
WEMS	Women in the Environmental Mutagen Society
WHI	The Women's Health Initiative
WHIMS	Women's Health Initiative Memory Study
WHS	Women's Health Study
WHSIG	Women's Health Special Interest Group
WIHS	Women's Interagency HIV Study
WIN	Weight-Control Information Network
WISE	Women's Ischemia Syndrome Evaluation (Study)
WRHR	Women's Reproductive Health Research
WSA	Women's Scientist Advisors Committee
YWAMI	Young Women with Acute Myocardial Infarction

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NIH Publication No. 09-7439