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

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

Fiscal Years 2001 & 2002

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

# Office of Research on Women's Health

and

# NIH Support for Research on Women's Health Issues

Fiscal Years 2001&2002

# *Preface*

The Advisory Committee on Research on Women's Health (ACRWH),[1] in concert with the Office of Research on Women's Health (ORWH) and the Coordinating Committee on Research on Women's Health, are pleased to provide this report describing the comprehensive and coordinated efforts of the ORWH and the NIH institutes and centers to address women's health issues through research and related activities supported in fiscal years 2001-2002. This report also provides corresponding information and analysis concerning levels of support for such research and related activities.

In accordance with the NIH Revitalization Act of 1993,

(4) The Advisory Committee shall—

(A) advise the Director of the Office on appropriate research activities to be undertaken by the national research institutes with respect to—

(i) research on women's health;

(ii) research on gender differences in clinical drug trials, including responses to pharmacological drugs;

(iii) research on gender differences in disease etiology, course, and treatment;

(iv) research on obstetrical and gynecological health conditions, diseases, and treatments; and

(v) research on women's health conditions which require a multidisciplinary approach;

(B) report to the Director of the Office on such research;

(C) provide recommendations to such Director regarding activities of the Office (including recommendations on the development of the methodologies described in subsection (c)(4)(C) and recommendations on priorities in carrying out research described in subparagraph (A)); and

(D) assist in monitoring compliance with section 492B regarding the inclusion of women in clinical research.

(5)(A) The Advisory Committee shall prepare a biennial report describing the activities of the Committee, including findings made by the Committee regarding—

(i) compliance with section 492B;

(ii) the extent of expenditures made for research on women's health by the agencies of the National Institutes of Health; and

(iii) the level of funding needed for such research.

[1] The current members of the ACRWH are listed on the page following the Preface.

(B) The report required in subparagraph (A) shall be submitted to the Director of NIH for inclusion in the report required in section 403.

(Public Law 103-43, 107, Stat. 22 (codified at 42 U.S.C. 289.a-1) [Sec. 486(A)] )

The information and data in this report were prepared and submitted by each of the NIH's institutes and centers and highlight significant research studies, achievements, and initiatives that have contributed to an increased knowledge of women's health. The ACRWH has reviewed the information submitted by the institutes and centers and the ORWH contained herein and believes that this report accurately reflects the breadth and depth of research and related activities through which the NIH fulfilled its mandate from the U.S. Congress to address women's health issues and women's inclusion in research in fiscal years 2001-2002.

In this report, the ORWH documents its role in catalyzing research and focusing on interdisciplinary research on women's health across the NIH institutes and centers, promoting and monitoring women's inclusion in clinical research, and developing programs to nurture women in biomedical careers during fiscal years 2001-2002. The office describes in some detail its programs to promote women's participation and advancement in biomedical careers through a number of programs carried out in collaboration with professional societies and universities, medical schools, and research institutions nationwide. Efforts to ensure NIH-wide compliance with Federal legislation and NIH guidelines mandating the appropriate inclusion of women in clinical research are also described in detail.

The Executive Summary features program highlights from each institute and center, as well as analyses of funding of research on specific diseases and conditions presented in tabular format. Full reports submitted by each institute and center constitute the greater part of this report. Research supported by the ORWH during fiscal years 2001 and 2002 is presented in the appendices.

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

## *Advisory Committee on Research on Women's Health, 2003*

### *Chairperson*

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

### *Executive Secretary*

**Joyce Rudick**
Director, Programs and Management
Office of Research on Women's Health
National Institutes of Health

### *Committee Members*

*Otis W. Brawley, M.D.*
Professor of Medicine
Associate Director for Cancer Control
Winship Cancer Institute- Emory University

*Myrna Blyth, M.A.*
Senior Vice President
Publishing Director and Editor-in-Chief
*Ladies Home Journal* and *More* Magazine

*Lee S. Cohen, M.D.*
Associate Professor of Psychiatry
Harvard Medical School
Massachusetts General Hospital

*Teri Fontenot, M.B.A.*
President and CEO
Woman's Hospital
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*Lorraine Anne Fitzpatrick, M.D.*
Professor of Medicine
Director, Women's Health Fellowship
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*Timothy R. B. Johnson, M.D.*
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Director Hispanic Center of Excellence
University of Texas Health Sciences Center at San Antonio

*Antonia C. Novello, M.D., M.P.H., Dr.P.H.*
Commissioner, New York State Department of Health

*Irene Pollin, M.S.W.*
Founder and President, Sister-to-Sister Foundation

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Vice President, Health Sciences and Medical Affairs
Dean, School of Allied Health and Life Sciences
New York Institute of Technology

*Sally A. Shumaker, Ph.D.*
Director, Women's Health Center of Excellence
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*Jackson T. Wright, Jr., M.D., Ph.D.*
General Clinical Research Center
Division of Clinical Hypertension
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# *Contents*

# *Introduction*

In accordance with the NIH Revitalization Act of 1993,[1] the Office of Research on Women's Health (ORWH) has worked with the staff members of the National Institutes of Health (NIH) institutes and centers and representatives of the NIH Coordinating Committee on Research on Women's Health (CCRWH),[2] which is made up of the Directors of each of the institutes and centers or their designated representatives, to prepare this biennial report describing NIH research and other efforts related to women's health in fiscal years 2001 and 2002. Through this report, ORWH also documents its role in catalyzing multidisciplinary and interdisciplinary research on women's health across the NIH institutes and centers, promoting and monitoring women's inclusion in clinical research, and developing programs to foster women's participation and advancement in biomedical careers. In addition, research projects supported by ORWH during fiscal years 2001 and 2002 are presented in the appendices.

A cursory review of the reports from the institutes and centers shows the tremendous expansion of studies and breadth of scientific knowledge already gleaned from studies conducted on topics related to women's health over the past decade. From investigations at the molecular level to community-based prevention studies and epidemiological surveys, research to better understand sex- and gender-based differences in health and disease has grown in both numbers of studies undertaken, as well as in the scientific complexity of topics studied.

This report, which has benefitted from the contributions of numerous NIH staff members and thoughtful review and comment by the members of the NIH Advisory Committee on Research on Women's Health (ACRWH),[3] reflects the tremendous diversity and depth of scientific studies and other programs designed to expand our knowledge of the role of sex and gender in health and disease in order to improve the health of both women and men alike. We are grateful to the many staff members of the institutes, centers, and offices who prepared the reports contain herein. Finally, we particularly appreciate the work of the NIH Office of Financial Management and the Office of Research on Women's Health in preparing this report.

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

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[1] (a) IN GENERAL – With respect to research on women's health, the Director of the Office shall, not later than February 1, 1994, and biennially thereafter, prepare a report—
(1) describing and evaluating the progress made during the preceding 2 fiscal years in research and treatment conducted or supported by the National Institutes of Health;
(2) describing and analyzing the professional status of women physicians and scientists of such Institutes, including the identification of problems and barriers regarding advancements;
(3) summarizing and analyzing expenditures made by the agencies of such Institutes (and by such Office) during the preceding 2 fiscal years; and
(4) making such recommendations for legislative and administrative initiatives as the Director of the Office determines to be appropriate.
(b) INCLUSION IN BIENNIAL REPORT OF DIRECTOR OF NIH – The Director of the Office shall submit each report prepared under subsection (a) to the Director of NIH for inclusion in the report submitted to the President and the Congress under section 403.'.
(b) REQUIREMENT OF SUFFICIENT ALLOCATION OF RESOURCES OF INSTITUTES – Section 402(b) of the Public Health Service Act (42 U.S.C. 282(b)) is amended—
(1) in paragraph (10), by striking 'and' after the semicolon at the end;
(2) in paragraph (11), by striking the period at the end and inserting '; and'; and
(3) by inserting after paragraph (11) the following paragraph:
(12) after consultation with the Director of the Office of Research on Women's Health, shall ensure that resources of the National Institutes of Health are sufficiently allocated for projects of research on women's health that are identified under section 486(b).'.

[2] The current members of the NIH Coordinating Committee on Research on Women's Health are listed on pp. 7 and 9.

[3] The current members of the ACRWH are listed on p. iii.

## *Advisory Committee on Research on Women's Health, November 2001*

| *Representative* | *Title and Affiliation* |
|---|---|
| Vivian W. Pinn, M.D.<br>*Chairperson* | Associate Director for Research on Women's Health<br>Director, Office of Research on Women's Health<br>Office of the Director, National Institutes of Health<br>Bethesda, Maryland |
| Joyce Rudick<br>*Executive Secretary* | Director, Programs and Management<br>Office of Research on Women's Health<br>Bethesda, Maryland |
| *Committee Members* | |
| Karen H. Antman, M.D. (2002) | Professor of Medicine and Pharmacology<br>Columbia University<br>Chief, Division of Medical Oncology<br>Columbia Presbyterian Comprehensive Cancer Center<br>New York, New York |
| Mary Chung, MBA (2005) | San Francisco, California |
| Frances J. Dunston, M.D., M.P.H. (2003) | Chair, Department of Pediatrics<br>Morehouse School of Medicine<br>Atlanta, Georgia |
| Lorraine Anne Fitzpatrick, M.D. (2004) | Professor of Medicine<br>Director, Women's Health Fellowship<br>Mayo Clinic and Foundation<br>Rochester, Minnesota |
| Marjorie K. Jeffcoat, D.M.D. (2005) | Rosen Professor and Chair<br>Department of Periodontics<br>The University of Alabama at Birmingham<br>School of Dentistry<br>Birmingham, Alabama |
| Ruth Katz, J.D., M.P.H. (2004) | Associate Dean for Administration<br>Yale University<br>New Haven, Connecticut |
| Mary-Claire King, Ph.D. (2003) | American Cancer Society Research Professor<br>Departments of Medicine and Genetics<br>University of Washington<br>Seattle, Washington |
| Marian C. Limacher, M.D. (2005) | Professor of Medicine<br>Division of Cardiovascular Medicine<br>University of Florida College of Medicine<br>Gainesville, Florida |
| Michael D. Lockshin, M.D. (2005) | Director and Professor<br>The Barbara Volcker Center for Women<br>& Rheumatic Disease<br>New York, New York |

| *Representative* | *Title and Affiliation* |
|---|---|
| John Molina, M.D. (2003) | Executive Director<br>Las Fuentes Health Clinic of Guadalupe<br>Guadalupe, Arizona |
| Antonia C. Novello, M.D., M.P.H., Dr.P.H. (2005) | Commissioner<br>New York State Department of Health<br>Albany, New York |
| Deborah E. Powell, M.D. (2002) | Office of Executive Dean<br>University of Kansas Medical Center<br>School of Medicine<br>Kansas City, Kansas |
| Barbara Ross-Lee, D.O., Ph.D. (2004) | Vice President, Health Sciences and Medical Affairs<br>Dean, School of Allied Health and Life Sciences<br>New York Institute of Technology<br>Old Westbury, New York |
| Rosalie Sagraves, PharmD., FCCP (2003) | Dean and Professor<br>University of Illinois<br>College of Pharmacy<br>Chicago, Illinois |
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| Nancy A. Fugate Woods, Ph.D., R.N., FAAN (2002) | Dean, School of Nursing<br>University of Washington<br>Seattle, Washington |
| Jackson T. Wright, Jr., M.D., Ph.D. (2005) | Division of Hypertension<br>Department of Medicine<br>Case Western Reserve University<br>School of Medicine<br>Cleveland, Ohio |
| Darlene Yee Melichar, Ed.D., CHES (2002) | Director and Professor, Gerontology Programs<br>College of Health and Human Services<br>San Francisco State University<br>San Francisco, California |

## *Advisory Committee on Research on Women's Health, October 2002*

| *Representative* | *Title and Affiliation* |
|---|---|
| Vivian W. Pinn, M.D.<br>*Chairperson* | Associate Director for Research on Women's Health<br>Director, Office of Research on Women's Health<br>Office of the Director, National Institutes of Health<br>Bethesda, Maryland |
| Joyce Rudick<br>*Executive Secretary* | Director, Programs and Management<br>Office of Research on Women's Health<br>Bethesda, Maryland |
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| Otis W. Brawley, M.D. (2006) | Professor of Medicine<br>Hematology and Oncology<br>Associate Director for Cancer Control<br>Emory University–Winship Cancer Institute<br>Atlanta, Georgia |
| Myrna Blyth, M.A. (2006) | Senior Vice President<br>Publishing Director and Editor-in-Chief<br>*Ladies Home Journal* and *More* Magazine<br>New York, New York |
| Frances J. Dunston, M.D., M.P.H. (2003) | Chair, Department of Pediatrics<br>Morehouse School of Medicine<br>Atlanta, Georgia |
| Teri Fontenot, M.B.A. (2006) | President and CEO<br>Woman's Hospital<br>Baton Rouge, Louisianna |
| Lorraine Anne Fitzpatrick, M.D. (2004) | Professor of Medicine<br>Director, Women's Health Fellowship<br>Mayo Clinic and Foundation<br>Rochester, Minnesota |
| Marjorie K. Jeffcoat, D.M.D. (2005) | Rosen Professor and Chair<br>Department of Periodontics<br>The University of Alabama at Birmingham<br>School of Dentistry<br>Birmingham, Alabama |
| Ruth Katz, J.D., M.P.H. (2004) | Associate Dean for Administration<br>Yale University<br>New Haven, Connecticut |
| Marian C. Limacher, M.D. (2005) | Professor of Medicine<br>Division of Cardiovascular Medicine<br>University of Florida College of Medicine<br>Gainesville, Florida |

| *Representative* | *Title and Affiliation* |
|---|---|
| Michael D. Lockshin, M.D. (2005) | Director and Professor<br>The Barbara Volcker Center for Women<br>& Rheumatic Disease<br>New York, New York |
| Martha A. Medrano, M.D., M.P.H. (2006) | Director, Hispanic Center of Excellence<br>University of Texas Health Sciences Center<br>at San Antonio<br>San Antonio, Texas |
| Jackson T. Wright, Jr., M.D., Ph.D. (2005) | Division of Hypertension<br>Department of Medicine<br>Case Western Reserve University<br>School of Medicine<br>Cleveland, Ohio |
| Antonia C. Novello, M.D., M.P.H., Dr.P.H. (2005) | Commissioner<br>New York State Department of Health<br>Albany, New York |
| Irene Pollin, M.S.W. (2006) | Founder and President<br>Sister to Sister Foundation<br>Chevy Chase, Maryland |
| Barbara Ross-Lee, D.O., Ph.D. (2004) | Vice President, Health Sciences and Medical Affairs<br>Dean, School of Allied Health and Life Sciences<br>New York Institute of Technology<br>Old Westbury, New York |
| Rosalie Sagraves, PharmD., FCCP (2003) | Dean and Professor<br>University of Illinois<br>College of Pharmacy<br>Chicago, Illinois |
| Sally A. Shumaker, Ph.D. (Pending) | Director, Women's Health Center of Excellence<br>Wake Forest University School of Medicine<br>Public Health Sciences<br>Winston-Salem, North Carolina |
| Robert A. Wild, M.D., M.P.H. (2003) | Professor and Chief<br>Section of Research and Education in Women's Health<br>Department of Obstetrics/Gynecology<br>University of Oklahoma Health Sciences Center<br>Oklahoma City, Oklahoma |

## *Coordinating Committee on Research on Women's Health Representatives, 2001*

| *Institute, Center, or Division* | *Representative* | *Title* |
|---|---|---|
| NIDA | CoraLee Wetherington | Women's Health Coordinator |
| NICHD | Judith Whalen | Associate Director for Science Policy Analysis and Communication |
| NHLBI | Barbara Liu | Deputy Director, Office of Science and Technology |
| NCRR | Dorothy Sogn | Medical Officer |
| NIAMS | Julia Freeman | Director, Centers Program |
| NLM | Angela Ruffin | Outreach Librarian |
| NIGMS | Pamela Marino | Program Director |
| NIEHS | Anne Sassaman | Director, Division of Extramural Research and Training |
| NCI | Anna Levy | Program Analyst |
| NIA | Taylor Harden | Assistant to the Director for Special Populations |
| NINR | Carole Hudgings | Program Director |
| NINDS | Patricia Turner | Program Analyst |
| NHGRI | Monique Mansoura | Policy Analyst |
| NEI | Ellen S. Liberman | Director, Lens, Cataract, and Glaucoma Programs |
| NIDCR | Pat Bryant | Program Director, Behavior and Health Promotion Research |
| NIDCD | Amy Donahue | Acting Chief, Hearing and Balance/Vestibular Sciences Branch |
| NIAID | Angela Magliozzi | Women's Health Program Coordinator |
| NIDDK | Susan Yanovski | Director, Obesity and Eating Disorders Program |
| NIMH | Mary Blehar | Chief, Women's Mental Health Program |
| NIAAA | Mary Dufour | Deputy Director |
| NIBIB | Donna Dean | Acting Director |
| FIC | Kathleen Michels | Program Official |
| CSR | Sooja Kim | Chief, Nutritional and Metabolic Sciences IRG |
| OIT | Joan Chamberlin | Office of Information Technology Information Officer |
| CC | Deborah Dozier-Hall | Assistant to Chief for Education |
| OD | Jan Hedetniemi | Director, Office of Community Liaison |
| NCCAM | Christine Goertz | Program Director |
| NCMHD | John Ruffin | Director |
| OAR | Judith Auerbach | Coordinator, Prevention Science and Behavioral and Social Science |
| OSE | Bonnie Kalberer | Contractor |
| OD | Donna Dean | Senior Advisor to the Acting Director, NIH |
| OD | Anne Thomas | Director, Office of Communications |
| OBSSR | Raynard Kington | Director |
| ODS | Paul Coates | Director |
| OE | Jim Alexander | Deputy Director |
| OSP | Cheryl McDonald | Senior Medical Officer |

## *Coordinating Committee on Research on Women's Health Alternates, 2001*

| *Institute, Center, or Division* | *Alternate* | *Title* |
|---|---|---|
| NIDA | Adele Roman | Deputy Women's Health Coordinator |
| NICHD | Estella Parrott | Program Director, Reproductive Sciences Branch |
| NHLBI | Carol E. Vreim | Deputy Director, Division of Lung Diseases |
| NCRR | Amy Swain | Health Science Administrator |
| NIAMS | Deborah N. Ader, Ph.D. | Director, Behavioral and Prevention Research Program |
| FIC | Sharon Hrynkow | Deputy Director |
| NIGMS | Caroline Julian | Program Assistant, Office of Program Analysis and Evaluation |
| NIEHS | Sheila Newton | Director, Office of Program Planning and Evaluation |
| NCI | Cherie Nichols | Director, Office of Science Planning and Assessment |
| NIA | Barbara Kellner | Technical Information Specialist |
| NINR | Janice Phillips | Program Director |
| NINDS | Lorainne Fitzsimmons | Program Analyst |
| NEI | Natalie Kurinij | Health Scientist Administrator |
| NIDCR | Dushanka Kleinman | Deputy Director |
| NIDCD | Nancy Freeman | Program Administrator |
| NIAID | Milton Hernandez | Director, Office of Special Populations |
| NIDDK | Mary Beth Kester | Office of Scientific Program and Policy Analysis |
| NIMH | Sherman Ragland | Deputy Associate Director for Special Populations |
| NIAAA | Diedra Roach | Health Science Administrator |
| NIBIB | Joan Harmon | Health Science Administrator |
| NCCAM | Marguerite Evans | Program Officer |
| CSR | Victoria Levin | Science Review Administrator |
| OD/OEO | Dorothy McKelvin | Contract Specialist |
| CC | Walter Jones | Deputy Director for Management and Operations |
| OPLA | Susan Persons | Senior Policy Analyst |
| OBSSR | Virginia Cain | Special Assistant to the Director |
| OSP | Lana Skirboll | Director |
| OER | Belinda Seto | Deputy Director |
| OAR | Susan Wise | Program Analyst, Policy and Analysis |
| NCMHD | Jean Flag-Newton | Deputy Director |
| OEODM | Joan Brogan | Deputy Director |

## *Coordinating Committee on Research on Women's Health Representatives, 2002*

| *Institute, Center, or Division* | *Representative* | *Title* |
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| NICHD | Judith Whalen | Associate Director for Science Policy Analysis and Communication |
| NHLBI | Barbara Liu | Deputy Director, Office of Science and Technology |
| NCRR | Sheila McClure | Health Scientist Administrator |
| NIAMS | Julia Freeman | Director, Centers Program |
| NLM | Angela Ruffin | Outreach Librarian |
| NIGMS | Pamela Marino | Program Director |
| NIEHS | Anne Sassaman | Director, Division of Extramural Research and Training |
| NCI | Anna Levy | Program Analyst |
| NIA | Taylor Harden | Assistant to the Director for Special Populations |
| NINR | Carole Hudgings | Assistant Director, Extramural Activities |
| NINDS | Patricia Turner | Program Analyst |
| NHGRI | Karen Hajos | Program Planning Analyst |
| NEI | Ellen S. Liberman | Director, Lens, Cataract, and Glaucoma Programs |
| NIDCR | Maria Canto | Program Director, Population Sciences Program |
| NIDCD | Lana Shekim | Director, Voice and Speech Program |
| NIAID | Angela Magliozzi | Women's Health Program Coordinator |
| NIDDK | Eleanor Hoff | Science Policy Analyst |
| NIMH | Mary Blehar | Chief, Women's Programs |
| NIAAA | Mary Dufour | Deputy Director |
| NIBIB | Donna Dean | Deputy Director |
| FIC | Kathleen Michels | Program Official |
| CSR | Sooja Kim | Chief, Nutritional and Metabolic Sciences IRG |
| CC | Deborah Dozier-Hall | Assistant to Chief for Education |
| NCCAM | Christine Goertz | Program Director |
| NCMHD | John Ruffin | Director |
| OAR | Judith Auerbach | Coordinator, Prevention Science and Behavior and Social Sciences |
| OSE | Bonnie Kalberer | Contractor |
| OC | John Burklow | Acting Director, Office of Communications |
| OBSSR | Raynard Kington | Director |
| ODS | Mary Francis Picciano | Senior Nutritionist |
| OE | Jim Alexander | Deputy Director |
| OSP | Cheryl McDonald | Senior Medical Officer |
| OCL | Tom Gallagher | Director |
| OEODM | Joan Brogan | Deputy Director |

## *Coordinating Committee on Research on Women's Health Alternates, 2002*

| *Institute, Center, or Division* | *Alternate* | *Title* |
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| NIDA | Adele Roman | Deputy Women & Gender Research Coordinator |
| NICHD | Estella Parrott | Medical Officer, Reproductive Sciences Branch |
| NHLBI | Carol E. Vreim | Deputy Director, Division of Lung Diseases |
| NCRR | Susan Kayar | Health Science Administrator |
| NIAMS | Charisee Lamar | Health Science Administrator |
| FIC | Sharon Hrynkow | Deputy Director |
| NIGMS | Ann Hagan | Deputy Associate Director for Extramural Activities |
| NIEHS | Sheila Newton | Director, Office of Program Planning and Evaluation |
| NCI | Cherie Nichols | Director, Office of Science Planning and Assessment |
| NIA | Barbara Kellner | Technical Information Specialist |
| NINR | Janice Phillips | Program Director |
| NINDS | Lorainne Fitzsimmons | Program Analyst |
| NEI | Natalie Kurinij | Health Scientist Administrator |
| NIDCR | Ruth Nowjack-Raymer | Program Director, Health Disparities Research |
| NIDCD | Amy Donahue | Acting Chief, Hearing & Balance/Vestibular Sciences Branch |
| NIAID | Milton Hernandez | Director, Office of Special Populations |
| NIDDK | Mary Beth Kester | Program Analyst |
| NIMH | Ernest Marquez | Associate Director for Special Populations |
| NIAAA | Diedra Roach | Health Science Administrator |
| NIBIB | Joan Harmon | Health Science Administrator |
| NCCAM | Marguerite Klein | Program Officer |
| CSR | Victoria Levin | Science Review Administrator |
| OEODM | O. Marcella Haynes | Chief, Diversity, Policy, Planning and Evaluation |
| CC | Walter Jones | Deputy Director for Management and Operations |
| OPLA | Susan Persons | Senior Policy Analyst |
| OBSSR | Virginia Cain | Special Assistant to the Director |
| OSP | Lana Skirboll | Director |
| OER | Belinda Seto | Deputy Director |
| OAR | Susan Wise | Program Analyst, Policy and Analysis |
| NCMHD | Jean Flag-Newton | Deputy Director |
| OCL | Walter Mitten | Community Relations Specialist |

# *Office of Research on Women's Health*

In 1983 the then Assistant Secretary for Health, Dr. Edward N. Brandt, established the Public Health Service Task Force on Women's Health Issues when he recognized the paucity of data specific to women's health and programs.[1] New concepts for federal initiatives for women's health began to evolve. A 1985 report, the *Task Force on Women's Health Issues,* delineated a series of criteria for "differentiating a health problem, condition, or disease as a woman's issue." The criteria included:

- diseases or conditions *unique* to women or some subgroup of women;
- diseases or conditions *more prevalent* in women or some subgroup of women;
- diseases or conditions *more serious* in women or some subgroup of women;
- diseases or conditions for which *risk factors* are different for women or some subgroup of women; or
- diseases or conditions for which *interventions* are different in women or some subgroup of women.[2]

The report 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."[3]

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

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

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

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

The Office of Research on Women's Health is under the direction of a Director who:

- advises the NIH Director and staff on matters relating to research on women's health;

[1] Public Law 103-43. National Institutes of Health Revitalization Act of 1993. 42 USC 289 (a)(1).
[2] NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 *Fed. Reg.* 14508 (1994).
[3] *Women's Health: NIH Has Increased Its Efforts to Include Women in Research* (GAO/HEHS-00-96, May, 2000).
[4] National Institutes of Health: Problems in Implementing Policy on Women Study Populations (GAO/T-HRD-90-38).

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

## ORWH and Research on Women's Health

### *Research Initiatives*

Great progress has been made in establishing women's health research as an integral part of NIH research programs. All of the NIH institutes and centers support extramural and intramural biomedical and behavioral research in the area of women's health.

ORWH also collaborates with the broader scientific, health professional, and advocacy communities to encourage meritorious research on women's health and to implement the recommendations from the report, *Agenda for Research on Women's Health for the 21st Century*.

A subcommittee of the Coordinating Committee on Research on Women's Health (CCRWH) reviews the many areas of research opportunities and recommends to ORWH scientific areas that are determined to be of special importance for expanding current initiatives or for developing new research programs. These areas are reviewed in terms of overarching approaches that apply to each research topic. The recommendations of CCRWH are then reviewed for approval by the Advisory Committee on Research on Women's Health. This list of research priorities is by no means comprehensive, nor is it intended that new studies be limited to those topics. Rather, those recommended priorities signify areas in which ORWH wishes to stimulate and encourage research on women's health.

Each year ORWH recognizes these priority areas for new initiatives or increased research focus. For the period FY 2001-2002, overarching approaches for research included recommendations for: 1) studies that address females across the life span as research subjects, especially those traditionally underrepresented in clinical research, such as those from diverse cultures, minority populations, girls and women, the elderly, rural or inner city women, those affected by poverty and low socioeconomic status, and women with disabilities; 2) investigations that foster a multidisciplinary basic, translational, behavioral, and clinical research relevant to women's health, especially on conditions which may be chronic and/or multisystemic; 3) integration of chemical and physical sciences, mathematics, bioengineering, bioinformatics, and bioimaging with biological sciences in relation to women's health, including the development of novel synthetic devices and biological approaches for tissue and organ regeneration and repair; and 4) support for new investigators that conducted research in priority areas of interest. A listing of specific research topical priorities for FY 2001-2002 is shown in Tables 1 and 2.

The ORWH research portfolio in FY 2001-2002 included major research initiatives that supported large-scale initiatives in priority areas of interest. Major cofunded research initiatives represent relatively large commitments of ORWH funding, many of which are responsive to Requests for Applications (RFAs) and Program Announcements (PAs) cosponsored with NIH ICs (Tables 3 and 4). During both FY 2001 (Table 5) and FY 2002 (Table 6), ORWH supported several new initiatives from RFAs that required a commitment for multi-year cofunding. Some of the RFAs include: the Autoimmunity Centers of Excellence (NIAID); Environmental Approaches to the Prevention of Obesity (NIDDK); Cooperative Reproductive Science Research Centers at Minority Institutions (NICHD); Sex Differences in Immune Response (NIAID); Neuropsychiatric

### *TABLE 1*
### *Research Priorities for Women's Health Research, FY 2001*

- Healthy Living and the Prevention of Chronic Disorders
- Interdisciplinary Approaches to Chronic Multisystemic Diseases with Multifactorial Etiology
- Mental Health and Addictive Disorders
- Reproductive Health
- Sexually Transmitted Diseases and Other Infections
- Caregiving and Health-related Quality-of-Life Issues
- Cancer
- Neurobiology
- Molecular and Biologic Basis for Sex Differences in Pharmacologic Response
- Complementary and Alternative Medicines and Dietary Supplements
- Specific Organ Systems

Systemic Lupus Erythematosus (NIAMS); the Global Health Research Initiative Program for New Foreign Investigators (FIC); and Vulvodynia – Systemic Epidemiological, Etiologic, or Therapeutic Studies (NICHD).

During FY 2001–2002, ORWH continued its cosponsorship of the Research Enhancement Awards Program (REAP), which identifies and supports meritorious projects relevant to women's health issues that are sent to ORWH by ICs and that otherwise would not have been funded by the ICs. The Office for Behavioral and Social Sciences Research (OBSSR) and the Office of Dietary Supplements (ODS) also cosponsored research grants under this program in FY 2001 and FY 2002. All REAP projects considered for funding by ORWH, OBSSR, and ODS had undergone scientific peer review and were recommended by an IC.

### *TABLE 2*
### *Research Priorities for Women's Health Research, FY 2002*

- Sex Differences in Health and Disease at the Genetic, Molecular, Cellular, and Functional Levels
- Healthy Living and the Prevention of Chronic Disorders
- Interdisciplinary Approaches to Chronic Multisystemic Diseases with Multifactorial Etiology
- Sex and Gender Differences in Response to Therapeutic Interventions
- Mental Health and Addictive Disorders
- Reproductive Health
- Infections, including Sexually Transmitted Diseases
- Caregiving and Health-related Quality-of-Life Issues
- Cancer
- Neurobiology
- Complementary and Alternative Medicines and Dietary Supplements
- Specific Organ Systems

### *TABLE 3*

### *Request for Applications and Program Announcements Sponsored by ORWH, FY 2001*

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

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

*Environmental Approaches to the Prevention of Obesity*
(NIDDK, NHLBI, NIEHS, NCMHD, OBSSR, ODP, CDC, ORWH) *(RFA-DK-02-021)*

*Cooperative Reproductive Science Research Centers at Minority Institutions*
(NICHD, ORMH, ORWH) *(RFA-HD-00-019)*

*Sex-based Differences in the Immune Response*
(NIAID, NINDS, NIAMS, ORWH, National Multiple Sclerosis Society) *(RFA-AI-01-005)*

*Neuropsychiatric Systemic Lupus Erythematosus*
(NIAMS, ORWH) *(RFA-AR-01-007)*

*HIV Pathogenesis in Women's Interagency HIV Study*
(NIAID, NICHD, NIDA, NIDR, NIDDK, NINDS, NCCAM, ORWH) *(PA-01-084)*

*New Approaches to the Pathogenesis and Treatment of Orofacial Pain*
(NIDR, ORWH) *(PA-01-108)*

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

### *TABLE 4*

### *Request for Applications and Program Announcements Sponsored by ORWH, FY 2002*

*Global Health Research Initiative Program for New Foreign Investors*
(FIC, ODS, NEI, NINDS, NIA, OBSSR, NIEHS, NIMH, ORWH) *(RFA-TW-02-002)*

*Stigma and Global Health Research Program*
(FIC, HRSA, NCMHD, NHGRI, NIAID, NIDR, NIMH, NINDS, NIAAA, NIDA, OAR, OBSSR, ORWH, Canadian Institutes of Health Research/Institute of Neurosciences, Mental Health and Addiction with the International Development Research Center) *(RFA-TW-03-001)*

*Cooperative Reproductive Science Research Centers at Minority Institutions*
(NICHD, NCRR, ORWH) *(RFA-HD-02-012)*

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

*Autoimmunity Centers of Excellence*
(NIAID, NIDDK, ORWH) *(RFA-AI-02-006)*

*Planning Grants for Research to Prevent or Reduce Oral Health Disparities*
(NIDR, NCMHD, ORWH) *(RFA-DE-02-005)*

*Research on Ethical Issues in Human Studies*
(NCI, NHLBI, NHGRI, NIA, NIAAA, NIAID, NICHD, NIDCD, NIDR, NIDDK, NIDA, NIEHS, NIGMS, NIMH, NINDS, NINR, NCCAM, FIC, OBSSR, ORWH) *(PA-02-103)*

*Vulvodynia – Systematic Epidemiologic, Etiologic, or Therapeutic Studies*
(NICHD, ORWH) *(PA-02-090)*

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

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

*HIV Pathogenesis in Women's Interagency HIV Study: Addendum to PA-01-084*
(NIAID, NICHD, NIDA, NIDR, NIDDK, NINDS, NCCAM, ORWH) *(PA-01-084)*

## *TABLE 5*
## *ORWH Cosponsored Research Initiatives, FY 2001*

| *Subject* | *Title* | *IC* | *Award Amount* |
|---|---|---|---|
| *Adolescent Health* | The National Study of Adolescent Health – ADD Health | NICHD | $ 50,000 |
| *Aging* | Age Difference of Spouses and Long-term Care | NIA | 86,538 |
| | A Fall Prevention Program for High-risk Elderly Women | NINR | 150,000 |
| *Alcohol and Other Substance Abuse* | Alcohol, HIV Risk Behaviors, and Sexual Victimization | NIAAA | 100,000 |
| | Sexual Identity and Drinking: Risk and Protection Factors | NIAAA | 55,224 |
| | Women with Schizophrenia and Co-occurring Substance Use Disorders | NIDA | 20,000 |
| *Cancer* | Growth Regulation of the Normal and Malignant Endometrium | NCI | 100,000 |
| | Clinical Trials of Two Human Papillomavirus-like Particle Vaccines | NCI | 300,000 |
| | Symptom Intervention for Older Women with Breast Cancer | NINR | 100,000 |
| *Cardiovascular Disease* | Evidence Report – Gender Differences in Cardiac Care | AHRQ | 250,000 |
| | Hormonal Regulation of Angiotensin Receptors | NIA | 100,000 |
| | Cardiovascular Disease Risk and Health in Postmenopausal Phytoestrogen Users | NHLBI | 144,795 |
| *Diabetes* | Diabetes Prevention Program (DPP) – Primary Prevention Program – Data Coordinating Center | NIDDK | 67,500 |
| | Diabetes Prevention Program (DPP) – Primary Prevention Trial | NIDDK | 67,500 |
| | Diabetes Prevention Program (DPP) | NIDDK | 21,000 |
| | Diabetes Prevention Program (DPP) | NIDDK | 22,000 |
| | NIDDM Primary Prevention Trial (DPT-2) | NIDDK | 22,000 |
| *Eating Disorders* | Meditation-based Treatment for Binge Eating Disorder | NCCAM | 172,095 |
| | Nociception in Bulimia Nervosa | NIDDK | 200,000 |
| *Endocrinology* | Mechanisms of Steroid Hormone Action in Brain | NIDDK | 100,000 |
| *Gastroenterology* | Cognitive Therapy as a Treatment for Irritable Bowel Syndrome | NIDDK | 100,000 |
| | Neurotensin's Role in Models of Irritable Bowel Syndrome-related Hyperalgesia | NIDDK | 50,000 |
| | Regional Cerebral Activation with Visceral Pain in Irritable Bowel Syndrome Controls | NIDDK | 100,000 |
| | Effect of Menstrual Cycle and Irritable Bowel Syndrome on Central Nervous System Processing of Gut Stimuli | NIDDK | 50,000 |
| | Biofeedback for Fecal Incontinence and Constipation | NIDDK | 75,000 |
| *Genitourinary* | Urine Loss and Prolapse in Nuns and Their Parous Sisters | NICHD | 331,779 |
| | A Randomized Surgical Trial: Burch vs. Sling | NIDDK | 115,000 |
| | Maryland Interstitial Cystitis Clinical Trials Group | NIDDK | 100,000 |

*(continued on page 16)*

*TABLE 5 (continued)*

***ORWH Cosponsored Research Initiatives, FY 2001***

| *Subject* | *Title* | *IC* | *Award Amount* |
|---|---|---|---|
| *Genitourinary (continued)* | Denver Autoimmunity Center of Excellence | NIAID | $ 75,000 |
| | Mechanism of Copaxone Therapy in Multiple Sclerosis | NIAID | 140,000 |
| | Penn Autoimmunity Center of Excellence | NIAID | 75,000 |
| | T Cell Reconstitution after Stem Cell Autograft | NIAID | 60,000 |
| | How Does Blockage of CD40/CD40L Prevent Autoimmunity? | NIAID | 100,000 |
| | Gene Mapping in Women with Systemic Lupus Erythematosus | NIAMS | 245,818 |
| | Studies of Collagen Gene Regulation in Two Murine Models | NIAMS | 200,000 |
| | Immune Mechanisms of Anti-CD40L Trial in Systemic Lupus Erythematosus | NIAMS | 50,000 |
| | c-Jun N-terminal Kinase and Joint Destruction in Rheumatoid Arthritis | NIAMS | 100,000 |
| | Cellular and Genetic Basis of Systemic Lupus Erythematosus | NIAMS | 185,000 |
| | Fine Specificity of Scleroderma Autoantibodies | NIAMS | 200,000 |
| | Registry and Repository of African Americans with Rheumatoid Arthritis | NIAMS | 200,000 |
| | A Model of Sjögren's Syndrome with Anti-Ro/La Antibodies | NIAMS | 200,000 |
| | Combining of N-of-1 Trials to Assess Fibromyalgia Therapies | NIAMS | 140,000 |
| | Mechanisms of Lupus Induction in L-Canavanine | NIEHS | 100,000 |
| *Infectious and Sexually Transmitted Diseases* | Mid-America Adolescent Sexually Transmitted Diseases Cooperative Research Center | NIAID | 50,000 |
| *Maternal–Child Health* | Nursing Support Intervention for Mothers of Prematures | NINR | 100,000 |
| *Menopause* | Predicting Onset Age and Length of Menopausal Transition | NIA | 100,558 |
| | Study of Women's Health Across the Nation II (SWAN II) | NIA | 250,000 |
| | Centers for Dietary Supplements Research: Botanicals | NCCAM | 100,000 |
| | Menopausal Transition, Mental Health, and Ethnicity | NIMH | 100,000 |
| | Menopausal Depression: Chronobiologic Basis | NIMH | 100,000 |
| *Mental Health* | Black Rural and Urban Caregivers' Mental Health Functioning | NIA | 150,000 |
| | Relationship of Morbidity and Mortality between Spouses | NIA | 380,000 |
| | Depression Self Management and Women with Disabilities | NICHD | 173,882 |
| *Musculoskeletal Systems* | Doxycycline Effect on Osteoarthritis Progression | NIAMS | 100,000 |
| | Glucocorticoids Alter the Birth and Death of Osteoblasts | NIAMS | 100,000 |
| | Low-dose Doxycline Effects on Osteopenic Bone Loss | NIDCR | 363,768 |
| *Neurology* | Estrogen-induced Hippocampal Seizure Susceptibility | NINDS | 35,000 |
| *Nutrition* | Food Choline Database Project | NHLBI | 50,000 |
| | Altered Calcium and Vitamin D Metabolism in Premenstrual Dysphoric Disorder | NIDDK | 100,000 |
| | Mechanism of Vulvodynia | NICHD | 19,046 |
| | Harvard School of Dental Medicine | NIDCR | 25,000 |
| | Treating Premenstrual Syndrome and Premenstrual Dysphoric Disorder: Research Versus Clinical Reality | NIMH | 100,000 |

*(continued on page 17)*

***TABLE 5** (continued)*

***ORWH Cosponsored Research Initiatives, FY 2001***

| *Subject* | *Title* | *IC* | *Award Amount* |
|---|---|---|---|
| *Pain* | Low Back Pain – A Multicenter Randomized Trial | NIAMS | 100,000 |
| | Pain Management in Temporomandibular Joint Disorders | NIDCR | 263,058 |
| *Pharmacology* | Gender and Risk of Drug-induced Cardiac Arrhythmias | NHLBI | 50,000 |
| | Endogenous Regulators of Drug Metabolism | NIGMS | 317,000 |
| *Physical Activity* | African American Women's Response to Physical Activity | NINR | 98,993 |
| *Pulmonology* | Lymphangioleiomyomatosis Patient Registry | NHLBI | 100,000 |
| *Reproductive Health and Developmental Biology* | Aging of Brain: Effects of Prenatal Nutrition | NIA | $ 100,000 |
| | Development and Differentiation in Reproductive Axis: Cooperative Reproductive Sciences Research at Minority Institutions | NICHD | 250,000 |
| | Fragile X Mental Retardation Gene Premutation | NICHD | 113,000 |
| | Neuroimmunology/Cytokine Alterations in Vulvodynia | NICHD | 180,954 |
| | Trigeminal Pain Mechanisms and Control | NIDCR | 151,174 |
| | Uterine Pain – Mechanisms and Modulation | NINDS | 100,000 |
| *Violence* | National Academy of Science Panel on Risk and Prevalence of Elder Abuse and Neglect | NIA | 75,000 |
| | Hispanic Battered Women's Experiences of Health Care: Biophysical and Immunologic Responses to Battering | NINR | 26,150 |
| | | NINR | 26,150 |

In collaboration with NIAID, ORWH cofunded four Autoimmune Centers of Excellence under RFA-AI-98-010. Research supported included clinical trials on the use of an antibody to Interleukin-12 for the treatment of multiple sclerosis and for inflammatory bowel disease; an evaluation of subcutaneous insulin vaccination to prevent the appearance of anti-islet auto antibodies in infants at high risk for the development of auto antibodies and disease; projects to study the therapy of autoimmune diseases by blocking co-stimulatory signals, focusing on the CD40-CD40L pathway; and studies of the immunopathogenesis of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, and scleroderma.

Other major areas of research support in FY 2001–2002 included continued support for the development and clinical trials testing of two human papillomavirus (HPV)-like particle vaccines with NCI. ORWH cofunded numerous autoimmune grants with NIAID and NIAMS, such as visual dysfunction and quality of life in multiple sclerosis, gene mapping in women with systemic lupus erythematosus, registry and repository of African Americans with rheumatoid arthritis, a model of Sjögren's syndrome with Anti-Ro/La antibodies, and fibromyalgia therapy clinical trials.

In the area of pain research, a major initiative continued during FY 2001 to study low back pain and common spinal disorders, as well as an RFA on Sex and Gender-related

## *TABLE 6*
## *ORWH Cosponsored Research Initiatives, FY 2002*

| *Subject* | *Title* | *IC* | *Award Amount* |
|---|---|---|---|
| *Aging* | Aging of Brain: Effects of Prenatal Nutrition | NIA | $ 100,000 |
| | A Fall Prevention Program for High-risk Elderly Women | NIA | 150,000 |
| *Alcohol and Other Substance Abuse* | Biobehavioral Trajectories to Alcohol Abuse: A Pilot Study | NIAAA | 100,000 |
| | Alcohol, HIV Risk Behaviors, and Sexual Victimization | NIAAA | 50,000 |
| | Gender and Sex Differences in Stimulant Action | NIDA | 296,133 |
| | Timing of Social Service Events on Women's Recovery | NIDA | 73,000 |
| | Women with Schizophrenia and Co-occurring Substance Use Disorders | NIDA | 20,000 |
| | Sexual Identity and Drinking: Risk and Protection Factors | NIAAA | 44,007 |
| *Cancer* | Clinical Trials of Two Human Papillomavirus-like Particle Vaccines | NCI | 600,000 |
| | Mitotic Checkpoint and Genomic Stability in Ovarian Cancer | FIC | 17,500 |
| | Tumor Progression and Apoptosis in Mouse Mammary Gland | FIC | 17,500 |
| | Acrogranin Function in the Ovary | FIC | 17,500 |
| | Ethnicity-based Proteomic Biomarkers in Breast Cancer | NCI | 100,000 |
| *Cardiovascular Disease* | Why is Cardiac Risk Increased in Rheumatoid Arthritis? | NIAMS | 100,000 |
| | Cardiovascular Risk in Former Gestational Diabetic Women | NINR | 100,000 |
| *Diabetes* | The Post-diabetes Prevention Program Follow-up Study | NIDDK | 300,000 |
| | Diabetes Prevention Program (DPP) Primary Prevention Program – Data Coordinating Center | NIDDK | 67,500 |
| | Diabetes Prevention Program (DPP) Primary Prevention Trial | NIDDK | 67,500 |
| | Diabetes Prevention Program (DPP) | NIDDK | 21,000 |
| | NIDDM Primary Prevention Trial (DPT-2) | NIDDK | 22,000 |
| | Diabetes Prevention Program (DPP) | NIDDK | 22,000 |
| *Endocrinology* | Plasticity of Hypothalamic Neurons: Estrogen Effects | NINDS | 100,000 |
| *Eye Disease* | Incidence of Late Macular Degeneration in Older Women | NEI | 230,000 |
| | Visual Dysfunction and Quality of Life in Multiple Sclerosis | NEI | 125,000 |
| *Gastroenterology* | Cognitive Therapy as a Treatment for Irritable Bowel Syndrome | NIDDK | 100,000 |
| | Biofeedback for Fecal Incontinence and Constipation | NIDDK | 75,000 |
| *Genitourinary* | Balkan Nephropathy: Environmental and Clinical Epidemiology | FIC | 17,500 |
| | Planning for Chinese HIV Prevention Training Program (PA02-022) Phase I – ICOHRTA – AIDS and Tuberculosis Grant Programs | FIC | 10,000 |
| | Typology of Street Prostitutes: HIV Risk and Well Being | NIDA | 71,000 |
| | HIV-related Oral Disease among Women in Harare | FIC | 34,523 |

*(continued on page 19)*

***TABLE 6** (continued)*

## *ORWH Cosponsored Research Initiatives, FY 2002*

| *Subject* | *Title* | *IC* | *Award Amount* |
|---|---|---|---|
| *Immunity and Autoimmunity* | Sex-based Differences in Antiviral Immunity and Systemic Lupus Erythematosus | NIAID | $ 50,000 |
| | Mechanism Regulating Neutrophil Activation in Pregnancy | NIAID | 50,000 |
| | Sex-based Differences in the Immune Response | NIAID | 50,000 |
| | Genetics of Rheumatoid Arthritis | NIAMS | 250,000 |
| | Cognitive Dysfunction Neuropsychiatric Systemic Lupus Erythematosus | NIAMS | 100,000 |
| | Brain Connections | NIAMS | 40,000 |
| | Identifying Genes for Neuropsychiatric Lupus | NIAMS | 20,000 |
| | Antibodies to NR2 in Systemic Lupus Erythematosus | NIAMS | 40,000 |
| | Brain Cell Death in MRL Mice: Targets and Mechanisms | NIAMS | 100,000 |
| | Tau Lymphocyte Dysfunction in Lupus Erythematosus | NIAMS | 100,000 |
| | Rheumatic Disease Sera: Probes of Disease Mechanism | NIAMS | 100,000 |
| | TGF-β Receptor Signaling in Scleroderma | NIAMS | 100,000 |
| | Autoimmunity Center of Excellence | NIAID | 75,000 |
| | Virginia Mason/University of Colorado Health Sciences Center Autoimmune Center | NIAID | 200,000 |
| | Autoimmunity: Treatment by Co-stimulatory Signal Blockade | NIAID | 75,000 |
| | Denver Autoimmunity Center of Excellence | NIAID | 75,000 |
| | Penn Autoimmunity Center of Excellence | NIAID | 75,000 |
| | T Cell Reconstitution after Stem Cell Autograft | NIAID | 60,000 |
| | How Does Blockage of CD40/CD40L Prevent Autoimmunity? | NIAID | 100,000 |
| | Mechanism of Copaxone Therapy in Multiple Sclerosis | NIAID | 140,000 |
| | EBNA-1 in Lupus | NIAID | 200,000 |
| | Sex Hormone Regulation of Innate Immunity in Women and Men | NIAID | 300,000 |
| | Investigating IL-6 Experimental Myasthenia Gravis | NIAID | 294,570 |
| | Mechanisms of T-cell-induced APC Cytotoxicity in Lupus | NIAMS | 100,000 |
| | Studies of Collagen Gene Regulation in Two Murine Models | NIAMS | 200,000 |
| | Fine Specificity of Scleroderma Autoantibodies | NIAMS | 200,000 |
| | Registry and Repository of African Americans with Rheumatoid Arthritis | NIAMS | 200,000 |
| *Infectious and Sexually Transmitted Diseases* | Sex in Viral Myocarditis | NIAID | 50,000 |
| | Mid-America Adolescent Sexually Transmitted Diseases Cooperative Research Center | NIAID | 50,000 |
| *Menopause* | Study of Women's Health Across the Nation II (SWAN II) | NIA | 250,000 |
| | Centers for Dietary Supplements Research: Botanicals | NCCAM | 100,000 |
| | Menopausal Depression: Chronobiologic Basis | NIMH | 100,000 |

*(continued on page 20)*

***TABLE 6** (continued)*

***ORWH Cosponsored Research Initiatives, FY 2002***

| *Subject* | *Title* | *IC* | *Award Amount* |
|---|---|---|---|
| *Mental Health* | Improving Antidepressant Adherence in Older Adults | NIMH | $ 100,000 |
| | Effects on Children of Treating Maternal Depression | NIMH | 50,000 |
| | Sex Differences in Self Evaluation: Social Factors | NIMH | 47,599 |
| | Health Survey of Two-spirited Native Americans | NIMH | 175,000 |
| *Musculoskeletal Systems* | Osteoarthritis Initiative | NIAMS | 800,000 |
| | New Methods for Monitoring Treatment for Osteoporosis | NIAMS | 100,000 |
| | Glucocorticoids Alter the Birth and Death of Osteoblasts | NIAMS | 100,000 |
| | Low-dose Doxycline Effects on Osteopenic Bone Loss | NIDCR | 308,924 |
| *Neurology* | Estrogen-induced Hippocampal Seizure Susceptibility | NINDS | 35,000 |
| *Nutrition* | Food Choline Database Project | NHLBI | 50,000 |
| | Altered Calcium and Vitamin D Metabolism in Premenstrual Dysphoric Disorder | NIDDK | 100,000 |
| *Obesity and Overweight* | Increasing Physical Activity Levels in Low-income Women | NIDDK | 178,750 |
| | Look AHEAD (Action for Health in Diabetes) | NIDDK | 100,000 |
| | Clinical and Experimental Study of Human Obesity | NIDDK | 100,000 |
| *Pain* | Low Back Pain – A Multicenter Randomized Trial | NIAMS | 100,00 |
| | Sex Differences in Opioid Analgesia | NIDA | 293,764 |
| | Trigeminal Pain Mechanisms and Control | NIDCR | 155,237 |
| | Pain Management in Temporomandibular Joint Disorders | NIDCR | 312,514 |
| | Research Registries and Repository for the Evaluation of Temporomandibular Muscle and Joint Disorders and Sjögren's Syndrome | NIDCR | 100,000 |
| *Physical Activity* | Physical Activity in Older Rural Midwestern Women | NINR | 26,188 |
| *Reproductive Health and Developmental Biology* | Intermediate Outcomes of Hysterectomy and Alternatives | AHRQ | 250,000 |
| | Variation in Cytokine and MMP Genes and Risk of PPROM | FIC | 17,5000 |
| | Characterization of Flagellar Proteins Involved in Sperm Motility | FIC | 17,500 |
| | Neuroimmunology and Cytokine Alterations in Vulvodynia | NICHD | 180,954 |
| | Control of Menstrual Bleeding Disturbances in Women | NICHD | 100,000 |
| | Mechanism of Vulvodynia | NICHD | 19,046 |
| | Development and Differentiation in Reproductive Axis: Cooperative Reproductive Sciences Research at Minority Institutions | NICHD | 250,000 |
| | Fragile X Mental Retardation Gene Premutation | NICHD | 113,000 |
| | Genotype and Phenotype Correlations in Infertility | NICHD | 100,000 |
| | Cellular and Molecular Mechanisms of Mammalian Ovulation | NICHD | 100,000 |
| | A National Training Program in Reproductive Medicine | NICHD | 100,000 |
| | Depo-Provera and Bone Mineral Densities in Premenopausal Women | NICHD | 183,750 |
| | Maternal Periodontitis and Adverse Pregnancy Outcome | NIDCR | 25,000 |
| *Violence* | Improving Interventions for Drug Abuse–Partner Violence | NIDA | 100,000 |

*TABLE 7*

***ORWH Special Projects, FY 2001***

| *Research Title* | *Cosponsor* | *Award Amount* |
|---|---|---|
| Governors' Spouses Initiative to Curb Underage Drinking | NIAAA | $100,000 |
| Preventive Hormone Therapy Decisionmaking on the World Wide Web | NIA | 176,575 |
| Reprinting of *Lupus: A Patient Care Guide for Nurses and Other Health Professionals* | NIAMS | 10,000 |
| Health Disparities Based on Sexual Orientation | DHHS | 3,000 |
| Pilot Study to Assess Older, Minority, Low-Income Women's Needs for Healthcare Information and Skill Development In Negotiating with Healthcare Providers for Services | UMBC | 24,999 |
| *Sister to Sister – Everyone Has A Heart* Women's Heart Day: Because a Woman's Heart is Different | | N/A |
| *Wish.net.org* | WISH-NET | 16,000 |

Differences in Pain and Analgesia Response, with NIDCR (DE-97-003). Under this RFA, research was conducted to evaluate sex-specific non-opioid mechanisms in pain modulation by sex; sex differences in regional μ-opioid receptor pain processing; sex differences in response to painful stimuli and its modulation by hormonal factors; and sex- and pregnancy-linked differences in the μ-opioid system. Additional pain research grants were funded that focus on temporomandibular joint disorders (TMJ), trigeminal pain mechanisms and control, and research registries and repository for TMJ devices.

In collaboration with NICHD, ORWH cosponsored several initiatives, including the Cooperative Reproductive Science Research Centers at Minority Institutions, and a second RFA focusing on vulvodynia research, including support for the neuroimmunology and cytokine alterations in vulvodynia. Additional research on menopause and menopausal symptoms include the continued long-term support for the Study of Women's Health Across the Nation, which ORWH co-supports with NIA's seven research centers that have recruited a multiracial/ethnic cohort of women. ORWH partnered with NCCAM and ODS to cofund a Center for Dietary Supplements Research on menopausal symptoms, and with NIMH on menopausal depression research.

NIDDK and ORWH cofund a number of important women's health research endeavors, including the long-term support for the Diabetes Prevention Program (DPP), the landmark study that demonstrated significant diabetes prevention benefits from lifestyle alternations and which is now in its followup phase. A second long-term collaboration focused on weight control in diabetes, called the Look-AHEAD trial (Action for Health in Diabetes). Additional grant support was provided for cognitive therapy for irritable bowel syndrome (IBS), neurotensin's role in models of IBS-related hyperalgesia, regional cerebral activation with biofeedback for fecal incontinence, the clinical and experimental study of human obesity, increasing physical activity levels in low-income women, and mechanisms of steroid hormone action in the brain.

In FY 2001, ORWH and the Agency for Healthcare Research and Quality (AHRQ) cofunded a major evidence report on the gender differences in cardiac care that will help to guide further deliberations in this area. The Phase II project built upon the findings and recommendations from the initial study that identified the scientific evidence and basis relating to sex and gender differences in coronary heart disease, its diagnosis, and subsequent treatment.

*TABLE 8*

***ORWH Special Projects, FY 2002***

| *Research Title* | *Cosponsor* | *Award Amount* |
|---|---|---|
| Sister to Sister Foundation: Everyone Has a Heart Health Fair | NHLBI | $ 20,000 |
| Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health | NIAMS | 8,700,000 |
| ▶ *Pharmacology of Antiepileptic and Psychotropic Medications during Pregnancy and Lactation* | | |
| ▶ *Role of Sex and Gender Differences in Substance Abuse Relapse* | | |
| ▶ *Genes, Androgens, and Intrauterine Environment in Polycystic Ovarian Syndrome* | | |
| ▶ *Sex Differences in Pain Sensitivity* | | |
| ▶ *Sex and Gender Factors in the Pathophysiology of Irritable Bowel Syndrome and Interstitial Cystitis* | | |
| ▶ *Mechanisms Underlying Female Urinary Incontinence* | | |
| ▶ *Birth, Muscle Injury, and Pelvic Floor Dysfunction* | | |
| ▶ *Genetic and Environmental Origins of Adverse Pregnancy Outcomes* | | |
| ▶ *Mechanisms by which Drug Transporters Alter Maternal and Fetal Drug Exposure during Pregnancy* | | |
| ▶ *Molecular and Epidemiologic Basis of Acute and Recurrent Urinary Tract Infections in Women* | | |
| ▶ *Sex, Stress, and Cocaine Addiction* | | |
| Governors' Spouses Initiative to Curb Underage Drinking | NIAAA | 100,000 |
| Curriculum for Colleges of Pharmacy | | 20,000 |
| Osteoarthritis Initiative | NIAMS | 800,000 |

The recommendations, considered by the Evidence Practice Centers and AHRQ, in order to complete a comprehensive evidence report on the prioritized set of questions that focus on the gender-based difference in diagnosis and treatment, both in-hospital and chronic, related to coronary heart disease. The study population is adult females, including major racial and ethnic minorities and the elderly. The final report from this project, *Management of Coronary Heart Disease in Women*, is in the clearance stage and will be available on the AHRQ website shortly.

## *TABLE 9*
## *ORWH Conferences and Workshops, FY 2001*

| *Research Title* | *Cosponsor* | *Award Amount* |
|---|---|---|
| International Conference on Cervical Cancer | NCI | $ 5,000 |
| Older Adults Health Information and the World Wide Web | NIA | 5,000 |
| Federation of American Society for Experimental Biology Research Conference on Autoimmunity | NIAID | 5,000 |
| Chronic Fatigue Syndrome Conference | NIAID | 37,500 |
| Health Disparities in Arthritis and Musculoskeletal and Skin Diseases – A Scientific Conference | NIAMS | 5,000 |
| 2001 ADD Health Users Conference and Skin Diseases – A Scientific Conference | NICHD | 5,000 |
| 6th International Conference on the Extracellular Matrix of the Female Reproductive Tract | NICHD | 5,000 |
| Endometriosis: Emerging and Intervention Strategies | NICHD | 5,000 |
| Clinical Pharmacology during Pregnancy: Addressing Clinical Needs through Science | FDA | 5,000 |
| The American Society for Cell Biology Meeting | NIEHS | 5,000 |
| The Science of Mind–Body Interactions Conference | NIMH | 5,000 |
| Using Research to Inform Patients of Breast Cancer Surgery Options | AHRQ | 5,000 |
| The National Lesbian Health Conference 2001: Challenges of the New Millennium | OWH/DHHS | 5,000 |
| A Generational Journey: Women Carrying the Vision Common Issues, United Voices Conference | SAMHSA | 7,500 |
| Treatment of Salivary Gland Disorders: Alternative Approaches An International Conference | NIDCR | 5,000 |
| Native American Cancer Survivors/Thrivers Conference | OMH/DHHS | 5,000 |
| Concepts and Strategies to Actively Monitor the Risk of Medication in Pregnancy: Enhancing Post-marketing Surveillance | CDC | 5,000 |
| Dietary Supplement Use in Women of Reproductive Age: What Do We Know? | NICHD | 5,000 |
| Intercultural Cancer Council 8th Biennial Symposium | NCI | 5,000 |
| Stigma and Global Health: Developing a Research Agenda | FIC | 5,000 |
| Native American Cancer Survivors/Thrivers Conference | OMH/DHHS | 5,000 |
| American Diabetes Association Session "Do Herbal Products Affect Quality-of-Life Issues for Women?" | ODS | 5,000 |
| The Role of Innate Immunity in the Etiopathology of Autoimmune Diseases | NIAID | 5,000 |
| Animal Models of Autoimmune Diseases – Are Current Models Adequate? | NIAID | 5,000 |
| Third International Conference on Women's Health | NCI | 5,000 |
| Differential Drug Use, HIV/AIDS, and Related Health Outcomes among Racial and Ethnic Populations | NIDA | 5,000 |

*TABLE 10*
*ORWH Conferences and Workshops, FY 2002*

| *Research Title* | *Cosponsor* | *Award Amount* |
|---|---|---|
| Endometrial Cancer Biology Workshop | NCI | $2,500 |
| Joint and Muscle Dysfunction of the Temporomandibular Joint | NIDCR | 5,000 |
| 2nd International Cervical Cancer Meeting | NCI | 5,000 |
| Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century | NIDDK | 5,000 |
| Workshop in Pelvic Pain | NICHD | 5,000 |
| Systemic Lupus Erythematosus: Targets for New Therapeutics | NIAMS | 5,000 |
| Minority Trainee Research Forum | NIDDK | 5,000 |
| Coming Face to Face with the Impact of Gender on Medical Care | | N/A |
| ADD Health Users Conference | NICHD | 5,000 |
| Perinatal Mood Disorders | NIMH | 5,000 |
| National Lesbian Health Conference 2002: Healing Works | OWS/DHHS | 5,000 |
| International Workshop on Autoantibodies as Predictors of Diseases | | 5,000 |
| The Eighth Annual John Diggs Lecture | | 1,500 |

## ORWH Research Priorities

A subcommittee of the Coordinating Committee on Research in Women's Health, chaired by Donna Vogel, M.D., Ph.D. and David Robinson, Ph.D., and composed of representatives from NIH institutes and centers, reviews the many areas of research opportunities and recommends to ORWH areas which are determined to be of special importance for expanding current initiatives or for developing new research programs. These areas are reviewed in terms of overarching approaches that apply to each area, as well as each research topic. This list is by no means comprehensive, nor should new studies be limited to those topics. Rather, those recommended here signify areas in which ORWH wishes to stimulate and encourage research on women's health.

ORWH also collaborates with the broader scientific, health professional, and advocacy communities to encourage meritorious research on women's health and to implement the recommendations from the report, *Agenda for Research on Women's Health for the 21st Century*. This report summarizes a series of national meetings that were held to revise the NIH agenda for research on women's health.

### Recommended ORWH Research Priorities for Fiscal Year 2001

#### *Overarching Approaches for Research on Women's Health*

- Inclusion of females across the life span as research subjects, especially in studies of factors contributing to health disparities among populations of women traditionally underrepresented in clinical research, such as those from diverse cultures, minority populations, girls and adolescents, the elderly, rural or inner-city women, those affected by poverty and low socioeconomic status, lesbians, and women with disabilities.
- Multidisciplinary basic, translational, behavioral, and clinical research relevant to women's health, especially on conditions which may be chronic and/or multisystemic.

- Integration of chemical and physical sciences, mathematics, bioengineering, bioinformatics, and bioimaging, with biological sciences in relation to sex and gender differences in women's health research.

## *Topical Research Priorities*

ORWH is particularly interested in supporting basic, translational, behavioral, and clinical research in women's health, especially to determine sex and gender or population factors, that pertain to (not listed in priority order):

- ***Cancer, including:***
  - Basic, etiological, genetic, and/or molecular studies that will elucidate the role of hormonal and environmental influences in carcinogenesis.
  - Lung cancer in women, including the examination of tobacco use and the role of sex and gender differences in the modifying effects of genetic polymorphisms.
  - The role of infectious factors, such as human papillomaviruses, in cervical cancer.
- ***Caregiving and Health-related Quality-of-Life Issues, including:***
  - The development and evaluation of effective strategies to improve the health-related quality of life for women and their families.
  - The effects of caregiving on the health of the care giver.
  - The examination of stress and coping styles in women with multiple/competing societal roles.
- ***Complementary and Alternative Medicines and Dietary Supplements, including:***
  - Building the evidence base for effective complementary and alternative medicines and dietary supplements as women's health products, in cooperation with NCCAM and ODS.
- ***Healthy Living and the Prevention of Chronic Disorders, including:***
  - The impact of diet, nutrition, hormones, exercise, and weight patterns.
  - The emerging epidemic of obesity and eating disorders, including basic mechanistic studies and strategies for prevention.
  - The impact of addictive behaviors, such as tobacco, alcohol, and illicit and licit drugs.
  - Tobacco and alcohol use and associated health effects, including developing and expanding scientific and behavioral investigations to address and eradicate tobacco use and other tobacco-associated health effects, including cancers of the head, neck, and cervix, with a focus on the potentiating effects of alcohol.
- ***Interdisciplinary Approaches to Chronic Multisystemic Diseases with Multifactorial Etiology, including:***
  - The study of genetic, infectious, environmental, molecular, and/or hormonal factors as they contribute to disorders affecting women.
  - The study of allergic, immune, and/or autoimmune diseases, including resistance and susceptibility genes, environmental influences, mechanisms of sex differences in immunological responses, target organ influence, role of innate immunity, development of surrogate markers, and immune therapy.
- ***Mental Health and Addictive Disorders, including:***
  - The study of neurobiological and psychological risk factors, including sex and gender differences, in the development of schizophrenia, as well as mood, anxiety, and eating disorders.
  - The role of sex and gender differences in the neurobiological and

psychological consequences (including drug abuse) of early trauma, physical and sexual assault, and elder abuse.

- The role of susceptibility to addiction in alcohol, tobacco, and licit and illicit drug use.

- ***Molecular and Biologic Basis for Sex Differences in Pharmacologic Response, including:***

  - The implications of special pharmacokinetics and pharmacodynamics of medications in men and women.

  - The implications of special pharmacokinetics and pharmacodynamics of medications during pregnancy.

- ***Neurobiology, including:***

  - The examination of sex and endocrine differences in manifestations of brain health and of brain disorders, especially epilepsy, brain attack (stroke), migraine, and neurodegenerative diseases, including Alzheimers and Parkinson's disease.

  - Sleep and other circadian rhythms.

  - Sex differences in acute and chronic pain conditions or syndromes, such as chronic and migraine headaches, fibromyalgia, chronic fatigue syndrome, and temporomandibular joint dysfunction.

- ***Reproductive Health, including:***

  - Pregnancy issues, such as low-birthweight infants; effects of infections, including oral infections and inflammation, on adverse pregnancy outcomes; other disease manifestations and treatments during pregnancy; prevention, diagnosis, and treatment of pregnancy complications, including fetal loss and the development of neural tube defects; and promoting increased safety and acceptability in the use of contraceptive options.

  - Non-pregnancy issues, such as reducing morbidity from myoma, endometriosis, abnormal uterine bleeding, uterine prolapse, polycystic ovarian syndrome, other gynecologic diseases, and menopause.

- ***Sexually Transmitted Diseases and Other Infections, including:***

  - The evaluation of sexually transmitted diseases, especially emerging pathogens, HIV/AIDS, topical microbicides, and human papillomaviruses.

- ***Specific Organ Systems, including:***

  - The impact of infectious agents and diabetes on cardiovascular, cerebrovascular, and peripheral vascular diseases.

  - Musculoskeletal system health, including chronic disorders and injuries in female athletes.

  - Gastrointestinal health disorders, including irritable bowel syndrome, liver disease, and inflammatory bowel syndrome.

  - Kidney and urologic health, including end-stage renal disease in women; eclampsia, diabetic, autoimmune, and analgesic-abuse nephropathy; interstitial cystitis and painful bladder syndromes; urinary tract infections; urinary incontinence; and pelvic floor disorders and conditions.

## Recommended ORWH Research Priorities for Fiscal Year 2002

### *Overarching Approaches for Research on Women's Health Including Sex and Gender Differences*

These themes apply to all listed priorities:

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

### *Topical Research Priorities*

ORWH is particularly interested in supporting basic, translational, behavioral, and clinical research in women's health, especially to determine sex and gender or other variables, that pertain to (not listed in priority order):

- ***Cancer, including:***
  - Basic, etiological, genetic, and/or molecular studies that will elucidate the role of hormonal and environmental influences in carcinogenesis.
  - Identification of markers of risk and disease, which can be used as targets for prevention, early detection, and treatment.
  - Cancers of the lung, head, neck, and cervix, including the examination of tobacco and alcohol use, and the role of sex and gender differences in the modifying effects of genetic polymorphisms.
  - The role of infectious factors and the immune environment in women's cancers.
- ***Caregiving and Health-related Quality-of-Life Issues, including:***
  - The development and evaluation of effective strategies to improve the health-related quality of life for women and their families.
  - The effects of caregiving on the health of the care giver.
  - The examination of stress and coping styles in women with multiple/competing societal roles.
- ***Complementary and Alternative Medicines and Dietary Supplements, including:***
  - Building the evidence base for effective complementary and alternative medicines and dietary supplements as women's health products, in cooperation with NCCAM and ODS.
- ***Healthy Living and the Prevention of Chronic Disorders, including:***
  - The impact of diet, nutrition, hormones, exercise, and weight patterns.
  - The emerging epidemic of obesity and eating disorders, including basic mechanistic studies and strategies for prevention.
  - The impact of addictive behaviors, such as tobacco, alcohol, and illicit and licit drugs.
  - Tobacco and alcohol use and associated health effects, including developing and expanding scientific and behavioral investigations to address and eradicate tobacco use and alcohol abuse, and other tobacco-associated health effects.

- ***Infections and Sexually Transmitted Diseases, including:***
  - The evaluation of emerging pathogens, sexually transmitted infections, HIV/AIDS, topical microbicides, and human papillomaviruses.
- ***Interdisciplinary Approaches to Chronic Multisystemic Diseases with Multifactorial Etiology, including:***
  - The study of genetic, infectious, environmental, molecular, and/or hormonal factors as they contribute to disorders affecting women.
  - The study of allergic, immune, and/or autoimmune diseases, including resistance and susceptibility genes, environmental influences, mechanisms of sex differences in immunological responses, target organ influence, role of innate immunity, development of surrogate markers, and immune therapy.
- ***Mental Health and Addictive Disorders, including:***
  - The study of neurobiological and psychological risk factors, including sex and gender differences, in the development of schizophrenia, as well as mood, anxiety, and eating disorders.
  - The role of sex and gender differences in the neurobiological and psychological consequences (including drug and alcohol abuse) of early trauma, physical and sexual assault, and elder abuse.
  - Developmental aspects, such as depression at puberty, postpartum major depression, and postpartum psychosis.
  - The role of susceptibility to addiction in alcohol, tobacco, and illicit and licit drug use.
- ***Neurobiology, including:***
  - The examination of sex and endocrine differences in manifestations of brain health and of brain disorders, especially epilepsy, brain attack (stroke), migraine, and neurodegenerative diseases, including Alzheimers and Parkinson's disease.
  - Sleep and other circadian rhythms.
  - Sex differences in acute and chronic pain conditions or syndromes, such as chronic and migraine headaches, fibromyalgia, chronic fatigue syndrome, and temporomandibular joint dysfunction.
- ***Reproductive Health, including:***
  - Reducing morbidity from myomas, endometriosis, abnormal uterine bleeding, uterine prolapse, polycystic ovarian syndrome, and other gynecologic diseases; and promoting increased safety and acceptability in the use of contraceptive options.
  - Effects of infections, including oral infections and inflammation, on adverse pregnancy outcomes; gestational diabetes and other disease manifestations and treatments during pregnancy; and prevention, diagnosis, and treatment of pregnancy complications, including fetal loss, low-birthweight infants, and the development of neural tube defects.
  - The menopausal transition.
- ***Sex and Gender Differences in Response to Therapeutic Interventions, including:***
  - Sex and age differences, as well as the impact of pregnancy and lactation, in pharmacokinetics, pharmacodynamics, drug efficacy, and side effects, including their genetic, molecular, and cellular bases; development of new methods of analysis.

- Sex and gender differences in behavioral interventions.
- Sex and gender differences in treatment choice, side effects, and compliance.

▶ ***Sex Differences in Health and Disease at the Genetic, Molecular, Cellular, and Functional Levels, including:***

- Chromosomal, genetic, gonadal, and phenotypic sex; differentiation and development.
- Cellular and physiological responses to hormonal and environmental agents.
- Animal models for the study of biological sex differences.

▶ ***Specific Organ Systems, including:***

- The impact of infectious agents and diabetes on cardiovascular, cerebrovascular, and peripheral vascular diseases.
- Musculoskeletal system health, including chronic disorders and injuries in female athletes.
- Gastrointestinal health disorders, including irritable bowel syndrome, liver disease, and inflammatory bowel syndrome.
- Kidney and urologic health, including end-stage renal disease in women; eclampsia, diabetic, autoimmune, and analgesic-abuse nephropathy; interstitial cystitis and painful bladder syndromes; urinary tract infections; urinary incontinence; and pelvic floor disorders and conditions.
- Ophthalmic diseases, including dry eye, with and without rheumatic disease, macular degeneration, and glaucoma.

# Request for Applications (RFAs) and Program Announcements (PAs) Sponsored by ORWH

## Fiscal Year 2001

### *Request for Applications*

▶ ***Building Interdisciplinary Research Careers in Women's Health***

*RFA-OD-02-001*

*Participating Institutes and Centers:*

Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

National Institute on Aging (*http://www.nia.nih.gov/*)

National Institute on Alcohol Abuse and Alcoholism (*http://www.niaaa.nih.gov/*)

National Institute of Arthritis and Musculoskeletal and Skin Disease (*http://www.niams.nih.gov/*)

National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

National Institute of Diabetes and Digestive and Kidney Diseases (*http://www.niddk.nih.gov/*)

National Institute of Mental Health (*http://www.nimh.nih.gov/*)

Office of Dietary Supplements (*http://ods.od.nih.gov/*)

Agency for Healthcare Research and Quality (*http://www.ahrq.gov/*)

▶ ***Cooperative Reproductive Science Research Centers at Minority Institutions***

*RFA-HD-00-019*

*Participating Institutes and Centers:*

National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

Office of Research on Minority Health (*http://www.ncmhd.nih.gov/*)

Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Environmental Approaches to the Prevention of Obesity***

  *RFA-DK-02-021*

  *Participating Institutes and Centers:*

  National Institute of Diabetes and Digestive and Kidney Diseases (*http://www.niddk.nih.gov/*)

  National Heart, Lung, and Blood Institute (*http://www.nhlbi.nih.gov/*)

  National Institute of Environmental Health Sciences (*http://www.niehs.nih.gov/*)

  National Center on Minority Health and Health Disparities (*http://www.ncmhd.nih.gov/*)

  Office of Behavioral and Social Sciences Research (*http://obssr.od.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

  Office of Disease Prevention (*http://odp.od.nih.gov/*)

  Centers for Disease Control and Prevention (*http://www.cdc.gov/*)

- ***Neuropsychiatric Systemic Lupus Erythematosus***

  *RFA-AR-01-007*

  *Participating Institutes and Centers:*

  National Institute of Arthritis and Musculoskeletal and Skin Disease (*http://www.niams.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Sex-based Differences in the Immune Response***

  *RFA-AI-01-005*

  *Participating Institutes and Centers:*

  National Institute of Allergy and Infectious Diseases (*http://www.niaid.nih.gov/*)

  National Institute of Neurological Disorders and Stroke (*http://www.ninds.nih.gov/*)

  National Institute of Arthritis and Musculoskeletal and Skin Disease (*http://www.niams.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

  National Multiple Sclerosis Society (*http://www.nationalmssociety.org/*)

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

  *RFA-OD-02-002*

  *Participating Institutes and Centers:*

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

  National Institute of Arthritis and Musculoskeletal and Skin Disease (*http://www.niams.nih.gov/*)

  National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

  National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

  National Institute of Diabetes and Digestive and Kidney Diseases (*http://www.niddk.nih.gov/*)

  National Institute on Drug Abuse (*http://www.nida.nih.gov/*)

  National Institute of Environmental Health Sciences (*http://www.niehs.nih.gov/*)

  National Institute of Mental Health (*http://www.nimh.nih.gov/*)

  Food and Drug Administration (*http://www.fda.gov/womens/default.htm*)

### *Program Announcements*

- ***Behavioral, Social, Mental Health, and Substance Abuse Research with Diverse Populations***

  *PA-01-096*

  *Participating Institutes and Centers:*

  National Institute of Mental Health (*http://www.nimh.nih.gov/*)

  National Institute on Drug Abuse (*http://www.nida.nih.gov/*)

  National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

  Office of Behavioral and Social Sciences Research (*http://obssr.od.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***HIV Pathogenesis in Women's Interagency HIV Study***

  *PA-01-084*

  *Participating Institutes and Centers:*

  National Institute of Allergy and Infectious Diseases (*http://www.niaid.nih.gov/*)

  National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

  National Institute on Drug Abuse (*http://www.nida.nih.gov/*)

  National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

  National Institute of Diabetes and Digestive and Kidney Diseases (*http://www.niddk.nih.gov/*)

  National Institute of Neurological Disorders and Stroke (*http://www.ninds.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

  National Center for Complementary and Alternative Medicine (*http://www.nccam.nih.gov/*)

- ***New Approaches to the Pathogenesis and Treatment of Orofacial Pain***

  *PA-01-108*

  *Participating Institutes and Centers:*

  National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

## Fiscal Year 2002

### *Request for Applications*

- ***Autoimmunity Centers of Excellence***

  *RFA-AI-02-006*

  *Participating Institutes and Centers:*

  National Institute of Allergy and Infectious Diseases (*http://www.niaid.nih.gov/*)

  National Institute of Diabetes and Digestive and Kidney Diseases (*http://www.niddk.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Cooperative Reproductive Science Research Centers at Minority Institutions***

  *RFA-HD-02-012*

  *Participating Institutes and Centers:*

  National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

  National Center for Research Resources (*http://www.ncrr.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Global Health Research Initiative Program for New Foreign Investors***

  *RFA-TW-02-002*

  *Participating Institutes and Centers:*

  Fogarty International Center (*http://www.fic.nih.gov/*)

  Office of Dietary Supplements (*http://ods.od.nih.gov/*)

  National Eye Institute (*http://www.nei.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

  National Institute of Neurological Disorders and Stroke (*http://www.ninds.nih.gov/*)

  National Institute on Aging (*http://www.nia.nih.gov/*)

  Office of Behavioral and Social Sciences Research (*http://obssr.od.nih.gov/*)

  National Institute of Environmental Health Sciences (*http://www.niehs.nih.gov/*)

  National Institute of Mental Health (*http://www.nimh.nih.gov/*)

- ***Pathobiology of Temporomandibular Joint Disorders***

  *RFA-DE-03-005*

  *Participating Institutes and Centers:*

  National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

  National Institute of Arthritis and Musculoskeletal and Skin Disease (*http://www.niams.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Planning Grants for Research to Prevent or Reduce Oral Health Disparities***

  *RFA-DE-02-005*

  *Participating Institutes and Centers:*

  National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

  National Center on Minority Health and Health Disparities (*http://www.ncmhd.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Stigma and Global Health Research Program***

  *RFA-W-03-001*

  *Participating Institutes and Centers:*

  Fogarty International Center (*http://www.fic.nih.gov/*)

  Health Research Services Administration (*http://www.hrsa.gov/*)

  National Center on Minority Health and Health Disparities (*http://www.ncmhd.nih.gov/*)

  National Human Genome Research Institute (*http://www.nhgri.nih.gov/*)

  National Institute of Allergy and Infectious Diseases (*http://www.niaid.nih.gov/*)

  National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

  National Institute of Mental Health (*http://www.nimh.nih.gov/*)

  National Institute of Neurological Disorders and Stroke (*http://www.ninds.nih.gov/*)

  National Institute on Alcohol Abuse and Alcoholism (*http://www.niaaa.nih.gov/*)

National Institute on Drug Abuse
(*http://www.nida.nih.gov/*)

Office of AIDS Research
(*http://www.nih.gov/od/oar/*)

Office of Behavioral and Social Sciences Research
(*http://obssr.od.nih.gov/*)

Office of Research on Women's Health
(*http://www4.od.nih.gov/orwh/*)

Canadian Institutes of Health Research/Institute of Neurosciences, Mental Health and Addiction
(*http://www.cihr-irsc.gc.ca/*)
with the International Development Research Center
*(http://www.idrc.ca/*)

## *Program Announcements*

- ***HIV Pathogenesis in Women's Interagency HIV Study: Addendum to PA-01-084***

  *PA-01-084*

  *Participating Institutes and Centers:*

  National Institute of Allergy and Infectious Diseases
  (*http://www.niaid.nih.gov/*)

  National Institute of Child Health and Human Development
  (*http://www.nichd.nih.gov/*)

  National Institute on Drug Abuse
  (*http://www.nida.nih.gov/*)

  National Institute of Dental and Craniofacial Research
  (*http://www.nidcr.nih.gov/*)

  National Institute of Diabetes and Digestive and Kidney Diseases
  (*http://www.niddk.nih.gov/*)

  National Institute of Neurological Disorders and Stroke
  (*http://www.ninds.nih.gov/*)

  Office of Research on Women's Health
  (*http://www4.od.nih.gov/orwh/*)

  National Center for Complementary and Alternative Medicine
  (*http://www.nccam.nih.gov/*)

- ***Pathophysiology and Treatment of Chronic Fatigue Syndrome***

  *PA-02-034*

  *Participating Institutes and Centers:*

  Office of Research on Women's Health
  (*http://www4.od.nih.gov/orwh/*)

  Office of Dietary Supplements
  (*http://ods.od.nih.gov/*)

  Office of Behavioral and Social Sciences Research
  (*http://obssr.od.nih.gov/*)

  National Center for Complementary and Alternative Medicine
  (*http://www.nccam.nih.gov/*)

  National Institute on Alcohol Abuse and Alcoholism
  (*http://www.niaaa.nih.gov/*)

  National Institute of Allergy and Infectious Diseases
  (*http://www.niaid.nih.gov/*)

  National Institute of Arthritis and Musculoskeletal and Skin Disease
  (*http://www.niams.nih.gov/*)

  National Institute of Child Health and Human Development
  (*http://www.nichd.nih.gov/*)

  National Heart, Lung, and Blood Institute
  (*http://www.nhlbi.nih.gov/*)

  National Institute of Environmental Health Sciences
  (*http://www.niehs.nih.gov/*)

  National Institute of Nursing Research
  (*http://www.nih.gov/ninr/*)

- ***Research on Ethical Issues in Human Studies***

  *PA-02-103*

  *Participating Institutes and Centers:*

  National Cancer Institute (*http://www.nci.nih.gov/*)

  National Heart, Lung, and Blood Institute (*http://www.nhlbi.nih.gov/*)

  National Human Genome Research Institute (*http://www.nhgri.nih.gov/*)

  National Institute on Aging (*http://www.nia.nih.gov/*)

  National Institute on Alcohol Abuse and Alcoholism (*http://www.niaaa.nih.gov/*)

  National Institute of Allergy and Infectious Diseases (*http://www.niaid.nih.gov/*)

  National Institute of Arthritis and Musculoskeletal and Skin Disease (*http://www.niams.nih.gov/*)

  National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

  National Institute on Deafness and Other Communication Disorders (*http://www.nidcd.nih.gov/*)

  National Institute of Dental and Craniofacial Research (*http://www.nidcr.nih.gov/*)

  National Institute of Diabetes and Digestive and Kidney Diseases (*http://www.niddk.nih.gov/*)

  National Institute on Drug Abuse (*http://www.nida.nih.gov/*)

  National Institute of Environmental Health Sciences (*http://www.niehs.nih.gov/*)

  National Institute of General Medical Sciences (*http://www.nigms.nih.gov/*)

  National Institute of Mental Health (*http://www.nimh.nih.gov/*)

  National Institute of Neurological Disorders and Stroke (*http://www.ninds.nih.gov/*)

  National Institute of Nursing Research (*http://www.nih.gov/ninr/*)

  National Center for Complementary and Alternative Medicine (*http://www.nccam.nih.gov/*)

  Fogarty International Center (*http://www.fic.nih.gov/*)

  Office of Behavioral and Social Sciences Research (*http://obssr.od.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Vulvodynia – Systematic Epidemiologic, Etiologic, or Therapeutic Studies***

  *PA-02-090*

  *Participating Institutes and Centers:*

  National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

- ***Women's Health in Sports and Exercise***

  *PA-02-115*

  *Participating Institutes and Centers:*

  National Institute of Arthritis and Musculoskeletal and Skin Disease (*http://www.niams.nih.gov/*)

  National Institute of Child Health and Human Development (*http://www.nichd.nih.gov/*)

  Office of Research on Women's Health (*http://www4.od.nih.gov/orwh/*)

# INTERDISCIPLINARY INITIATIVES

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

ORWH funded 11 new Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs). Funding for the centers will total approximately $11 million per year for 5 years with cofunding by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Child Health and Human Development (NICHD), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), the National Institute of Environmental Health Sciences (NIEHS), and the Food and Drug Administration (FDA.) These centers will provide new opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health.

Each SCOR will promote interdisciplinary collaborations and develop a research agenda bridging basic and clinical research on sex and gender factors underlying a priority health issue. The SCOR program will complement other federally supported programs addressing women's health issues. Such programs include: the Building Interdisciplinary Research Careers in Women's Health (BIRCWH), the Women's Reproductive Health Research Career Development Centers (WRHR), and numerous NIH RFAs and PAs.

This is the first time ORWH has taken the lead in developing and funding a new research initiative relating to women's health. The multidisciplinary nature of the centers will provide innovative approaches to advancing research on the role of sex- and gender-related health effects. The research scope of the SCORs stems from three sources: the Institute of Medicine (IOM) report, *Exploring the Biological Contributions to Health – Does Sex Matter?*, *An Agenda for Research on Women's Health for the 21st Century*, and from recommendations from the National Institutes of Health institutes and centers. The multidisciplinary nature of these centers will provide opportunities for innovative approaches to research on the role of sex- and gender-related health effects.

Thirty-six applications containing 184 projects were received in response to the SCOR RFA-OD-02-002; but one was withdrawn by the applicant prior to review. Applications were reviewed in two phases due to the number and diversity of the projects. Phase one reviewers provided critiques and scores based on scientific merit of the individual projects.

There was no review meeting for Phase one. Scores and critiques were made available to Phase two reviewers through the Internet-Assisted Review System. Phase two reviewers read the critiques and scores of each application prior to attending the review session. The Phase two committee consisted of investigators experienced in running centers funded by NIH institutes. Overall scores were determined by the combination of the two-phase review.

SCORs were selected on the basis of having at least three highly meritorious interdisciplinary research projects that explore an important issue related to sex and gender health differences, joined by a common theme. 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. Research priority areas, including mental health, reproductive health, pain disorders, and urinary tract health, will be addressed by grantees of this new ORWH initiative.

The primary institute program director will review the annual progress reports submitted by the SCORs, and will provide a yearly report on the scientific progress of the grantee. The ORWH SCOR Coordinator will oversee the applications to coordinate policy issues for the overall program. The SCOR Coordinator will make site visits, arrange annual meetings of the investigators, and write reports on the program for the Director of ORWH.

Research priority areas, including mental health, reproductive health, pain disorders, and urinary tract health, will be addressed by the new centers. The following section outlines SCOR themes, center directors, individual projects, and affiliations.

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

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

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

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

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

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

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

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

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

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

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

## Building Interdisciplinary Research Careers In Women's Health

The Office of Research on Women's Health developed an institutional career development award for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Programs. These programs support research career development of junior faculty members, known as Interdisciplinary Women's Health Research (IWHR) Scholars, who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, clinical, and/or health services research relevant to women's health.

The goal of this initiative is to promote the performance of research and transfer of findings that will benefit the health of women. The programs will accomplish these goals by bridging advanced training with research independence, as well as bridging scientific disciplines or areas of interest. This will increase the number and skills of investigators at awardee institutions through a mentored research experience leading to an independent scientific career addressing women's health concerns. This RFA uses the NIH Mentored Research Scientist Development Program Award (K12) mechanism.

A need was identified for expanded support for interdisciplinary research bridging the completion of training with an independent career in research addressing women's health, as described in the *Agenda for Research on Women's Health for the 21st Century, A Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century*, Volume 2, pp. 187-198, "Career Issues for Women Scientists," and pp. 223-228, "Multidisciplinary

Perspectives." ORWH has as one of its priorities "facilitating research initiatives that foster multidisciplinary collaborations." Program grant awards from this RFA met the specified need by providing clinical, health or life sciences, or public health departments, centers, and institutes, both developing and established, an opportunity to build national capacity for junior investigators in women's health research, here defined as including research on sex and gender differences, as well as research on factors that contribute to disparities in health status or health outcomes for different populations of women.

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

In FY 2001, ORWH convened a meeting of the Program Officials from each awardee institution. Issues, success stories, and problems were discussed in an open forum. Each institution reported on their status of the scholars recruited and updated the group on the program to date. In FY 2002, ORWH convened the second meeting and the following recommendations were made.

### *Future Plans and Recommendations*

- Development of database for tracking scholars
- Convening scholars research symposium
- Expansion of BIRCWH Program
- Increase name recognition for the BIRCWH Program
- Develop a permanent group of BIRCWH Scholars
- Develop a scholar exchange program between sites
- Improve outcome assessment and reporting of program successes, such as publications, grants received, and positions obtained
- Partner with other institutions, such as Veteran's Affairs, who have fellowship programs
- Bring current and former BIRCWH Scholars together once a year, at the same time each year
- Link the websites of all research sites, and link them to the ORWH website
- Use the same terminology to identify BIRCWH Scholars currently receiving funding; former scholars could be termed "BIRCWH Alumni"
- Bring current scholars into NIH to meet program officers and talk to grant people. (NIH/scholar meetings are part of BIRCWH II.)

**BIRCWH I Scholar Activities**

Twelve BIRCWH Scholars from BIRCWH I Centers participated in the March 21, 2002 ACRWH meeting and described their programs. ORWH invited BIRCWH I centers to each send a BIRCWH Scholar to participate in this ACRWH meeting. Timothy Johnson, M.D., Principal Investigator for the Michigan Initiative for Women's Health: Career Development Program, the NIH-funded BIRWCH site, introduced and moderated the panel of BIRCWH Scholars. He described the program as a Mentored Junior Faculty Career Development Award (K12), originally envisioned by Dr. Vivian Pinn and conceptualized by Dr. Donna Vogel and Ms. Joyce Rudick.

For this discussion, Dr. Johnson asked six of the current scholars to participate in a panel to discuss four areas of their BIRCWH Program: education and training background; a brief overview of individual research topics and interests; a description of the relationship between the scholar and her/his mentor; and a description of what participation in the BIRCWH Program has meant to their research careers.

- ***Kim Boggess, M.D.***
  *Cornell University; State University of New York/StonyBrook Medical School; completed a Residency in OB-GYN at the University of Washington in Seattle*

  Dr. Boggess' chief research interest is high-risk pregnancies. Dr. Boggess studied herpes expression and shedding during pregnancy as part of a 1-year sexually transmitted diseases training grant, and was introduced to basic scientific research while studying placental pathology and metabolism during a Society for Maternal-Fetal-Medicine Foundation Fellowship. Following 2 years on the faculty of Duke University, she was recruited to the University of North Carolina (UNC) due to her interest in infectious diseases and pregnancy outcome, particularly in high-risk pregnancies. She was awarded a BIRCWH Scholarship after several months on the UNC faculty.

  Dr. Boggess noted the BIRCWH Scholarship has funded her research in chronic maternal infection during pregnancy, particularly around peri-conception and peri-implantation, and has provided "protected time" to conduct research. Also, the formal and structured mentorship fostered by the BIRCWH Program has allowed the identification of mentors in OB-GYN and other disciplines, thereby fostering truly interdisciplinary work. Other helpful aspects of the BIRCWH Program include faculty development, grant writing, development of mentors, and tutelage in writing for and presenting at national meetings.

- ***Susan Brundage, M.D., M.P.H., FACS***
  *Trauma Surgeon and Assistant Professor of Surgery at the Baylor College of Medicine; Medical Degree from the University of Iowa College of Medicine; Residency in General Surgery at the George Washington University Medical Center; Fellowship in Trauma and Surgical Critical Care and Masters in Public Health, supported by NIH and CDC, from the University of Washington in Seattle; Board certified in general surgery, trauma, and critical care*

  Dr. Brundage reported that trauma is a major public health problem and the number one killer of women between the ages of 1 and 44. It is also the number one etiology of years of potential life lost. Dr. Brundage said that county hospitals specializing in trauma are too busy to allow time for research. She concluded that without the BIRCWH Program it would be difficult to find the mentors, and the research time, to be a true academic surgeon.

- ***Paulina Essah, M.D.***
  *Assistant Professor of Internal Medicine at the Virginia Commonwealth University and the Medical College of Virginia Hospital; Medical Degree from Johns Hopkins Medical School; Internal Medicine Residency at the University of Missouri in Kansas City*

  Dr. Essah's primary research interest is the relationship between type 2 diabetes and obesity in women. Her major research project is looking at interventions to reduce visceral adipose tissue in type 2 diabetic obese women, primarily those of reproductive age and pre-menopausal women. "The advantage of being a BIRCWH Scholar is the protected time it allows," Dr. Essah said. Previously, she spent all of her time on clinical work. Now, she spends 75 percent of her time on research, with the remainder on clinical work. She has taken formal courses and training in clinical research and plans to participate in a grant writing workshop. After she completes the BIRCWH training

program, Dr. Essah hopes to become an independent investigator. BIRCWH has given her the time and opportunity to improve her knowledge and education in clinical research, for which she is grateful.

- ***Josephine Kasa-Vubu, M.D.***
  *Pediatric Endocrinologist and Assistant Professor in Pediatrics in the Department of Pediatrics at the University of Michigan; Board certified in Pediatrics and Pediatric Endocrinology; Medical Training and Degree from the University of Louvain in Belgium; Specialty Training in General Pediatrics and Pediatric Endocrinology at the University of Michigan in Ann Arbor; completed a Fellowship in Pediatric Endocrinology*

  Dr. Kasa-Vubu is focusing her research in the area of puberty and young adulthood and investigating the effect of environmental insults, mostly exercise, on the reproductive potential of young adults. Although a pediatrician, she is interested in the 16 to 20 age group in young women. There is very little normative data on adolescent young women ages 16 to 20. Most health care advice is inferred from data from older women. Support from the BIRCWH award freed up time to allow her to focus on clinical studies and study the effect of exercise on normal gonadotropin profiles. Dr. Kasa-Vubu also praised the opportunity provided by the BIRCWH Program to sit down regularly with other BIRCWH Scholars, to share their interests, and to look beyond the field of endocrinology.

- ***Catherine Lewis, M.D.***
  *Assistant Professor of Psychiatry, University of Connecticut Health Center; studied Medicine at Yale University School of Medicine and completed a Residency in General Psychiatry at the University of Michigan; completed a Fellowship in Forensic Psychology at Yale*

  Dr. Lewis is currently studying the impact of ethnicity and socioeconomic status on health service utilization in a maximum-security women's prison in Connecticut, where she performs structured interviews and prospectively follows women, doing chart review and monitoring their mental health to see how well they utilize health care services. As a BIRCWH Scholar, Dr. Lewis relies on having protected research time and has developed "amazing" mentorships. Her initial studies were primarily descriptive. To take the step into nondescriptive studies as an M.D. is extremely challenging and the Ph.D. consultation allows her to take the step to be a neophyte researcher. BIRCWH has provided support that allowed her to develop the courage to take this step.

- ***Ann Rasmusson, M.D.***
  *Assistant Professor of Psychiatry, Yale University School of Medicine; Undergraduate work at North Dakota State University in Medicine; M.D. from the University of Chicago; Pediatric Residency at Johns Hopkins Children's Medical and Surgical Center*

  Dr. Rasmusson transferred to Yale for a Postdoctoral Fellowship in Neuropsychopharmacology at the Yale Child Study Center, where she focused on anxiety disorders in children; researched animal models and the effect of stress on prefrontal cortical function; performed an adult Residency in Psychiatry at Yale, and was Medical Director of in-patient treatment at the Veterans Administration National Center for Post Traumatic Stress Disorder (PTSD), where she studied men with Vietnam combat-related PTSD. Dr. Rasmusson described her BIRCWH Program and expressed gratitude for the opportunity to research gender differences in hypothalamic-pituitary-adrenal axis regulation. She is using the program to investigate the additional confound of nicotine use on women with PTSD. Her mentors are very helpful, particularly for providing an interdisciplinary focus.

The remaining BIRCWH Scholars introduced themselves:

- ***Bettina Mittendorfer, Ph.D.***
  *Research Instructor in the Department of Medicine at Washington University School of Medicine; Ph.D. in Nutritional Biochemistry/ Metabolism from the University of Texas Medical Branch; completed Postdoctoral Research Fellowship at Washington University; Visiting Scientist at the University of Dundee in Scotland and Harokopio University in Athens, Greece*

  Dr. Mittendorfer is researching the effect of gender on substrate metabolism, particularly differences in lipid and lipoprotein metabolism between men and women. The BIRCWH Program enabled her to obtain a grant to study gender differences, as well as a junior faculty position.

- ***Erica Gunderson, Ph.D.***
  *Research Scientist in the Division of Research, University of California at San Francisco, which joined forces with Kaiser Permanente to apply for the BIRCWH Scholarship Program; Bachelor's Degree in Biology from Stanford University; joint Master's of Public Health and Nutritional Sciences from the University of California at Berkeley; practiced for 14 years in diabetes and pregnancy care in California as a Public Health Nutritionist; Ph.D. in Epidemiology, University of California at Berkeley*

  Dr. Gunderson's research focuses on the effect of pregnancy on women's health, including the physiologic, metabolic, physical, and emotional challenges for pregnant women, and how pregnancy affects long-term health. Dr. Gunderson is particularly interested in the effect of pregnancy on cardiovascular disease and type 2 diabetes in women and changes in risk factors for those diseases. Her current research uses data from the Cardia Study, a multicenter cohort study on coronary artery risk development in young adults that was funded by NHLBI in the 1980s. Dr. Gunderson is studying women in that cohort to investigate the effect of having babies on changes in serum lipids, serum glucose, weight, and central adiposity in those women. The BIRCWH Program has been instrumental in allowing Dr. Gunderson to progress in her research career.

- ***Javier I. Torrens, M.D., FACP***
  *Assistant Professor, OB-GYN and Women's Health, New Jersey Medical School; medical training at Boston University School of Medicine; U.S. Army Health Professional Scholarship; Internal Medicine Residency and sub-specialty training in Medical Endocrinology at Walter Reed Army Medical Center; on the staff of the Hispanic Center of Excellence in the New Jersey Medical School's Department of Medicine*

  Before the BIRCWH Program, Dr. Torrens felt he was lacking significant mentorship in studying how health behaviors influence the genetic expression of diabetes and the metabolic syndrome, primarily in non-Mexican American Latino women. As a BIRCWH Scholar at the New Jersey Medical School, Dr. Torrens found mentors who supported his transition from an unstructured program into a very rigorous training program, where he is attending classes with graduate students and studying human genetics and advanced biology in preparation for researching, at the molecular level, how environmental factors lead to the expression of disease.

- ***Michele Martin, Ph.D.***
  *Assistant Professor of Medicine, Division of Preventive Medicine, University of Alabama at Birmingham; Doctoral Degree in Clinical Psychology from University of Alabama at Birmingham*

  Dr. Martin has pursued studies of women with fibromyalgia, studies of breast and cervical cancer prevention in women from underserved communities, and studies on the gap in mortality in breast cancer patients between African American and caucasian patients. She thanked the Advisory Committee for not only their investment in the BIRCWH Scholars, but also their belief in them. Through

the BIRCWH Program, she has learned she can recruit participants and conduct research. Her current research topic is American women who are hypertensive and the impact of exercise on this problem.

- ***Alice Thornton, M.D.***
  *Assistant Professor of Medicine, University of Kentucky at Lexington; M.D. Degree at Marshall University; trained in Internal Medicine at the Bowman Gray School of Medicine at Wake Forest University; trained in Infections Diseases at Indiana University*

  Dr. Thornton joined the Division of Infectious Diseases at the University of Kentucky, where she has been a BIRCWH Scholar for the last year and a half. She directed her research efforts to trichomoniasis, but needed support in the area of sexually transmitted diseases (STDs), which was lacking at the University of Kentucky. She was able to network with her former colleagues at Indiana to obtain the mentoring to pursue her research topic. Dr. Thornton said she appreciates the opportunity, which BIRCWH affords, to network with mentors to do interdisciplinary studies in STDs and epidemiology.

- ***Lisa Kane-Low, Ph.D.***
  *Bachelors' Degree in Nursing, University of Michigan; Midwifery Degree, University of Illinois in Chicago; Education Program for Midwifery at the University of Michigan; Ph.D. Degree, Interdisciplinary Studies, in the School of Nursing*

  Through the BIRCWH Program, Dr. Low researched birth care practices for adolescents, focusing on intervention strategies and the role of doulas, and doing cost analysis of birth care practice strategies while looking for better inclusive models for prenatal and postpartum care for adolescents, in particular, but also for all women. At the University of Michigan, Dr. Low enjoys an interdisciplinary environment with the BIRCWH Scholars, and is able to take advantage of multiple mentors in the whole program who are actively involved with all of the scholars. She appreciates having protected time, since her appointment is in the medical school.

A discussion followed the BIRCWH Scholars panel and presentations, in which both Scholars and ACRWH attendees acknowledged the advantages of the BIRCWH Program, as well as the challenges to continuing the new model of interdisciplinary women's health research stimulated by the BIRCWH Program.

**BIRCWH II (FYs 2002 through 2006)**

Based upon the impressive interest from the scientific community and the response to BIRCWH I, ORWH reissued the BIRCWH I RFA (RFA-OD-02-001) in December 2001 with minor changes. ORWH received 36 Letters of Intent. Applications will be received through March 14, 2002. This RFA will use the National Institutes of Health's Mentored Research Scientist Development Program Award (K12) mechanism. The K12 awards will be for a period of 5 years. The anticipated award date is September 30, 2002. A need has been identified for expanded support for interdisciplinary research bridging the completion of training with an independent career in research addressing women's health, including sex and gender similarities or differences.

The goal of this initiative is to promote the performance of research and transfer of findings that are relevant to women's health, including sex and gender similarities or differences in biology, health, or disease. The programs will accomplish this by bridging advanced training with research independence, as well as bridging professions, scientific disciplines, or areas of interest. This will increase the number and skills of investigators at awardee institutions through a mentored research and career development experience leading to an independent interdisciplinary scientific career addressing women's health. Research on sex and gender similarities or differences is a continuing priority for ORWH. Program grant awards resulting from this RFA will meet the specified needs by providing clinical, health or life sciences, or public health departments,

centers, and institutes, both developing and established, an opportunity to build a national capacity for junior investigators in women's health research, including research on sex and gender differences, as well as research on factors that contribute to disparities in health status or health outcomes for different populations of women.

In addition to ORWH, seven NIH institutes, the NIH Office of Dietary Supplements, and the Agency for Healthcare Research and Quality (AHRQ) cosponsor this program. By uniting cosponsors from a breadth of scientific areas, the program encourages researchers from different disciplines to apply their knowledge in new "ways to study important topics in women's health, including sex and gender factors in health and disease." Awardee institutions are: Boston University, Brown University, Duke University, Magee-Women's Health Corporation, University of Maryland, SUNY Downstate Medical Center, Oregon Health and Science University, University of Pennsylvania, Stanford University, Tulane University, University of Utah, and Vanderbilt University.

- ***SUNY Downstate Women's Health Research: From Molecules to Therapies***

  **SUNY Downstate Medical Center**
  **Brooklyn, New York**
  **Principal Investigator:** ***Dr. John Larosa***

  Downstate proposes a program that will link SUNY Downstate Medical Center in research and training collaborations with two minority institutions, Kings County Hospital and the Arthur Ashe Urban Health Institute. The program is organized into mentored research areas as a function of groups of research team mentors. Scholars will have opportunities to interact with over 18 mentors. Six core research areas, spanning basic and clinical aspects related to women's health, are planned: sex and gender differences in pain and analgesic response; early detection of breast cancer; neurological disorders and epilepsy; diabetes; progression of AIDS using a variety of methodological expertise; and health care disparities and well being.

- ***Utah BIRCWH Career Development Program in Women's Health***

  **University of Utah**
  **Salt Lake City, Utah**
  **Principal Investigator:** ***Dr. Eli Adashi***

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

- ***Duke BIRCWH***

  **Duke University**
  **Durham, North Carolina**
  **Principal Investigator:**
  ***Dr. R. Sanders Williams***

  Duke University joins forces with North Carolina Central University to design a program to contribute to improvement in women's health. The research plan revolves around four main themes: clinical trials and outcomes, decision-making research, health disparities, and basic and translational research, which includes a wide array of topics such as the genetics and molecular biology of either breast or ovarian cancer, neuromuscular physiology, and pharmacology of the pelvic floor to the molecular biology of nicotine addiction. Over 25 mentors, cutting across both disciplines and professions, are involved. Two tracks will serve scholars with

substantial or limited prior research experience. Scholars also have the opportunity of working towards a Master's Degree in Health Sciences or Clinical Research.

- ***Oregon Scholars in Women's Health Research Across the Lifespan***

  **Oregon Health & Science University**
  **Portland, Oregon**
  **Principal Investigator:**
  ***Dr. Christine Cassel***

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

- ***University of Pennsylvania Career Development in Women's Health Research and Gender***

  **University of Pennsylvania**
  **Philadelphia, Pennsylvania**
  **Principal Investigator:**
  ***Dr. Jerome Strauss***

  This program, located in the Center for Research for Reproduction and Women's Health at the University of Pennsylvania, involves 33 mentors who are built around six research clusters: brain and behavior; metabolism and aging; cell and tissue homeostasis; hormones, reproduction, and urologic function; infection and immunity; and cardiac and pulmonary. The program plans to have a steady state of scholars and, depending on their background, this might include enrollment in a M.S. or Ph.D. program. Two phases are planned, the first being a period of mentored research training prior to transition into the second phase of independent research with faculty appointment.

- ***Magee-Women's Health Corp BIRCWH***

  **Magee-Women's Research Institute**
  **Pittsburgh, Pennsylvania**
  **Principal Investigator:**
  ***Dr. James Roberts***

  This program will be orchestrated through the Magee-Women's Research Institute to provide an integrated approach to interdisciplinary research in women's health, focused on four themes that cover women's health from preconception to aged women: gender-specific developmental biology, women's behavioral health, prevention of adverse reproductive outcomes and chronic diseases, and aging and cancer. Scholars in this program will have the option of working with the 36 mentors whose research areas are encompassed under the umbrella of the four theme leaders.

- ***Vanderbilt BIRCWH***

  **Vanderbilt University**
  **Nashville, Tennessee**
  **Principal Investigator:**
  ***Dr. Rose Robertson***

  This program represents a partnership between Vanderbilt University and Meharry Medical College. The research plan is designed around six interdisciplinary research themes: cancer and neoplasia, cardiovascular and diabetes, clinical pharmacology, neurosciences and behavioral health, endometrial biology and reproductive toxicology, and health services and outcomes research. Selected scholars will have the opportunity to interact with 25 mentors from a variety of departments

and schools, including the school of medicine, clinical departments, preventive medicine, psychiatry, and the Institute for Public Policy Studies.

- *Tulane BIRCWH*

  **Tulane University**
  **New Orleans, Louisiana**
  **Principal Investigator:** ***Dr. Paul Whelton***

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

- *Maryland's Organized Research Effort in Women's Health*

  **University of Maryland**
  **Baltimore, Maryland**
  **Principal Investigator:**
  ***Dr. Patricia Langenberg***

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

- *Brown University BIRCWH Career Development Program*

  **Women & Infants Hospital**
  **Providence, Rhode Island**
  **Principal Investigator:**
  ***Dr. Donald Coustan***

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

- *Stanford Mentoring and Interdisciplinary Research in Women's Health*

  **Stanford University**
  **Stanford, California**
  **Principal Investigator:**
  ***Dr. Linda Guidice***

  Stanford University proposes a center with the theme of mentoring in women's health research from bench to bedside, from basic to clinical research. Over 23 mentors from a variety of disciplines encompassing twelve major research areas under basic and clinical research divisions including: midlife aging and cardiovascular disease; adolescent health; medical information technology; medicine, CV, and diabetes; cancer; reproductive and urogenital health; genetics; cancer biology; and tissue engineering. Scholars will have two pathways available – basic and clinical research.

- ***Boston University's Interdisciplinary Research Careers in Women's Health***

  **Boston Medical Center**
  **Boston, Massachusetts**
  **Principal Investigator:**
  ***Dr. Rebecca Silliman***

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

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

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

In July 1989, an *NIH Memorandum on Inclusion* stated that research solicitations should encourage inclusion of women and minorities and require a rationale if excluded, and that executive secretaries of scientific review groups should ensure that responsiveness to policy would be addressed and indicated in summary statements. In 1990, the Congressional Caucus for Women's Issues requested the U.S. General Accounting Office (GAO) to conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, in Congressional testimony, indicated that the implementation of the policy for the inclusion of women was slow, not well communicated, that gender analysis was not implemented, and that the impact of this policy could not be determined. 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 the scientific merit review.

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

- that NIH ensure that women and minorities and their subpopulations be included in all human subject 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,

[5] Public Law 103-43. National Institutes of Health Revitalization Act of 1993. 42 USC 289 (a)(1).

- NIH initiates programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as volunteers in clinical studies.

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

Strategies to ensure 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 cochaired with a senior IC official, meets on a regular basis, focusing on consistent and widespread adherence to NIH guidelines by all ICs. Working in collaboration with the Office of Extramural Research (OER), the Office of Intramural Research (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 the participation of women and minority participants in NIH-funded research.

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

A variety of outreach activities were initiated to explain the revised policy to the scientific research community and to

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

clear up common misunderstandings about the new requirements. Recognizing the importance of both recruitment and retention of human subject volunteers, NIH issued several articles and an outreach notebook, *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research*, that outlines elements of outreach processes, offers practical suggestions, and provides references to additional sources of information. This outreach notebook also includes the full text of the 1994 implementation guidelines, as well as a questions and answers document to provide more detailed policy guidance and some of the more commonly asked questions. ORWH also has available a full report of its workshop on "Recruitment and Retention of Women in Clinical Studies."

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

## Continuing Implementation and Monitoring Activities

Following a Congressional request for an assessment of NIH's progress in implementing the 1994 guidelines on including women in clinical research, the GAO issued a report in May, 2000, entitled *Women's Health—NIH Has Increased Its Efforts to Include Women in Research*.[7] The conclusions of this report showed that in the past decade NIH made significant progress in implementing a strengthened policy on including women in clinical research and highlighted several examples, including:

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

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

- that the requirement be implemented that Phase III clinical trials be designed

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

and carried out to allow for the valid analysis of differences between women and men and communicate this requirement to applicants, as well as requiring peer review groups to determine whether each proposed Phase III clinical trial is required to have such a study design, and that summary statements document the decision of the initial reviewers; and

- that the NIH staff who transmit data to the inclusion tracking data system receive ongoing training on the requirements and purpose of the system.

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

- In October 2001, the NIH Policy and *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research* and Amended Notice to the *Guide for Grants and Contracts* were updated and posted on the Internet with links to the ORWH home page and NIH web page, *Inclusion of Women and Minorities Policy Implementation* at: *http://grants.nih.gov/grants/funding/women_min/women_min.htm*. These documents supercede the 1994 *Federal Register* notice (*http://grants.nih.gov/grants/guide/notice-files/not94-100.html*) and the August 2000 notice in the *NIH Guide to Grants and Contracts* (*http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html*). These updated versions incorporate the definition of clinical research, as reported in the 1997 Report of the NIH Director's Panel on Clinical Research and the Office of Management and Budget Directive 15 "racial and ethnic categories to be used when reporting population data." They also provide additional guidance on reporting analyses of sex and gender and racial and ethnic differences in intervention effects for NIH-defined Phase III clinical trials.

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

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

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

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

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

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

Following completion of the updated guidelines and instructions, training to ensure compliance with this policy will be provided to NIH program and review officials, grants and contracts management staff, and current and prospective research investigators. Since August 2000, several training initiatives have been implemented:

- As part of an NIH Symposium: Human Subjects Update, the revised policy on inclusion of women and minorities and the revised NIH Instructions to Reviewers Guidelines for Evaluating the Inclusion of Women and Minorities as Subjects in Clinical Research were used as the basis for a required training session for NIH staff in October 2000. This symposium focused on the updated human subjects policy and the way in which it would be implemented. The training session included a question and answer session that provided an opportunity to emphasize the importance of the policy and the importance of reviewer evaluation of the changes related to valid analyses in Phase III clinical trials. About 450 were in attendance, 400 viewed the session at satellite centers, and another 175 participated through videocast. The training materials are permanently archived in the training materials for NIH staff at *http://odoerdb2.od.nih.gov/oer/training/esa/human_subjects/esa_hs_symposium.htm*.

- An additional training session, Grants Policy Update: Humans and Animals, was held in December, 2000. Several hundred additional extramural and intramural researchers were trained.

The inclusion of human subjects in clinical research studies was included among the topics addressed during the session. The training materials may be found at *http://odoerdb2.od.nih.gov/oer/training/esa/grants_policy_update/esa_grants_policy_update.htm*.

- In December 2000, the NIH Tracking and Inclusion Committee held a training session for all NIH program and grants management staff to discuss with members of the technical team, data entry and collection issues regarding the current population tracking system and IMPAC II, as well as offer suggestions for the development of the new population tracking module.

- In July 2001, NIH issued the newly revised Applications for a DHHS Public Health Service Grant (PHS 398, rev. 5/01). The instructions in the PHS 398 (rev. 5/01) describe the requirements for designing Phase III clinical trails to provide valid analysis by sex and gender and race and ethnicity. These instructions continue to be the most frequently accessed NIH documents by the research, review, and NIH staff communities.

- In January 2002, a videocast training session was held on Sex and Gender and Minority Inclusion in Clinical Research. This session was developed for all program, grants management, review, and contract staff who administer clinical research and provided information on the updated policies and procedures on sex and gender and minority inclusion. A comprehensive training manual explaining the new policies and procedures was developed as a training resource. The training session and manual is electronically available for all NIH staff.

- In May 2002, an additional training session, Inclusion of Children, Women, and Minorities: What SRAs and Reviewers Need to Know!, was held for the Center for Scientific Review on the updated policies and procedures on sex and gender and minority inclusion. This session highlighted the requirements and issues for scientific review staff.

- The Clinical Center now has available a web-based educational module for the comprehensive training programs for intramural and other research investigators. All principal investigators are required to complete the Clinical Research Training Course for Intramural Investigators, or equivalent, prior to implementing a protocol, and consideration is being given to making this a requirement for all investigators.

NIH has monitored aggregate demographic data for study populations through the existing NIH computerized tracking system since fiscal year 1994, and tracking the inclusion of women and minorities in clinical trials has been implemented in all ICs. The NIH Tracking and Inclusion Committee continues to work on ways to refine and improve data collection methods and the quality of the data entered by each IC into this system. The NIH Subcommittee Reviewing Inclusion Issues also collected comments on the tracking system used prior to 2000 and identified issues relating to data entry, including quality control and the mechanisms of data entry. In May 2002, NIH successfully deployed a new population tracking system for monitoring the inclusion of women and minorities in clinical research. This system provides easier data entry and project monitoring for NIH staff, creates clear and timely NIH reports on inclusion data, incorporates the 1997 Office of Management and Budget standards for the classification of federal data on race and ethnicity, and is consistent with the newly revised PHS Form 398 and PHS Form 2590 (rev. May, 2001). The re-engineered population tracking system continues to be refined based on input from the NIH user community.

- In May 2002, NIH published an online users guide and began offering 2-hour Population Tracking System demonstrations to accompany the launch of the new system. To date, ten 2-hour sessions have been

conducted with one session archived for subsequent staff training.

- Since July 2002, eight 3-hour, in-depth, hands-on training sessions have been provided to NIH staff on the use of the new population tracking system. Training materials for the hands-on course are available electronically to NIH staff as resource material.

In addition to training NIH staff on the updated guidelines for monitoring the inclusion of women and minorities in clinical research and the purpose of the new tracking system, NIH staff is providing outreach to the scientific community to help increase understanding of the revised inclusion policy and OMB requirements. These include:

- In 2002, NIH staff presented Sex and Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!, a 1-hour workshop on the revised inclusion policy and OMB requirements at two NIH Regional Seminar meetings. Each meeting involved 400 extramural scientists and administrators. An additional presentation was made to faculty and students at the NIH Warren G. Magnuson Clinical Center.

- The slide show for Sex and Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know! was made available to institute and center staff to assist them in working with the extramural community.

- The *Outreach Notebook for the NIH Guidelines on Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research* has been revised and was published in the fall of 2002. The revised *Outreach Notebook* includes additional information for principal investigators on the updated NIH inclusion policy, the 1997 OMB requirements for reporting race and ethnicity data, information for submitting an application, application submission, peer review, and funding. The publication will be posted on the NIH website for the inclusion of women and minorities policy implementation at *http://grants.nih.gov/grants/funding/women_min/women_min.htm*, as well as on the ORWH website at *http://www4.od.nih.gov/orwh/fy97-98trkg.pdf*.

- In addition, the Questions and Answers section of the *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research* is currently being revised and will be published as Frequently Asked Questions (FAQs) on the NIH website for the inclusion of women and minorities policy implementation at *http://grants.nih.gov/grants/funding/women_min/women_min.htm*, as well as on the ORWH website at *http://www4.od.nih.gov/orwh/fy97-98trkg.pdf*. These FAQs are being developed to provide additional guidance to researchers and NIH staff and accompany the *Outreach Notebook*.

These training and outreach efforts are designed to improve understanding of the sex and gender and minority inclusion policy, and assist investigators and NIH staff to appropriately address 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.

NIH staff continue to monitor, document, and work with grantees and contractors to ensure compliance with the inclusion policy. Program officials provide technical assistance to investigators as they develop their applications and proposal throughout the application process. Review officials introduce and discuss with reviewers the Guidelines and Instructions for Reviewing the Inclusion of Women and Minorities in Clinical Research, as well as the instructions and requirements for designing Phase III Clinical Trials, in order that valid analyses can be conducted for sex and gender and ethnic and racial differences. At the time of award and submission of progress reports, program officials monitor and verify that inclusion policy requirements are met. When new and competing continuation applications that are selected for payment

are deficient in meeting policy requirements, grants management staff and program officials will withhold funding until the principal investigator has satisfactorily addressed the policy requirements.

## NIH Aggregate Extramural and Intramural Population Data

When assessing inclusion data, enrollment figures should not be directly compared to the national census figures. The goal of the NIH policy is not to satisfy any quotas for proportional representation, but rather to conduct biomedical and behavioral research in such a manner that the scientific knowledge acquired will be generalizable to the entire population of the United States. The numbers of women or minority subgroups included in a particular study depends upon the scientific question addressed in the study and the prevalence among women and minority subpopulations of the disease, disorder, or condition under investigation. Initial Review Groups are instructed to focus on scientific considerations when assessing the planned enrollment for a particular study.

The aggregate data enable NIH to measure inclusion in order to formulate more specific questions about gaps in enrollment and to design studies to respond to those questions. Data compiled in future years will allow for longitudinal examination of trends and continued monitoring of compliance. Aggregate data are reported annually by fiscal year. The data tables included in this comprehensive report are the final reports from the old tracking system that relied solely on data submitted using the previous 1977 OMB standards for collecting and reporting data on ethnicity and race. Future reports will rely on the new population tracking system and will include data reported according to both the 1977 and the 1997 OMB standards. Projects that began using the old standard will continue to be reported according to the 1977 OMB standard, but all new projects will be reported according to the 1997 standard. As a result, comparisons will no longer be possible between the data reported in previous years and data reported for this year.

Previous inclusion reports and aggregate enrollment figures for FY 1994 through FY 1999 for women and men and minority groups may be found on the ORWH website at *http://od.nih.gov/orwh/inclusion.html*. Following the format of the aggregate extramural data tables (Tables 11 through 18), the aggregate data figures for on- and off-site intramural research protocols (Tables 19 and 20) are combined and presented as one single data table rather than as separate data tables for on- and off-site intramural research protocols.

Analysis of the FY 2000 inclusion data show that substantial numbers of both women and minorities have been included as research subjects in Phase III clinical trials and other human subject research studies, in both intramural and extramural programs. During FY 2000, more than 95 percent of applications involving human subjects met the inclusion requirements as submitted to the Initial Review Group. Of those selected for award, more than 96 percent were determined to have met the inclusion requirements as submitted. All of the remaining 4 percent of applications selected for award were required to address and satisfactorily resolve any issues pertaining to the inclusion requirements prior to funding.

Aggregate enrollment data for extramural Phase III trials funded in FY 2000 (Table 12) show that approximately 70.9 percent of the subjects were women, an increase of 7.6 percent from FY 1999 (Table 11). Among minority subjects,[8] representation in Phase III trials (Tables 11 and 12) was highest for black (not Hispanic) subjects (12.1 percent), and lowest for American Indian/Alaskan Native subjects (0.7 percent), a decrease of 0.5 and 0.1 percent, respectively. Asian/Pacific Islander subjects were 1.9 percent of the extramural Phase III subjects for FY 2000, a decrease of 2.9 percent from FY 1999; Hispanic subjects were 5.6 percent, a decrease of 0.5 percent; and white (not Hispanic) subjects were 72.7 percent,

[8] Racial and ethnic categories are in accord with the Office of Management and Budget Directive No. 15.

an increase of 5 percent from FY 1999. Over 9 million subjects were included in the research projects covered by the tracking system in FY 2000. This snapshot of aggregate enrollment data for FY 2000 extramural studies (Table 18) shows that approximately 61.3 percent of the subjects were women, 38.4 percent were men, and 0.4 percent were not identified by sex or gender. Overall, the number of women participants decreased by 0.3 percent, the number of men increased by 0.7 percent, and the number of subjects that did not identify their sex or gender decreased by 0.2 percent, compared to FY 1999 (Table 17).

The Tracking and Inclusion Committee conducted an analysis of the FY 2000 and 1999 extramural and Phase III research protocols and noted differences in the numbers and percentages of subjects that identified their race and ethnicity in those that did not identify their sex and gender. In response to these findings, committee representatives reviewed their institute's data and reconvened the committee to discuss possible explanations. In many cases, the changes in percentages between FY 1999 and 2000 were attributable to the ending of previously reported studies where enrollments involved between 20,000 to 300,000 participants per study. Although other new studies were launched in FY 2000, enrollment for these new studies is just beginning. Other reasons for the fluctuations between FY 1999 and 2000 enrollment percentages included: improved reporting and corrections of errors by investigators; and recognition that information on sex and gender and ethnicity and race is obtained voluntarily from study participants and, as a result, some participants will elect not to report this information, i.e., the information is "Unknown." Data entry error was also an issue addressed by NIH staff; the aggregate report data tables reflect reconciled data.

***TABLE 11***

***Aggregate Enrollment Data for Extramural Phase III Protocols Funded, FY 1999***

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 2,132 | 13,314 | 37,827 | 17,097 | 221,098 | 22,484 | 313,952 |
| | 0.7 | 4.2 | 12.0 | 5.4 | 70.4 | 7.2 | 63.3 |
| Male | 1,590 | 10,697 | 24,605 | 12,950 | 114,416 | 16,447 | 180,705 |
| | 0.9 | 5.9 | 13.6 | 7.2 | 63.3 | 9.1 | 36.5 |
| Unknown | 4 | 6 | 80 | 37 | 310 | 649 | 1,086 |
| | 0.4 | 0.6 | 7.4 | 3.4 | 28.5 | 59.8 | 0.2 |
| **Total** | **3,726** | **24,017** | **62,512** | **30,084** | **335,824** | **39,580** | **495,743** |
| | **0.8** | **4.8** | **12.6** | **6.1** | **67.7** | **8.0** | **100.0** |

Number of Protocols: 589

*FY 99 Data Table Comments:*
Substantial numbers of women and minorities are enrolled in Phase III research protocols funded in 1999.
There were more females (313,952 or 63.3 percent) than males (180,705 or 36.5 percent) enrolled in Phase III research protocols.
Among minority subjects, the largest racial minority group is black, non-Hispanic at 62,512 or 12.6 percent.
The smallest identified racial group is American Indian/Alaska Natives at 3,726 or 0.8 percent.

### *TABLE 12*

### *Aggregate Enrollment Data for Extramural Phase III Protocols Funded, FY 2000*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 2,521 | 8,920 | 46,303 | 20,889 | 309,289 | 24,457 | 412,379 |
| | 0.6 | 2.2 | 11.2 | 5.1 | 75.0 | 5.9 | 70.9 |
| Male | 1,558 | 2,205 | 23,606 | 11,606 | 113,068 | 16,042 | 168,085 |
| | 0.9 | 1.3 | 14.0 | 6.9 | 67.3 | 9.5 | 28.9 |
| Unknown | 0 | 7 | 201 | 57 | 445 | 563 | 1,273 |
| | 0.0 | 0.5 | 15.8 | 4.5 | 35.0 | 44.2 | 0.2 |
| **Total** | **4,079** | **11,132** | **70,110** | **32,552** | **422,802** | **41,062** | **581,737** |
| | **0.7** | **1.9** | **12.1** | **5.6** | **72.7** | **7.1** | **100.0** |

Number of Protocols: 645

*FY 00 Data Table Comments:* Substantial numbers of women and minorities are enrolled in Phase III research protocols funded in 2000.
There were more females (412,379 or 70.9 percent) than males (168,085 or 28.9 percent) enrolled in Phase III research protocols.
Among minority subjects, the largest racial minority group is black, non-Hispanic at 70,110 or 12 percent.
The smallest identified racial group is American Indian/Alaska Natives at 4,079 or 0.7 percent.

### *TABLE 13*

### *Aggregate Enrollment Data for Extramural Phase III Research Protocols Funded (Excluding Male- and Female-only Protocols), FY 1999*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 1,422 | 9,070 | 22,144 | 10,939 | 68,168 | 19,571 | 131,314 |
| | 1.1 | 6.9 | 16.9 | 8.3 | 51.9 | 14.9 | 45.9 |
| Male | 1,557 | 10,109 | 21,097 | 11,589 | 94,761 | 15,099 | 154,212 |
| | 1.0 | 6.6 | 13.7 | 7.5 | 61.4 | 9.8 | 53.8 |
| Unknown | 4 | 6 | 80 | 37 | 310 | 423 | 860 |
| | 0.5 | 0.7 | 9.3 | 4.3 | 36.0 | 49.2 | 0.3 |
| **Total** | **2,983** | **19,185** | **43,321** | **22,565** | **163,239** | **35,093** | **286,386** |
| | **1.0** | **6.7** | **15.1** | **7.9** | **57.0** | **12.3** | **100.0** |

Number of Protocols: 396

*FY 99 Data Table Comments:* There were 589 protocols of which 114 were women-only protocols and 34 were men-only protocols.
The largest identified racial group is white, non-Hispanic at 163,239 or 57.0 percent.
The largest identified racial minority group is black, non-Hispanic at 43,321 or 15.1 percent.
The smallest identified racial minority group is American Indian/Alaska Native at 2,983 or 1.0 percent.

## *TABLE 14*

## *Aggregate Enrollment Data for Extramural Phase III Research Protocols Funded (Excluding Male- and Female-only Protocols), FY 2000*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 1,383 | 1,750 | 21,977 | 10,567 | 74,761 | 19,541 | 129,979 |
| | 1.1 | 1.3 | 16.9 | 8.1 | 57.5 | 15.0 | 45.4 |
| Male | 1,526 | 2,096 | 21,469 | 11,125 | 103,862 | 15,145 | 155,223 |
| | 1.0 | 1.4 | 13.8 | 7.2 | 66.9 | 9.8 | 54.2 |
| Unknown | 0 | 7 | 201 | 57 | 445 | 563 | 1,273 |
| | 0.0 | 0.5 | 15.8 | 4.5 | 35.0 | 44.2 | 0.4 |
| **Total** | **2,909** | **3,853** | **43,647** | **21,749** | **179,068** | **35,249** | **286,475** |
| | **1.0** | **1.3** | **15.2** | **7.6** | **62.5** | **12.3** | **100.0** |

Number of Protocols: 444

*FY 00 Data Table Comments:* There were 645 protocols of which 121 were women-only protocols and 34 were men-only protocols.
The largest identified racial group is white, non-Hispanic at 179,068 or 62.5 percent.
The largest identified racial minority group is black, non-Hispanic at 43,647 or 15.2 percent.
The smallest identified racial minority group is American Indian/Alaska Native at 2,909 or 1.0 percent.

## *TABLE 15*

## *Aggregate Enrollment Data for Extramural Research Protocols Funded (Excluding Male- and Female-only Protocols), FY 1999*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 29,853 | 167,725 | 504,250 | 258,584 | 1,318,085 | 197,183 | 2,475,680 |
| | 1.2 | 6.8 | 20.4 | 10.4 | 53.2 | 8.0 | 50.1 |
| Male | 29,459 | 159,956 | 420,593 | 216,121 | 1,402,815 | 197,582 | 2,426,526 |
| | 1.2 | 6.6 | 17.3 | 8.9 | 57.8 | 8.1 | 49.1 |
| Unknown | 288 | 855 | 4,179 | 16,084 | 5,820 | 16,840 | 44,066 |
| | 0.7 | 1.9 | 9.5 | 36.5 | 13.2 | 38.2 | 0.9 |
| **Total** | **59,600** | **328,536** | **929,022** | **490,789** | **2,726,720** | **411,605** | **4,946,272** |
| | **1.2** | **6.6** | **18.8** | **9.9** | **55.1** | **8.3** | **100.0** |

Number of Protocols: 5,049

*FY 99 Data Table Comments:* There were 7,948 extramural protocols of which 888 were women-only protocols and 328 were men-only protocols.
The largest identified racial group is white, non-Hispanic at 2,726,720 or 55.1 percent.
The largest identified racial minority group is black, non-Hispanic at 929,022 or 18.8 percent.
The smallest identified racial minority group is American Indian/Alaska Native at 59,600 or 1.2 percent.

### *TABLE 16*

### *Aggregate Enrollment Data for Extramural Research Protocols Funded (Excluding Male- and Female-only Protocols), FY 2000*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 40,261 | 354,982 | 459,924 | 345,866 | 2,183,755 | 205,104 | 3,589,892 |
| | 1.1 | 9.9 | 12.8 | 9.6 | 60.8 | 5.7 | 50.2 |
| Male | 40,567 | 345,952 | 421,657 | 333,218 | 2,105,264 | 274,424 | 3,521,082 |
| | 1.2 | 9.8 | 12.0 | 9.5 | 59.8 | 7.8 | 49.3 |
| Unknown | 205 | 2,779 | 4,128 | 1,827 | 10,053 | 16,167 | 35,159 |
| | 0.6 | 7.9 | 11.7 | 5.2 | 28.6 | 46.0 | 0.5 |
| **Total** | **81,033** | **703,713** | **885,709** | **680,911** | **4,299,072** | **495,695** | **7,146,133** |
| | **1.1** | **9.8** | **12.4** | **9.5** | **60.2** | **6.9** | **100.0** |

Number of Protocols: 5,897

*FY 00 Data Table Comments:* There were 8,785 protocols of which 975 were women-only protocols and 360 were men-only protocols.
The largest identified racial group is white, non-Hispanic at 4,299,072 or 60.2 percent.
The largest identified racial minority group is black, non-Hispanic at 885,709 or 12.4 percent.
The smallest identified racial minority group is American Indian/Alaska Native at 81,033 or 1.1 percent.

### *TABLE 17*

### *Aggregate Enrollment Data for All Extramural Research Protocols Funded, FY 1999*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 33,991 | 829,502 | 653,412 | 313,065 | 2,468,041 | 254,403 | 4,552,414 |
| | 0.7 | 18.2 | 14.4 | 6.9 | 54.2 | 5.6 | 61.6 |
| Male | 29,707 | 247,475 | 451,895 | 221,781 | 1,633,898 | 202,372 | 2,787,128 |
| | 1.1 | 8.9 | 16.2 | 8.0 | 58.6 | 7.3 | 37.7 |
| Unknown | 288 | 855 | 4,179 | 16,084 | 5,820 | 17,913 | 45,139 |
| | 0.6 | 1.9 | 9.3 | 35.6 | 12.9 | 39.7 | 0.6 |
| **Total** | **63,986** | **1,077,832** | **1,109,486** | **550,930** | **4,107,759** | **474,688** | **7,384,681** |
| | **0.9** | **14.6** | **15.0** | **7.5** | **55.6** | **6.4** | **100.0** |

Number of Protocols: 7,948

*FY 99 Data Table Comments:* More females (4,552,414 or 61.6 percent) than males (2,787,128 or 37.7) are enrolled in aggregate Extramural Research protocols.
The largest identified racial group is white, non-Hispanic at 55.6 percent.
The largest identified racial minority group is black, non-Hispanic at 15.0 percent.
The smallest identified racial minority group is American Indian/Alaska Natives at 0.9 percent.

## TABLE 18

## *Aggregate Enrollment Data for All Extramural Research Protocols Funded, FY 2000*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 45,828 | 728,385 | 650,459 | 422,476 | 3,797,984 | 295,742 | 5,940,874 |
| | 0.8 | 12.3 | 10.9 | 7.1 | 63.9 | 5.0 | 61.3 |
| Male | 42,000 | 372,842 | 436,833 | 345,394 | 2,243,973 | 280,166 | 3,721,208 |
| | 1.1 | 10.0 | 11.7 | 9.3 | 60.3 | 7.5 | 38.4 |
| Unknown | 205 | 2,779 | 4,128 | 1,827 | 10,053 | 16,167 | 35,159 |
| | 0.6 | 7.9 | 11.7 | 5.2 | 28.6 | 46.0 | 0.4 |
| **Total** | **88,033** | **1,104,006** | **1,091,420** | **769,697** | **6,052,010** | **592,075** | **9,697,241** |
| | **0.9** | **11.4** | **11.3** | **7.9** | **62.4** | **6.1** | **100.0** |

Number of Protocols: 8,785

*FY 00 Data Table Comments:* More females (5,940,874 or 61.3 percent) than males (3,721,208 or 38.4 percent) are enrolled in aggregate Extramural Research protocols.
The largest identified racial group is white, non-Hispanic at 62.4 percent.
The largest identified racial minority group is Asian/Pacific Islanders at 11.4 percent.
The smallest identified racial minority group is American Indian/Alaska Natives at 0.9 percent.

## TABLE 19

## *Aggregate Enrollment Data for Intramural Research Protocols Funded (Includes On- and Off-site), FY 1999*

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 9,910 | 242,790 | 55,288 | 20,863 | 654,775 | 49,002 | 1,032,628 |
| | 1.0 | 23.5 | 5.4 | 2.0 | 63.4 | 4.7 | 47.3 |
| Male | 8,810 | 204,676 | 44,756 | 16,588 | 823,213 | 33,894 | 1,131,937 |
| | 0.8 | 18.1 | 4.0 | 1.5 | 72.7 | 3.0 | 51.8 |
| Unknown | 22 | 94 | 239 | 27 | 3,195 | 16,274 | 19,851 |
| | 0.1 | 0.5 | 1.2 | 0.1 | 16.1 | 82.0 | 0.9 |
| **Total** | **18,742** | **447,560** | **100,283** | **37,478** | **1,481,183** | **99,170** | **2,184,416** |
| | **0.9** | **20.5** | **4.6** | **1.7** | **67.8** | **4.5** | **100.0** |

Number of Protocols: 1,439

*FY 99 Data Table Comments:* There were more males (1,131,937 or 51.8 percent) than females (1,032,628 or 47.3 percent) enrolled in aggregate Intramural Research protocols.
Differences in the enrollment of males and females is attributed primarily to improvements in reporting procedures (i.e., ensuring gender declaration and recording at enrollment).
The racial minority group with the largest increase in enrollment is Hispanic – an increase of 75 percent from FY 98 to FY 99.
The number of black, non-Hispanic enrollees increased by 30 percent from FY 98 to FY 99.
The largest identified racial minority group is Asian/Pacific Islanders at 446, 918 or 20.5 percent.
The large Asian/Pacific Islander population is due in part to a large clinical study being conducted in Vietnam.
The smallest identified racial minority group is American Indian/Alaskan Native at 18,692 or 0.9 percent.
Patient enrollment in the Intramural Research Program at the Warren Grant Magnuson Clinical Center increased by 45 percent in FY 99, compared to FY 98.

*TABLE 20*

***Aggregate Enrollment Data for Intramural Research Protocols Funded (Includes On- and Off-site), FY 2000***

| | American Indian/ Alaska Native | Asian/Pacific Islanders | Black (non-Hispanic) | Hispanic | White (non-Hispanic) | Other/ Unknown | Total |
|---|---|---|---|---|---|---|---|
| | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* | *Number/ Percent* |
| Female | 9,042 | 198,427 | 53,713 | 29,928 | 546,363 | 30,475 | 867,948 |
| | 1.0 | 22.9 | 6.2 | 3.4 | 62.9 | 3.5 | 45.8 |
| Male | 7,991 | 192,775 | 54,470 | 19,392 | 715,671 | 29,380 | 1,019,679 |
| | 1.1 | 18.9 | 5.3 | 1.9 | 70.2 | 2.9 | 53.8 |
| Unknown | 1 | 71 | 22 | 131 | 405 | 8,758 | 9,388 |
| | 0.0 | 0.8 | 0.2 | 1.4 | 4.3 | 93.3 | 0.5 |
| **Total** | **17,034** | **391,273** | **108,205** | **49,451** | **1,262,439** | **68,613** | **1,897,015** |
| | **0.9** | **20.6** | **5.7** | **2.6** | **66.5** | **3.6** | **100.0** |

Number of Protocols: 1,427

*FY 00 Data Table Comments:* There were more males (1,019,679 or 53.8 percent) than females (867,948 or 45.8 percent) enrolled in aggregate Intamural Research protocols.
Differences in the enrollment of males and females is attributed primarily to improvements in reporting procedures (i.e., ensuring sex and gender declaration and recording at enrollment).
The racial minority group with the largest increase in enrollment is Hispanic – an increase of 75 percent from FY 99 to FY 00.
The number of black, non-Hispanic enrollees increased by 8 percent from FY 99 to FY 00.
The largest identified racial minority group is Asian/Pacific Islanders at 391,273 or 20.6 percent.
The large Asian/Pacific Islander population is due, in part, to a large clinical study being conducted in Vietnam.
The smallest identified racial minority group is American Indian/Alaskan Native at 17,034 or 0.9 percent.

Substantial numbers of women and minorities were also included in NIH intramural studies in FY 2000 (Table 20). Approximately 45.8 percent of intramural subjects were women and 53.8 percent were men. Among minority subjects, representation in intramural studies was highest for Asian/Pacific Islander subjects (20.6 percent), and lowest for American Indian/Alaskan Native subjects (0.9 percent). Black (not Hispanic) subjects represented approximately 5.7 percent of the subjects; Hispanic subjects 2.6 percent; and white (not Hispanic) subjects represented 66.5 percent of the intramural research study population. Approximately 2 million subjects were included in the tracking system from intramural research projects in FY 2000.

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

## WHI Minority Investigator Career Development Award, FY 2001

ORWH cosponsored an RFA with NIAMS and NIA to provide Career Development Awards (K01 or K08) to minority scientists to facilitate participation in the Women's Health Initiative. These serve two purposes: first, to enhance the research skills, training, and development of the individual awardees; and, second, to enhance the diversity of the investigator teams currently carrying out this project. Scientists and clinicians thus trained will contribute to the nurturing of the next generation of clinical investigations. ORWH supported three awards in FY 1997, and four in FY 1998 and FY 1999.

# ORWH CAREER DEVELOPMENT PROGRAMS
## FISCAL YEARS 2001 AND 2002

### *FY 2001 Supported Awards*

- Title: *Stress and Immune Functioning in Women with A Family History of Cancer*
  Institute: NIAMS
  Awardee: Paige A. McDonald, Ph.D.
  Institution: Howard University Cancer Center Washington, DC (Year 3)

  This study aims at the causes of morbidity and mortality associated with chronic diseases among women; strengthening the applicant's present training and ability to conduct psychoneuroimmunological research through course work, laboratory training, and clinical experience; familiarizing the applicant with all phases of research; and developing the applicant's ability to conduct independent research and obtain independent funding.

- Title: *Ethnicity, Body Composition, Bone Density, and Breast Cancer*
  Institute: NIAMS
  Awardee: Zhao Chen, Ph.D.
  Institution: University of Arizona Tucson, AZ (Year 4)

  This study aims to recruit Hispanic postmenopausal breast cancer cases to: 1) form a Hispanic postmenopausal breast cancer case-control study comparing bone mineral density among Hispanic breast cancer patients recruited in the proposed study as cases and Hispanic women from the Women's Health Initiative observation study group in Arizona as controls; and 2) examine the interrelationship between bone mineral density and breast cancer in Hispanic postmenopausal women; to assess the role of body composition in the relationship between bone mineral density and breast cancer in Hispanic postmenopausal women; to identify risk factors for, and links between, osteoporosis and breast cancer in Hispanic postmenopausal women; and to compare results of the proposed study with results from other ethnic groups in the WHI when they are available.

## Summer Research Program for High School Students, FY 2002

The National Institutes of Health has just announced the fourteenth annual Summer Research Program for High School Students. This program exposes students from a diverse background, including at least 50 percent women and a high percentage of underrepresented minorities, to biomedical research at a time when they are still forming their future plans and thereby enhances the possibility that they will choose science careers.

All Metropolitan Washington high schools are invited to nominate their two best science majors for the program. The students can be either juniors or seniors. From this pool of applicants (approximately 150 students), 25 students are selected based on academic achievement, aptitude, and interest in future careers in scientific disciplines, as well as on the evaluation by teachers or previous preceptors. In addition, the program provides for up to 15 students to return for a second and even third year.

Selected students work in one of the research laboratories at NIH, becoming involved in ongoing research protocols and experiencing what a research career would be like first hand. They meet as a group on Wednesdays from 11:30 am to 1:30 pm

with Dr. Michael Gottesman, DDIR, and/or Dr. Joan Schwartz, Assistant Director, OIR. Over the summer, each student gives a talk on his/her summer project, thus providing training in oral presentations. The laboratory mentor works closely with the student to develop a presentation that will be readily understandable by other students.

### *Objectives for the 2002 High School Student Program*

- To increase the knowledge base of modern biomedical research, as well as familiarity with techniques by empirically performing a subset of techniques through participation in a laboratory project,
- To develop a network of NIH scientists to serve as consultants for their future career paths, and
- To encourage a diversity of students to consider a career in biomedical research.

For the program, scholar candidates with an interest in disadvantaged populations will be particularly sought. Limited experience and advanced tracks feature individualized curricula. Among a total of 24 mentors, seven from obstetrics-gynecology form a subgroup of reproductive health, with 17 others from a diverse group of 11 different departments.

## Achieving Excellence in Science

ORWH, in conjunction with The American Society for Cell Biology and the National Institute of Environmental Health Sciences, convened Achieving Excellence in Science (AXXS) '99 to explore the roles of scientific societies in advancing science by building the careers of all women in science, from the predoctoral stage to the senior scientist level. The workshop was held December 9-10, 1999, as a satellite meeting to The American Society for Cell Biology's Annual Meeting in Washington, DC. More than 140 participants representing more than 50 scientific societies, organizations, and government agencies gathered to:

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

The full report on AXXS '99 is available on-line at *www4.od.nih.gov/axxs/*. As follow-up to the AXXS meeting in December 1999, ORWH developed, designed, launched, and now maintains an AXXS web page, which will serve as a primary resource for women in biomedical sciences *(http://www4.od.nih.gov)*.

In FY 2001, the following plans were developed for an initiative called ACT. The ACT team has a clear objective – to move quickly from AXXS plans to society-driven initiatives to advance the careers of women in science by turning plans into actions to advance the careers of women in science. Specifically, this project moves to implement two to three initiatives into societies and/or academic institutions within the first 6 months. Further, it is intended to refine one or more complex initiatives (e.g., mentoring) and move them into one or more societies and/or academic institutions within the first year. Future plans include a meeting in spring 2002, AXXS 2002, hosted by the National Academy of Sciences for clinical societies.

It is the mission of AXXS to make women more visible and to advance their careers by increasing the recognition of their scientific accomplishments. Formal mechanisms and processes to support the development of women scientists will be created, supporting the engendering of networking and mentoring opportunities and increasing the public's awareness of opportunities for women in science. It is crucial that more women occupy leadership roles in societies and that these societies understand that diversity is critical to their unique mission.

- ***Achieving XXcellence: The Role of Professional Societies in Advancing Women's Careers in Science and Clinical Research***

  The Committee on Women in Science and Engineering (CWSE) of the National Academy of Sciences held a $1^1/_2$ day workshop, in July 2002, to gather representatives of clinical societies and discuss ways for the societies to enhance the participation of women scientists in the clinical research workforce. The workshop was a followup to AXXS 1999, in which representatives of science societies gathered to identify ways to improve the advancement of women in their respective fields.

## *Goals of the 2002 Meeting*

- Identify barriers to success in biomedical careers for women,
- Share strategies for promoting careers, and
- Develop effective programs to build careers.

Focus was placed on identifying initiatives and action items that clinical societies can adopt, ways for clinical societies to disseminate successful strategies, and ways to collaborate among societies. Data from several sources confirm what has been characterized variously as the leaking/hemorrhaging of women advancing to senior positions in the academic biomedical research pathway. Thus, a significant pool of talent is wasted or underutilized in the biomedical enterprise with associated financial implications. Perpetuating this situation, there are fewer senior women to serve as role models and mentors. Moreover, recent studies at several institutions have revealed subtle differences in resources made available to women versus men that may negatively impact career development for women. Adding to the complexity of the situation, primary care responsibility for children and aging parents more often compete with the time women can devote to career than men at the same level, and women often have a collaborative research and leadership style that can be mistaken for lack of independence or credit assignment for achievements.

With these issues in mind, what specific barriers exist and what initiatives and action items can clinical societies adopt to facilitate more gender balance and advancement of women's careers in research, both basic and clinical? Breakout groups were formed to ponder these questions and report back to the reassembled body. Not surprisingly, there was significant overlap regarding recommendations between the various groups.

The following are examples of strategic ideas and action items that emerged from these "think tanks":

- ***Utilize a networking strategy to inculcate values and effect change in the current scientific culture/mindset that prevents optimal capitalization of women resources;***
  - Incorporate mentorship into promotion criteria to recognize the critical role of mentoring in academic success.
  - Expand the accepted notion of scholarship to include collaborative/team ventures and increase appreciation of clinical research.
  - Collect data and disseminate information regarding: how leadership within professional societies reflects its member demographics; costs of faculty recruitment versus retention (wisdom suggests that it will be cost saving to retain and recruit women from within); collect or develop models – websites, directories, programs, and practices.
  - Promote mentoring via awards, including financial and national recognition.
  - Reward department chairs who effectively develop women's careers.
  - Develop criteria for excellence in clinical research and present the criteria to a committee of deans for diffusion to all academic health centers.

- Initiate society report cards to recognize discipline and institutional successes.
- Inform the public of the value of clinical research via outreach efforts.
- Feature career development and leadership workshops within society programming.
- Contribute to funding or cosponsor NIH funding for proposed AXXS initiatives.

▶ ***AXXS evaluated the collected recommendations from this meeting and propose action items to adopt in a forthcoming report. AXXS is actively seeking to collect, evaluate, and publish strategies that have been developed and utilized successfully by different groups. The American Society for Cell Biology and the American Psychological Society have both contributed several strategies. AXXS distributed a booklet of strategies at the meeting for consideration by other groups and their website will offer more.***

**AXXS Goals**

**Goal 1: A new cultural norm for women.**
Where gender bias is eliminated, women's leadership and communication styles are honored, the image and perception of women are highly valued, and science and family are compatible roles for women and men in this society.

**Goal 2: Equity with male counterparts.**
Where women are equally represented in their disciplines and societies, compared to their male counterparts, and where women's society memberships, honorary awards, grants, faculty positions, leadership roles, pay rates, journal editorships, and so forth, are on a par with men.

**Goal 3: High visibility and recognition.**
Where there is widespread professional respect for the accomplishments and contributions of women scientists, large numbers of well-known women deliver keynote addresses, and women routinely receive awards for their scientific achievements.

**Goal 4: Mentoring as an integral part of career development and advancement for women.**
Where mentoring is gender-neutral and encompasses both one-to-one and institutional programs, characterized by men seeking out women mentors, and the mentoring of women as an integral part of high schools, academia, professional societies, and scientific organizations and institutions.

**Goal 5: Varied and valued career options for women.**
Where expanded career possibilities for women in science are widely promoted and highly visible at all stages of the career pathway; more teen girls opt to take high school science, an incubator environment provides conditions favorable to the advancement of women in science; and greater numbers of mid- and upper-level women scientists remain on chosen career tracks.

**Goal 6: Readily available networking, resources, and support.**
Where women have access to, and are included in, non-gender-biased networks, which are both formal and informal, as well as faculty and employer sponsored.

**Goal 7: Professional advancement and skill building through scientific societies.**

Where there is significant support within societies to help women in science to advance their careers, in the form of mechanisms to promote an individual's career, funding for skill building and development, affirmative public statements from scientific societies, and job access and advancement through societies.

**Goal 8: Inner and outer empowerment.**

Where women are comfortable with themselves and their careers, feel valued and effective, and hold empowered attitudes free from any victim-like mentality (inner empowerment); and where there is collaboration and exchange from peers and role models, and MIT-type studies initiated.

The workshop focused on: 1) initiatives and action items clinical societies can adopt within their organizations to enhance women's advancement in the clinical research field; 2) ways for clinical societies to disseminate successful strategies to advance women's careers; and 3) ways that clinical societies can collaborate to promote women's contributions to their fields. The ACTeam encourages and assists scientific societies and other professional organizations to implement and sustain initiatives to advance the careers of women in science.

In June 2000, the Office of Research of Women's Health sponsored a followup meeting to prioritize and refine the AXXS '99 initiatives and to develop action plans for implementing these initiatives, both within and across scientific societies. The four key strategies that came from that meeting are: Enhance Women in Leadership Positions; Enhance Mentoring Programs; Promote the Visibility of Women in Science; and Gather, Evaluate, and Publish Best Practices. These were presented at the FY 2002 meeting.

### Effective Practices

Effective practices are programs, policies, or other initiatives within and/or offered by an organization that are proven tools for the advancement of women in science.

- ***Effective practices may fit into, but are not limited to, the following categories:***
  - Leadership Development Mentoring,
  - Professional Advancement Women's Committees, and
  - Increasing Women's Representation and Visibility.

One of the key strategies that emerged from the followup meeting to AXXS 99 was to "gather, evaluate, and publish" best practices. The Core ACTeam created a submission form and put out a call for such practices beginning in October 2001.

***Submission Format***

- Name of Sponsoring Organization
- Title of the Effective Practice
- Aim/Intention of the Effective Practice
- Description of the Effective Practice
- Description of how organization knows the Effective Practice is successful
- Contact information for those who desire more information about the Effective Practice

## *Developing Country Scientist Program at NIH Fogarty International Center*

In FY 2002, in conjunction with FIC, ORWH will support a meeting with experts to consider this new program and how it could meet the needs of women scientists in particular. The funding would bring together senior scientists from the developing world to provide insights into the obstacles faced by women in academic and public health institutions in those settings. FIC, OIR, and other NIH partners develop and support a program to expand participation in the

Visiting Program from the developing world, provide supplementary training in addition to scientific training, and support, on a competitive basis, re-entry grants on the scientists' return home.

The NIH Visiting Program provides opportunities for young scientists from abroad to learn research techniques and conduct related research in all fields of biomedicine and behavioral science. On their return home, these scientists are encouraged to compete for NIH extramural awards, to partner with U.S. scientists on collaborative research projects, and to assume leadership positions. As NIH works to address global health challenges and to advance critical areas of science – HIV/AIDS, malaria, tobacco-related illness, and the health challenges facing women – scientists from the developing world contribute their scientific and cultural knowledge, which allows them to design and conduct research studies that are scientifically valid and that take into account local, as well as international, cultural norms.

Of the roughly 2,500 foreign scientists in the NIH Visiting Program, only 20 are from sub-Saharan Africa. This trend is similar for Asia, with the notable exceptions of India and China, and for most of Latin America. In addition, based on consults with current Visiting Fellows, there is a perceived need for supplementary training in areas that would bolster skills to take on leadership positions on their return home. Further, Visiting Fellows would be more likely to return home and to continue to work productively in their field if small amounts of re-entry support could be provided.

## Association for Women in Science Seminar Series

The Association for Women in Science (AWIS) Bethesda Chapter was founded in 1994 to address the issues and concerns of women in science. ORWH provided support for the 2001-2002 Eighth and Ninth AWIS Bethesda Chapter Seminar Series, Strategies for Success in Science. Seminars included: Exploring Informatics Careers: Paths in the Neurosciences and Molecular Biology; A Report on the Status of Women Faculty in Science at MIT: An Update; Employment Opportunities for Scientists at Federal Agencies; Science and Business: Working in Industry; and Career and Family: Challenges and Rewards. In FY 2002, seminars were included under Networking for Career Success.

## Women's Reproductive Health Research Career Development Centers

ORWH joined NICHD in the development of a Request for Applications to invite institutional career award applications for Women's Reproductive Health Research Career Development Centers in FYs 1998 and 1999. These centers support research career development of obstetrician-gynecologists, known as Women's Reproductive Health Research (WRHR) scholars, who recently completed postgraduate clinical training and were commencing basic, translational, and/or clinical research relevant to women's health. The goal of this initiative is to promote the performance of research on women's reproductive health and transfer findings that will benefit the health of women. The centers serve to bridge clinical training with independent research, 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 issues.

In FY 1998, 12 centers were funded: Magee-Women's Hospital, Pittsburgh; Oregon Health Sciences University; Stanford University; University of California, San Francisco; University of California, Los Angeles; University of Cincinnati; University of Pennsylvania; University of Texas Health Sciences Center/Houston; University of Texas Medical Branch/Galveston; University of Washington; Wake Forest University School of Medicine; and Wayne State University, Detroit. In FY 99, eight centers were added: Brigham and Women's Hospital;

Case Western Reserve University; Columbia University; University of Alabama at Birmingham; University of California, San Diego; University of Colorado; University of Rochester; and University of Utah. Funding in FY 2001 continues for the 20 centers at the same funding levels.

## ORWH/NIH Re-entry Program

The ORWH Re-entry Program was developed in 1992 as a pilot program to help fully trained scientists (women and men) re-establish careers in biomedical or behavioral science after taking time off to care for children or parents, or to attend to other family responsibilities. This program was originally started as a pilot program to encourage fully trained women and men to re-enter an active research career after taking time off to attend to family needs. The success of this pilot program was the impetus to expand the program across NIH. All NIH ICs support the program. The aim of these supplements is to encourage fully trained individuals to re-enter research careers within the missions of all the program areas of NIH. This program will provide administrative supplements to existing NIH research grants for the purpose of supporting full- or part-time research by these individuals in a program geared to bring their existing research skills and knowledge up to date. It is anticipated that, at the completion of the supplement, the scientist will be in a position to apply for a career development (K) award or for a research award. ORWH currently provides funding of $20,000 for each of 2 years. In FY 2001, ORWH sponsored two new re-entry candidates and continued Year 2 funding for two others.

- Title: *Computerized Radiographic Analysis of Bone Structure*
  PI: Maryellen L. Giger, Ph.D.
  University of Chicago
  Awardee: Tamara Vokes, M.D.

  The research examines the ability of texture analysis to detect bone fragility *in vivo* (estimated from prevalent vertebral fractures) and compare its predictive value to methods currently used for diagnosing osteoporosis. The study subjects undergo texture analysis, assessment of bone mass by several commonly used methods, and examination of lateral spine for prevalent vertebral fractures. The presence and degree of prevalent vertebral fractures will be used to diagnose and quantify bone fragility. The diagnostic performance of texture analysis (with and without heel bone mineral density [BMD]) in detecting the prevalent vertebral fractures will be compared to that of methods currently used for diagnosing osteoporosis (central and peripheral BMD, and heel ultrasound).

  The study subjects will be postmenopausal women recruited from the pool of patients referred to the Bone Clinic for bone density measurement as part of their routine medical care. We plan to study 650 subjects over 2.5 years. We will make a special effort to include patients who are likely to have vertebral fractures based on their appearance, history of fractures, or age.

  The proposed research is closely related to the research objectives of the parent grant. Dr. Vokes has significant clinical experience and a large cohort of patients with osteoporosis and will be in a unique position to recruit the patients for the studies proposed in the parent, as well as in the supplemental, grant. Furthermore, as a director of the Endocrinology Clinic of which the densitometry program is a part, she is responsible for the day-to-day densitometry operation and will be able to identify suitable candidates for enrollment into the proposed studies. Because of her enthusiasm and interest in research, she has already made significant contribution to further developing the project described in the parent grant. The supplement would provide her with protected time, which would allow her to actually carry out the exciting and promising studies proposed in the parent grant, as well as in the supplemental grant.

Despite the success and accomplishments achieved during her fellowship training and early faculty appointment, she voluntarily chose to make a change in her career path after having her first daughter. Consequently, she took a position as a clinical endocrinologist in a multi-specialty group, which allowed greater flexibility and enabled her to be with her children and provided a much more vital understanding of the importance of clinical research in bringing state-of-the-art care to the physician-patient encounter. In 1999, she returned to academic medicine at the University of Chicago as an Assistant Professor of Clinical Medicine in the Section of Endocrinology. Based upon these successes, Dr. Vokes has applied for an NIH K award so this re-entry grant may only be needed for 1 year. (3 R01 AR42739-04A2S1)

▶ Title: *Mononuclear Phagocyte Function in Immunologic Diseases*
PI: Robert Kimberly, M.D.
University of Alabama at Birmingham
Awardee: Julie G. Baskin, Ph.D.

Dr. Baskin took time off from her research career for child-rearing purposes from 1993 to present. She completed a postdoc and published a manuscript on this work in 1995, and also taught in high school and at the university level during this time.

Dr. Baskin's research will initially focus on the analysis of a series of a-chain receptor chimeras in order to characterize the unique contributions of each a-cytoplasmic domain. Using cells lines (P388D1, RBL, and IIA1.6) transfected with wild type and cytoplasmic domain truncation mutants, she will define the impact of the cytoplasmic domain on early signal transduction and gene transcription. This research is proposed for several reasons: 1) it will require that she master techniques of molecular biology to construct the chimeric receptors; 2) it will require that she master transfection and assessment of expression by flow cytometry; 3) it will require that she master techniques related to signal transduction; and 4) it will provide the opportunity to become familiar with gene expression arrays.

The research training environment and the mentoring relationship between the Principal Investigator and the candidate are tightly interwoven and will provide rigorous training in research methods and a strong appreciation for interdisciplinary challenges and opportunities. The accelerating impact of the human genome project has heightened awareness of the convergence and interdependence of clinical and more fundamental scientists, and a basic understanding of pathophysiologic mechanisms and molecular techniques will help inform research initiatives, not only at the bench but also in the clinic. This understanding is also essential for the application of new diagnostic technologies and therapeutic modalities that are now reaching into the effective practice of medicine.

The interdisciplinary environment, fostered by the University-wide Interdisciplinary Arthritis and Musculoskeletal Center, positions Dr. Baskin at the intersection between mechanism-based research, its application to clinical medicine, and its impact on disease outcomes. Furthermore, the new opportunities developed within the University of Alabama's Arthritis and Musculoskeletal Center, including its methodology core and its biomedical research cores, underscore the range of expertise and technologies available to the candidate.

Systemic lupus erythematosus is an autoimmune disease characterized by the production of multiple autoantibodies. These autoantibodies, including IgG antibodies specific for nuclear material, form immune complexes with autoantigens. Circulating immune complexes can deposit in tissues, induce inflammation, and cause organ damage, including glomerulonephritis. Mononuclear phagocytes that bear cell surface receptors for the Fc portion of immunoglobulin facilitate clearance of these circulating immune complexes and

therefore can potentially influence disease susceptibility. (3R01AR33062-19S1)

- Title: *Renal Functional Derangements in Hypertension*
  P.I. Gabriel L. Navar, Ph.D.
  Tulane University School of Medicine
  Awardee: Shirley A. Williams-Scott, Ph.D.

  Dr. Scott was awarded a minority supplement that is being converted to a re-entry supplement cofunded by NHLBI and ORWH. She will work with the senior faculty and staff at Tulane University Medical School Physiology Department. The focus of this activity is to define and characterize the mechanisms responsible for the intrarenal hormonal, microcirculatory, and transport derangements that occur in ANG II-dependent hypertension and to develop an understanding of the experimental methods used to study renal uptake, and augmentation of intrarenal ANG II levels during ANG II-induced hypertension. Dr. Scott will work with Dr. Navar for the next 4 years to develop the skills and knowledge to become an independent investigator in renal physiology with a focus on the hypertensinogenic influence of ANG II. In keeping with the overall objective of the parent grant, the applicant will perform pertinent studies that will define and characterize mechanisms responsible for microvascular and tubular reabsorption derangements that occur in ANG II-dependent hypertension. (Year 2) (5 R01 HL23671-19)

- Title: *Impacts of Managed Care on Substance Abuse Services Linkages*
  P.I.: Joseph P. Morrissey, Ph.D.
  University of North Carolina–Chapel Hill
  Awardee: Kathleen Thomas, Ph.D.

  This interorganizational study examines the effect of managed care on linkages between outpatient drug abuse treatment programs and both primary care and mental health services. This 29-month re-entry supplement request will provide support for Dr. Thomas who has had a break in her career for child-rearing responsibilities.

  Dr. Thomas will undertake a more in-depth assessment of the costs of interagency linkages than proposed in the original application. She will focus on understanding how service relationships are impacted by the introduction or intensification of managed care payment practices for providers serving persons with dual substance abuse and mental disorders. Her work will investigate how to cost out linkages between treatment units and other mental health and primary care agencies, determine the most cost-effective linkage to meet a specific goal, develop a strategy for measuring the effectiveness of the linkages, and consider ways to extend this system-level study to the client level. Dr. Thomas plans to develop a research plan for such a study and submit it as a separate R01. (Year 2) (5 R01 DA13016-01)

## Sackler Scholars NIH U.S.–Israel Student Exchange Program

In conjunction with the NIH Office of Intramural Research, a Bi-national Student Exchange Program in Women's Health Studies was initiated in FY 2001, and continued in FY 2002, with the Sackler Faculty of Medicine, Tel Aviv University (TAU), Tel Aviv, Israel. Preliminary arrangements, such as scholar applications, review, and logistics, began in FY 2000.

This program aims to expose excellent M.D.-Ph.D. or Ph.D. Israeli students in the biomedical field to the leading research programs at NIH. The program encourages those interested in research related to women's health, whether basic, patient oriented, or population based. The program should facilitate and enhance biomedical research in Israel, establish scientific collaborations between Israel and NIH, and train promising students for postdoctoral studies at NIH. The Sackler Faculty of Medicine

represents the largest medical faculty in Israel with two medical schools (an Israeli program and an American-international school), a dental school, a school of health professions, a school of continuing medical education, and a graduate school. To attain the best medical and scientific education for better service to the community, the best training opportunities are required and NIH, as the largest biomedical research institute in the world, offers a unique location for this education. The new program offers an opportunity to present new horizons for research into women's health issues and should provide a pioneering model for other medical faculties and other countries.

A joint TAU–NIH committee will choose the best students to join the program each year, with a maximum of ten at any given time. These students will have an Israeli advisor and an American advisor. The students perform 10-months per year of research in the Israeli laboratory and up to 2 months per year in an NIH laboratory, for a total of 4 to 5 years of research. Once a year the American supervisors will visit Israel for a joint scientific meeting of all enrolled in the program. In FY 2002, five students were supported for a summer experience in NIH intramural laboratories.

## ORWH–Office of Science Education Programs

The partnership between ORWH and the Office of Science Education (OSE) in FY 01-02 supported educational programs for pre-college-age students and those interested in health, with materials and resources that complement those found in schools and communities. These programs are developed with a focus on the important role education plays in providing young people, especially adolescent girls, with the tools necessary to deal successfully with the many risks to health that they will encounter throughout their lives.

### ORWH–OSE Speakers Bureau

The Speakers Bureau is a program designed to increase national visibility of NIH through employees who are available to speak at schools and other organizations about NIH research. Speakers are from a variety of occupations, including administrators, healthcare workers, librarians, and historians, as well as research scientists and clinicians. They address a total of 49 topics, such as osteoporosis, depression, and breast and ovarian cancer, with 340 subtopics. The speakers are diverse in their fields of expertise and their gender, race, and ethnic background.

#### Highlights

The program director continued to respond to requests to recruit new volunteers, and to provide additional resources to the community. During fiscal 2002, 228 requests for speakers were made on the web (an increase over the 122 from the previous year). Seventy-six of the 101 speakers who participated during the year received requests. Of the 228 requests received, 106 were accepted with an audience potential of 2,650 to 2,867 students and 2,264 to 2,464 adults. Of the 228 requests, a total of 167 came from local public school systems, private and charter schools, and local colleges. The public schools made 70 percent of the requests; the private and charter schools, 10 percent; and a surprising 20 percent from colleges. In addition, organizations in South Dakota, Georgia, New York, Florida, Pennsylvania, and Illinois requested assistance for special events.

#### Speakers

Of the 101 speakers participating in the program during the year, 87 remained active at the end of the year, a 28 percent increase from the previous year. During this period of time, 14 speakers dropped out and 30 volunteered to participate. Of the 87 active speakers, 15 came from Fort Detrick (NCI and USAMRIID), and 56 from NIH, representing 17 of the 27 NIH institutes and centers. In March 2002,

27 speakers and volunteers attended a training session for the Speakers Bureau. They heard from an experienced teacher and an experienced speaker, and were given information on the ethics involved in speaking for NIH and of sponsored travel.

#### PRESENTATIONS

Much of the activity of the Speakers Bureau resulted from the program director's continued promotion through presentations at an NIH Committee Management Officers Meeting, the MIST (Minorities in Science and Technology) conference at George Washington University, the Frederick Research Festival, the NIH Health and Safety Expo, and to groups such as the MCPS Student Academy of Science Sponsors and the NIH Fellows Committee.

### Women are Scientists Video and Poster Series

Colorful, informative videos and posters for middle-school students that feature women scientists are designed to stimulate the interest of girls in science at a time when they are making decisions about the course choices that may affect their career options later. In the middle-school years, many girls are discouraged from pursuing advanced levels of study in math and science. This series is intended to make them aware of the many interesting and rewarding careers in the medical sciences, and the educational requirements necessary to pursue them.

#### HIGHLIGHTS

The supply of the first video kit, Women are Surgeons, has been exhausted and back orders are received regularly. Plans to reprint the kit are underway. The second two video kits, Women are Pathologists and Women are Researchers, have also been extremely popular. The total Women are Pathologists kits distributed in FY 2002 were 2,554; the total kits distributed of Women are Researchers was 3,202. The materials were featured in an article that appeared in the electronic bulletin of the Triangle Coalition. The coalition is a Washington, DC-based nonprofit organization comprising more than 100 organizations with representation from business, education, and scientific and engineering societies. The coalition provides a forum for the three sectors to work together to promote the improvement of science, mathematics, and technology education.

A forth video is under development. The contract was awarded at the end of the fiscal year and three outstanding women scientists have agreed to participate in the project. Dr. Margaret Nosek also agreed to work on the project, providing overview information. She is developing a searchable database for young women with disabilities who are interested in careers in medical research. This database will fit into the new Life Works science career information website being developed by OSE.

### Women in Science Poster Series

A series of free posters, with a companion website, is aimed primarily at middle-school girls. The series emphasizes that science and medical research offer many different career paths, all of which are open to women.

#### HIGHLIGHTS

Three posters were available in FY 2002. The research areas represented in the three posters – neuroscience, heart disease, and cancer research – were the same as the research areas covered in an earlier joint ORWH–OSE project, Curriculum Online. This was done based on the theory that linking various projects would enhance each, as well as the program as a whole. Distribution of the posters has been accomplished primarily at science teacher conferences attended by OSE, and by mail through a request form on the website. The posters have been especially popular at conferences, where materials that focus on women in science are lacking.

## Howard Hughes Medical Institute Summer Program

This program gives students who successfully completed a Howard Hughes Medical Institute internship the opportunity to return to NIH for a second summer. Through the program,

returning students further develop or complete their research projects, thus gaining a greater understanding of the total research process. Students are able to present their research at a conference, submit an abstract for publication, and/or help other students.

Ten students – six girls and four boys – returned to laboratories for a second summer. One student was selected as an Intel Science Talent Search semifinalist and was awarded a $1,000 scholarship and $1,000 for her school. Several of the students are authors on manuscripts that have been or will be submitted for publication.

## Undergraduate Scholarship Program for Individuals from Disadvantaged Backgrounds

ORWH sponsors scholars through the Undergraduate Scholarship Program for Individuals from Disadvantaged Backgrounds (UGSP). The Office of Loan Repayment and Scholarships is responsible for the development and management of UGSP. UGSP provides scholarships to undergraduate students who have been competitively selected from a nationwide pool of candidates. An average of 15 scholarships are awarded each year. In FY 2001, ORWH provided funding for three scholars. The following is a summary report on the ORWH-sponsored scholars:

- ***Ms. Shari Lee,*** a student at Delaware State University, received a UGSP award to complete her undergraduate studies in Biology. She performed her Summer 2001 research training under the mentorship of Dr. Steven Jacobson, National Institute of Neurological Disorders and Stroke, on the role of human herpes virus in multiple sclerosis, and received an impressive evaluation. She presented a poster, The Association of Human Herpes Virus-6 and Multiple Sclerosis, at the NIH Poster Day in August 2001. Based on financial support provided through the ORWH–UGSP partnership, she also presented this poster at the Annual Biomedical Research Conference for Minority Students in Orlando, Florida. Ms. Lee graduated with a 3.87 GPA, and has been accepted to the doctoral program in Pharmacology, University of Pennsylvania. During the Summer 2002, she will be training with Dr. J. Carl Barrett, National Cancer Institute, whose laboratory focuses on cancer biosystems and aging.

- ***Ms. Yvette Green***, also a student at Delaware State University, received scholarship support to complete her undergraduate studies in Biology. She performed her Summer 2001 research training under the mentorship of Dr. Orna Cohen-Fix, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), studying yeast genetics, and received an excellent evaluation. She presented a poster, Mutational Analysis of the Budding Yeast Anaphase Inhibitor, PDS1, at NIH Poster Day in August 2001. Based on financial support provided through the ORWH–UGSP partnership, she also presented this poster at the Annual Biomedical Research Conference for Minority Students in Orlando, Florida. Ms. Green graduated with a 3.78 GPA, and has been accepted to the doctoral program in Genetics at Rutgers University. During the summer 2002, she will continue her research training with Dr. Cohen-Fix in NIDDK, studying yeast genetics.

- ***Ms. Sabrina Martyr,*** a student at the University of the Virgin Islands, received scholarship support to complete her undergraduate studies in Chemistry. She performed her summer 2001 research under the mentorship of Dr. Sanford Markey, National Institute of Mental Health, studying the use of mass spectrometry, and received an excellent evaluation. She presented a poster, Structural Studies of DNA Synthesome Proteins Using Mass Spectroscopic Methods, at NIH Poster Day in August 2001. Ms. Martyr will graduate with a 3.4 GPA in Chemistry. During the summer 2002 she will train with Drs. Mark Gladwin and Griffin Rodgers in the Clinical Center and NIDDK. She will continue her research

training at NIH for a full year, focusing on sickle cell disease, before pursuing doctoral studies.

The support of these undergraduate students by ORWH has allowed them to focus on their studies and receive excellent research training and skill enhancement activities at NIH. These students exemplify measurable development in their biomedical research careers, evidenced, in part, through their acceptances to doctoral programs. They were honored and recognized as ORWH–UGSP scholars on June 7, 2002.

## Office of Education

### *Programs for NIH Trainees, FY 2001 and 2002*

ORWH provides essential support to the Office of Education (OE) for the design and implementation of programs that foster the professional development of NIH trainees, in particular the postdoctoral fellows in both clinical and basic research programs across all institutes and centers. During FY 2002, ORWH-supported programs were again implemented to enhance the training experiences of participants in the NIH Postbaccalauteate Intramural Research Training (IRTA) Program, as well.

***Programs for Postdoctoral Trainees***

- **Survival Skills Workshops**

  In 2002, the OE planned and implemented a broad-based educational program designed to provide NIH postdoctoral fellows with the requisite skills necessary to compete for and sustain careers in biomedical research and science-related occupations. Beth Fischer and Michael Zigmond of the consulting firm Assimilating Survival Skills into Scientific Training (ASSIST) conducted the following workshops:

  - *Writing Research Articles*

    This workshop focused on 20 essential steps to publishing a scientific paper. Fifty-six participants also learned how to prepare effective tables and graphs and examined effective strategies for dealing with common problems, such as writer's block.

  - *Teaching*

    This workshop was targeted to postdoctoral fellows who have an interest in teaching courses at FAES or at local colleges or universities. It focused on the basics of effective course design, such as selecting a textbook, developing a syllabus, and designing examinations. The workshop also included strategies for balancing an individual's teaching and research goals.

  - *Job Hunting*

    This workshop covered when and how to seek career opportunities; what employers look for; researching positions; and writing effective cover letters, CVs, resumes, statements of interest, and letters of recommendation.

  - *Negotiating*

    In this workshop, conducted by Laurie Weingart of Carnegie Mellon University, participants learned the skills that are necessary when negotiating a job offer. The fellows were divided into pairs in order to role-play specific situations and were asked to share these experiences.

  - *Management Skills*

    This workshop focused on learning how to manage a laboratory and to supervise employees and postdoctoral fellows.

  - *Interviewing*

    This workshop focused on interviewing and covered the following topics: information to find out; who to talk with; questions to expect; how to convince the interviewer that you have the required skills; questions that you should ask; how to deal with inappropriate or illegal questions; and strategies for moving in pairs.

*Science Communication Classes*

- **Writing about Science**

  Taught in a workshop format, this course teaches fellows how to write articles suitable for publication in peer-reviewed scientific journals. Participants learned how to write a research paper using their own laboratory data. During the course, they critiqued the work of others and learned about responsible authorship; the process of publication; dealing with editors and reviewers; and other issues related to scientific writing.

- **Speaking about Science**

  This course was offered for 4 weeks in March, June, and September. The course was offered in the morning, and then a second session was offered in the evening. The course provided participants with information on how to become an exemplary speaker, to excel in job interviews, and how to deliver scientific presentations using visual aids, including video feedback.

- **Advanced Speaking about Science**

  This course is designed to assist NIH postdoctoral fellows in building upon the lessons of the introductory course, provide vocal and other technical instruction, discuss new methods of presentation, and offer a forum for in-depth assistance on each class member's needs.

- **Fellows Award for Research Excellence**

  The Fellows Award for Research Excellence (FARE) competition is an annual program that allows postdoctoral and clinical fellows at NIH to compete for a travel award to be used to attend a domestic scientific meeting. ORWH contributes $250 to each award. The program provides support for a maximum of 25 percent of the contestants. In FY 01-02, ORWH supported a total of 323 awards.

- **NIH Postdoctoral Job Fair**

  The NIH Postdoctoral Job Fair featured 31 exhibitors from academe, biotechnology firms, and government. The program was run by the Office of Education with some assistance from the Fellows Committee.

*Programs for Postbaccalaureate Trainees*

- **Postbac Poster Day**

  The third annual Postbaccalaureate Poster Day, held on May 8, 2002, provided an opportunity for 160 postbaccalaureate trainees to share their research with the NIH community. This is double the size of the program in 2001. The participants represented virtually all institutes and centers with intramural programs.

- **NIH Academy Curriculum**

  The NIH Academy, a postbaccalaureate program for recent college graduates with an interest in pursuing careers that address the issue of domestic health disparities, enrolled its third class during the academic year 2002-2003. ORWH support covered honoraria for four speakers who discussed a range of topics, including oral presentations, interviewing techniques, public health programs, and the Institute of Medicine's report on health care and minorities.

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# *Executive Summary*

## *Overview*

NIH continues to increase its total funding for research on women's health, with critical advances being achieved. In FY 2002, the actual NIH-wide funding for research on women's health amounted to over $3 billion. All of the NIH grant-making institutes and centers (ICs) devote some of their funds to this area of research.

Major women's health research areas being funded by NIH include: diabetes; cardiovascular disease; cancer; autoimmunity; HIV/AIDS; preventive behaviors, such as sound nutritional practices; eating disorders, such as obesity; and physical activity. All of these areas have potential impact on reducing the incidence, morbidity, and mortality associated with a host of diseases important to women's heath.

A major trend across NIH has been in the area of sex and gender in basic biology and clinical studies. NIH has seen an increase in research grant applications examining the sex and gender differences in many health areas. Such an example has also been the increase in research focused on gender differences in substance abuse. ORWH and NIDA are funding a number of grants that are examining the gender and sex differences in stimulant action, and treatment outcomes. Based on the cumulative results, there is now accumulating evidence to suggest that the antecedents, consequences, and mechanisms of drug abuse and addiction are not identical in males and females, and that gender is an important variable in treatment and prevention.

In the area of cardiovascular disease, ORWH cofunded, with the Agency for Healthcare Research and Quality (AHRQ), an important project, the Evidence Report on Gender Differences in Cardiac Care. Heart disease is the leading cause of mortality in American women, with over 366,000 deaths each year. Heart disease can also lead to disability and a significantly decreased quality of life. Yet public polls continue to show that most women are not aware of their increased risk, continuing to believe it primarily affects men. With the goal of emphasizing the importance of this area of sex and gender research, this ORWH–AHRQ report will compile all of the recent findings that relate to the known or potential differences in the diagnosis and treatment of cardiac disease in men versus women. By highlighting these findings, researchers and policy makers will be better able to see where future research is needed, as well as building on existing findings.

Cancer remains a major cause of morbidity and mortality for women globally, second only to heart disease. During this 2-year period, NCI supported major programs in breast, ovarian, and lung cancer research. All of these cancers have funded programs within the Specialized Programs of Research Excellence (SPOREs) that promote interdisciplinary research to encourage the movement of basic research findings from the laboratory to the clinic and community-based populations.

During this period, NCI and ORWH have targeted its grant portfolio to selected areas, such as vaccine development. ORWH continues to cofund NCI-sponsored clinical trials for two human papillomavirus (HPV) 16-based vaccines to prevent the transmission of HPV, and therefore the prevention of cervical cancer. To date, the vaccines have been well tolerated, and induced a consistent antibody response. The HPV-16 strain variation, considered high-risk, has been postulated as a risk factor for cervical cancer. Globally, the incidence of invasive cervical cancer is approximately 400,000 cases annually; so scientific advances in this area would directly impact women's health.

For many years, NIH has supported a broad range of autoimmunity research. Although most autoimmune disorders disproportionately affect girls and women, a major emphasis of recent research grants has been to exploit this sex and gender difference as a way to elucidate the underlying etiology of these disorders. In FY 02, NIH cofunded research grants that targeted sex hormone regulation of innate immunity in women and men, or sex-based differences in immunity or the immune response.

Even in areas where NIH has had a long record of cofunding, such as in diabetes prevention research, the trend in FY 01 and FY 02 was to focus on sex and gender differences, especially if there are existing health disparities. In FY 01, the Diabetes Prevention Program (DPP), the landmark project that enrolled 68 percent women and 48 percent minority participants, reported that the risk of developing type 2 diabetes could be markedly reduced through life style changes, such as moderate weight loss and exercise. In FY 02, DPP went into long-term follow-up of these participants to examine the late effects of the study interventions on the development of diabetes and cardiovascular complications, especially in minority women. Women with diabetes have an increased risk of heart disease, which is two- to six-times more common in diabetic than non-diabetic women. Understanding the factors that contribute to excess heart disease in diabetic women is of critical importance, especially because data indicate that these women have not experienced the decline in heart disease mortality that has been observed in the general population.

Along with diabetes research, NIH and ORWH continue to fund research related to eating disorders ranging from obesity to anorexia and bulimia. Most of the research support has focused on obesity because of its dominant impact on women's health. Looking at a woman's life span, critical periods such as the menopausal transition create important windows for study. ORWH has maintained an active research grant portfolio in the area of menopause, such as cofunding the SWAN study (Study of Women's Health Across the Nation) with NIA and other NIH ICs, exploring complementary and alternative medicine for menopausal symptoms, menopausal depression, and alternatives to hysterectomy, etc.

NHLBI supports a wide range of basic, clinical, and epidemiological research on diseases that affect women and has administrative responsibility for the NIH Women's Health Initiative (WHI). Some of the program highlights include launch of "The Heart Truth," a campaign to make women aware of their vulnerability to heart disease and of ways in which they can reduce their risk for hypertension, high blood cholesterol, smoking, overweight, physical inactivity, and diabetes. All of these risk factors play a role in the development of heart disease in women. Recent findings from WHI, and the NHLBI Women's Angiographic Vitamin and Estrogen (WAVE) trial, have produced persuasive evidence that, contrary to long-held expectations, use of postmenopausal hormone therapy is not useful in primary and secondary prevention of heart disease, and may actually be harmful.

During the period 2001 and 2002, the "face" of HIV/AIDS changed because of the increased incidence observed in girls and women. During this period, women comprised 47 percent of the adults living with HIV/AIDS internationally. Within the United States, women represent an estimated 30 percent of new HIV infections. Around the world, more women than men are dying from HIV/AIDS. Women experience HIV/AIDS differently from men in a number of important respects, some of which are physiological and some of which are social. For example, women progress to AIDS at lower viral load levels and higher CD4 counts than do men, a finding that might have implications for care and treatment of HIV-infected women.

Internationally, women have benefited less than men from the advances in AIDS medications in terms of reduced mortality. From a societal perspective, women are the primary care providers to children and the elderly, so when young and middle-aged women die from AIDS, their dependents usually have disruptions in their care. Based

on these changes, multiple NIH institutes and centers increased the number of research grants in HIV/AIDS to include such international sites as Haiti, South Africa, Uganda, Botswana, Zimbabwe, and China. Future collaboration will continue in this area across NIH, as well as with other federal partners. Because of the continued urgency of the situation and its effects on women, this area will continue to be a priority for all of NIH.

NIH funds much research on osteoporosis, a skeletal disorder marked by reduced bone strength that predisposes a person to an increased risk of fractures. It is estimated that some 10 million women in the United States have osteoporosis and another 18 million have low bone mass and are at risk for osteoporosis. Recent funding has examined bone biopsy specimens from patients with osteoporosis before and after treatment with daily injections of recombinant human parathyroid hormone (PTH). Treatment for 18 or 36 months with daily injections of PTH were shown to increase the structural integrity of the bone. This effect explains the action of PTH treatment to reduce the incidence of osteoporosis-related fractures.

In FY 02, NIH, led by NIAMS and NIA, funded the Osteoarthritis Initiative, a public-private partnership between a number of NIH ICs, ORWH, and four pharmaceutical firms. This large study will eventually enroll 5,000 study participants aged 50 and above who are at high-risk for developing symptomatic knee osteoarthritis. Four clinical sites and one data coordinating center have been funded to establish and maintain a natural history database that will include clinical evaluation data and radiological images, and a biospecimen repository.

Traditionally, reproductive health has been central to women's health research. Several NIH ICs support a variety of research grants such as pelvic floor disorders, pelvic and uterine pain, and adverse outcomes of pregnancy. The reproductive health of women will continue to be a research priority, even with the expansion of the concepts of women's health as going beyond their reproductive condition. During the next years, ORWH will continue to work with the ICs to develop new research projects and to fund research in such areas as fibroids, endometriosis, pelvic floor disorders, and pregnancy, including eclampsia.

Table 22 in this report summarizes the trends in overall NIH funding categorized as "women only", "men only", or research that will benefit both men and women. For FY 01 and FY 02, 77.7 and 79.5 percent of NIH research funding, respectively, was directed at diseases and disorders common to both men and women, or to basic science studies that could equally affect the understanding of health or disease in women or men. In FY 02, this amounted to $22.5 billion, and includes research that equally or inseparably benefits men and women alike, for example, many basic research studies. Focusing on research directed at conditions and diseases unique to women also continued to increase in actual dollars, as did that for conditions unique to men. In FY 01, this research totaled over $2.9 billion, while male-focused research exceeded $1.5 billion. While the actual research funding categorized as women only and men-only also increased in FY 02, these categories decreased in terms of a percentage of the total NIH funding.

In FY 01 and 02, there were increases in clinical research funding across NIH and by ORWH. Nearly $8.5 million was directed by ORWH toward cofunding some area of clinical research, including autoimmunity, diabetes, menopause and alternatives to hysterectomy, complementary and alternative medicine, osteoarthritis, mental health, gynecological, and dental research.

This entire FY 01–02 report demonstrates the great strides that have been made to expand the scientific base of NIH research on women's health. With the overarching trends of undertaking sex and gender analysis and reducing health disparities, future research has an even greater potential for enhancing the health status for all women and men.

# *Highlights of Institute and Center Activities*

## Fogarty International Center

The Fogarty International Center (FIC) promotes and supports scientific research and training internationally to reduce disparities in global health. In particular, FIC supports international research training and capacity building in the developing world. FIC's research and training programs address a wide range of topics, including infectious diseases, maternal and childhood conditions that contribute to maternal and infant mortality and morbidity, population dynamics, environmental and occupational health, bioethics, and biodiversity.

As part of its effort to reduce global health disparities, FIC supports a number of research training programs that address women's health conditions. In particular, the FIC International Research and Training Program in Population and Health supports research training in reproductive processes; contraceptive development; and demographic studies of population health issues, including rapid societal changes, societies under stress, and aging. The FIC International Maternal and Child Health Research and Training Program addresses the continued high levels of maternal, perinatal, and infant mortality and morbidity in many countries. The FIC AIDS International Training and Research Program funds training that supports research to address issues of HIV infection that have particular relevance for women: stigma associated with HIV/AIDS, perinatal transmission of HIV, HIV transmission through breast feeding, female-controlled methods to reduce sexual transmission of HIV (including microbicides, biomedical interventions, and behavioral interventions), and interventions appropriate for adolescent girls. The Fogarty International Research Collaboration Award (FIRCA), a small grants program that fosters international research partnerships between NIH-supported U.S. scientists and their collaborators in the developing world, provides the opportunity for a wide spectrum of research on women's health problems and issues. Some examples of research supported by the FIRCA program include pre-eclampsia, fetal intrauterine growth restriction, ovarian cancer, and breast cancer.

In FY 2002, FIC launched the Stigma and Global Health Research Program in partnership with several other NIH Institutes and with the ORWH. The first awards under this program, to be made in FY 2003, will address the role of stigma in health, and on how to intervene to prevent or mitigate its negative effects on the health and welfare of individuals, groups and societies worldwide. Applications are expected on research projects to study how stigma associated with specific health conditions interacts with individual or group characteristics (such as gender, race, religion, sexual orientation and nationality.) It is expected that some projects will explore the linkages between gender and stigma and how these linkages impact health-seeking behavior of individuals, families and groups, among other topics.

## National Cancer Institute

The National Cancer Institute's (NCI's) research programs in fiscal years 2001 and 2002 addressed cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

*Please note:* Incidence and mortality statistics reported for 2003 will be age-adjusted to the 2000 U.S. population standard. Previous statistics based on the 1970 population standard should not be compared to new data generated from 2000 age-adjusted population standard. Additionally, some of the rates, particularly for different racial/ethnic groups, will be changed as the new statistics are calculated.

Cancer continues to take a devastating toll on American women. By the end of 2003, an estimated 658,800 women will have been

diagnosed with cancer, and approximately 270,600 women will have died of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer. In the 1990s, cancer incidence rates for all cancers decreased for men and remained relatively stable for women. Cancer mortality rates for both women and men declined through the 1990s. However, lung cancer mortality rates for women have been increasing. Breast cancer incidence rates showed little change in the 1990s, but death rates have declined by about 3 percent per year since 1995. Statistics also show that more people are living with cancer. As of January 1999, there were 8.9 million people, or 3 percent of the U.S. population, who were cancer survivors, and 56 percent of these survivors were women.

NCI is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. In 2000, NCI formally established an Office of Women's Health. Organizationally located within the Office of Science Planning and Assessment, the Office of Women's Health is responsible for assisting in planning, evaluating, and coordinating activities related to cancers in women. Among the other programs and activities in NCI that focus on women's cancers are the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, and the multidisciplinary Breast Cancer and Gynecologic Malignancies Faculties of NCI intramural researchers. NCI staff participate in multiple, diverse relevant scientific partnerships and collaborative activities with other federal and non-federal scientists.

NCI supports and coordinates broad-based research programs investigating all aspects of cancer in men and women. Through its strategic planning process, NCI has identified many of the questions that need to be answered, areas of research and care that need to be further investigated, and infrastructure that needs to be strengthened to advance our knowledge in the study of cancer. By focusing research on areas with high potential, we have the opportunity to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application. The strategies are outlined in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004* (*http://plan2004.cancer.gov/*) and include descriptions of areas that will advance discovery and its application and address areas of public health emphasis. As part of the planning process, NCI convenes Progress Review Groups (PRGs) to assist in setting priorities for organ site-specific research. Between 1998 and 2002, ten PRG reports were completed including breast, colorectal, lung, and gynecologic cancers. Following release of the reports, NCI develops strategic plans for implementing PRG recommendations. Reports for all completed PRGs, strategic plans, and additional information are available at *http://prg.nci.nih.gov*.

To develop more effective approaches to cancer prevention, early detection, and treatment, we need to better understand the interactions between inherited genetic and environmental factors. Consortia and resource networks bring multidisciplinary researchers together to pool data and resources for large population studies. For example, NCI Breast and Ovarian Cancer Family Registries and the Cancer Genetics Network provide resources for characterizing predisposing genes in high-risk families. Increasing knowledge of the molecular changes that cause cancer enables us to identify potential targets for prevention and treatment drug discovery. New technologies help to define the molecular signatures of cancer cells and the microenvironment with which they interact. Recent exciting advances in proteomics have resulted in a new procedure for recognizing patterns of protein expression in normal and cancerous blood samples. A test for early detection of ovarian cancer using proteomics is now in clinical trials.

Advances in imaging and biosensor technologies are resulting in improved cancer detection, diagnosis, and treatment through the development of novel imaging agents, improved functional imaging methods, and the development of molecular and digital imaging databases. Investigators are studying the use of digital mammography to enhance the interpretation of conventional

mammography. Tools such as ultrasound, molecular resonance imaging, and positron emission tomography are being studied for their potential to improve the accuracy of screening and diagnosis of breast and other cancers.

Ongoing and planned initiatives support research to understand disease and treatment-related effects and develop effective interventions to improve quality of life and disseminate clinical guidelines to improve quality of care. Numerous initiatives focus on research on the social, cultural, environmental, biological, and behavioral determinants of cancer, and how they contribute to disparities in cancer care and prevention in population groups that are disproportionately impacted by cancer. For example, The Center to Reduce Cancer-Related Health Disparities (CRCHD) has identified, as a high priority, the need to understand and reduce the high rate of cervical cancer mortality in some regions of the United States. During 2001 and 2002, the CRCHD has consulted with experts from these regions and from other federal and state health agencies to develop interventions that ultimately reduce this preventable cancer.

The devastating impact of tobacco use and exposure to tobacco is being addressed by studies to better understand the genetic and environmental factors involved in tobacco addiction, screening trials in current and former smokers, clinical research to identify behavioral and pharmaceutical interventions for prevention and treatment of addiction, and better treatments for tobacco-related cancers. NCI has taken the lead in a public/private partnership effort to address the high rate of tobacco-related cancers in women and adolescent girls. Recommendations from a priority-setting meeting held in early 2003 will provide the basis for the development of action plans to increase our understanding of the sex-based differences in women's smoking behaviors, susceptibility to tobacco addiction and tobacco-related cancers, and translation of current knowledge to effective prevention and treatment interventions.

NCI supports a broad program of clinical research to develop new agents and novel approaches for the prevention, early detection, and treatment of cancer. Clinical trials to evaluate improved and novel prevention, detection, and treatment strategies are carried out within a clinical trials infrastructure that includes NCI Cancer Centers, Cooperative Clinical Trials Groups, Specialized Programs of Research Excellence, and the Community Clinical Oncology Program (CCOP) and minority-based CCOPs.

## The National Center for Complementary and Alternative Medicine

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

The 1999 National Health Interview Survey found that 28.9 percent of the 30,801 respondents had used at least one CAM

therapy in the past year and that CAM use was higher among women (33.4 percent) than men (24 percent). Rates of CAM use were highest among 45- to 54-year-old females (40 percent) and women with 16 or more years of education (42.6 percent). In this survey, the CAM therapies most commonly used were spiritual healing or prayer, herbal medicine, and chiropractic therapies. However, many other CAM practices within the five aforementioned domains are also used. CAM therapies are used to treat a broad range of health conditions by both men and women, including back and neck problems, allergies, fatigue, arthritis, headaches, diabetes, and cardiovascular disease. CAM therapies for women treat a variety of conditions such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and urinary tract problems. Thus, NCCAM's research portfolio includes investigations focused on a variety of diseases, using a myriad of CAM therapeutic interventions.

## NATIONAL CENTER FOR RESEARCH RESOURCES

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

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

The *Clinical Research Division* provides clinical research infrastructure for medical scientists who conduct patient-oriented research. This research may be supported by the NIH or by funds provided though other federal, state, and local agencies, and the private sector. The division administers programs to increase the opportunities for clinicians to be involved in patient-oriented research; to procure and distribute a wide variety of human tissues and organs for medical research; to provide vectors for clinical trials of gene therapies; and to support meetings and workshops dedicated to understanding or treating human diseases. The division also participates in federal set-aside programs designed to support innovative clinical research, with commercial potential, conducted by small business ventures.

The *Comparative Medicine Division* provides high quality, disease-free models and specialized animal research facilities for biomedical investigators. This is accomplished by: supporting the development of a wide range of research models, including nonhuman primates, rodents, aquatic species, and invertebrates; providing access for biomedical researchers to an array of important biological materials such as viruses, bacteria, fungi, cell lines, and genetic material; supporting the identification and development

of new and improved animal models for the study of human diseases; supporting training for veterinarians; and supporting the improvement of the health and well being of laboratory animals. The division supports research activities at eight National Primate Research Centers.

The *Research Infrastructure Division* expands the Nation's ability to conduct biomedical and behavioral research by developing research infrastructure of all kinds. This includes support for renovation of biomedical and clinical research laboratories and animal facilities, recruitment of new faculty, performance of pilot projects, and acquisition of research equipment. Support from this division is provided to predominantly minority-serving institutions that award doctorates in the health or health-related sciences, and institutions in states that have historically had limited NIH support. This support enables junior college, baccalaureate, and master's degree-granting institutions to significantly enhance their capacity to conduct biomedical and behavioral research by developing and strengthening formal, collaborative agreements with research-intensive, doctoral degree-granting institutions. The goal of these funding programs is to encourage scientists to work with educators and community organizations to improve science education and the public's understanding of health-related science, to increase the interest of young people in science careers, and to make biomedical research participation accessible to all Americans.

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

## National Center on Minority Health and Health Disparities

The National Center on Minority Health and Health Disparities (NCMHD) was authorized by Public Law 106-525, the *Minority Health and Health Disparities Research and Education Act of 2000,* and established in January 2001. The mission of the center is to promote minority health and lead, coordinate, support, and assess the NIH effort to reduce and ultimately eliminate health disparities. In this capacity, the NCMHD will: conduct and support basic, clinical, social, and behavioral research; promote research infrastructure and training; foster emerging programs; disseminate information; and reach out to minority and other health disparity communities.

The Congress has authorized the NCMHD to develop a Strategic Research Plan and Budget that will guide all of the NIH's health disparities activities, in collaboration with the NIH Office of the Director and the other Institute and Center (IC) Directors at NIH. The NCMHD has also been given the authority to fund three core programs to enhance the research capacity of institutions engaged in biomedical and behavioral research to the field of health disparities, as well as to attract more individuals from minority and underserved populations to this area of research. These programs, which have been successfully launched with substantial assistance from the other NIH ICs, lay the foundation for NCMHD efforts to eliminate the health disparities in this country:

- *Centers of **EX**cellence in **P**artnership for **C**ommunity **O**utreach, **R**esearch on Health Disparities, and **T**raining (Project EXPORT) Program* supports the conduct of research, research training, and community outreach activities in the field of health disparities at Centers of Excellence.

- *Research Endowment Program* is designed to build minority health and other health disparities research capacity at Health Resources and Services Administration (HRSA) Section 736 Centers of Excellence.

- *Loan Repayment Programs* aim to increase the participation of health professionals in health disparities research and to increase the participation of individuals from disadvantaged backgrounds in clinical research.

The center also administers the *Research Infrastructure in Minority Institutions (RIMI) Program* to provide support for institutions that enroll a significant number of students from minority health disparity populations to develop and enhance their capacity and competitiveness to conduct biomedical or behavioral research.

NCMHD programs provide an opportunity for the center to focus its efforts to eliminate health disparities by funding the expansion of the infrastructure of institutions that are committed to health disparities research and support the education and training of racial and ethnic minorities, as well as the medically underserved.

## NATIONAL EYE INSTITUTE

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

The major causes of blindness (glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer than men do on average, more women than men are affected by these age-related eye diseases in the United States.

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

## NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The National Heart, Lung, and Blood Institute (NHLBI) supports a wide range of basic, clinical, and epidemiological research on diseases of the heart, blood vessels, lungs, and blood; uses of blood and management of blood resources; and sleep disorders. The NHLBI also has administrative responsibility for the NIH Women's Health Initiative.

Highlights of FY 2001 and 2002 activities include the following:

- Building upon years of research to identify modifiable risk factors associated with development of heart disease in women – hypertension, high blood cholesterol, smoking, overweight, physical inactivity, diabetes – NHLBI has launched *The Heart Truth*, a campaign to make women aware of their vulnerability to heart disease and of ways in which they can reduce their risk.

- NHLBI is placing much emphasis on addressing heart disease risk factors that begin to develop during adolescence. It currently supports the *Girls Health Enrichment Multisite Studies (GEMS)* to prevent excessive weight gain in black girls as they go through puberty and the *Trial of Activity for Adolescent Girls (TAAG)* to prevent the decline of physical activity that typically occurs in girls during adolescence.

- Data from the *Women's Ischemia Syndrome Evaluation (WISE)* study, which investigated issues related to the presentation of chest

pain and diagnosis of coronary heart disease (CHD) in women, are being used to develop specific messages for women about heart attack symptoms as part of the *Act in Time to Heart Attack Signs* campaign. The campaign, which targets patients and the general public as well as physicians, encourages recognition of heart attack symptoms and calling 911 as soon as symptoms begin. Additionally, results from the WISE study are helping shape future directions of research on CHD in women.

- Recent findings from the NIH *Women's Health Initiative* and the NHLBI *Women's Angiographic Vitamin and Estrogen (WAVE)* trial have produced persuasive evidence that, contrary to long-held expectations, use of postmenopausal hormone therapy is not useful in primary or secondary prevention of heart disease, and may, in fact, be harmful.

## National Human Genome Research Institute

The National Human Genome Research Institute (NHGRI) leads the National Institutes of Health's contribution to the International Human Genome Project (HGP), which has as its primary goal the sequencing of the human genome. As this project nears successful completion, the NHGRI's mission has expanded to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease. NHGRI continues to develop research tools that will accelerate scientists' understanding of the molecular basis of disease and ultimately lead to improved diagnostic, prevention, and treatment strategies.

NHGRI also supports research to study the ethical, legal, and social implications of genomic research. NHGRI has designated five major goals which include: 1) examine issues surrounding the completion of the human DNA sequence and the study of human genetic variation; 2) examine issues raised by the clinical integration of new genetic technologies and information into health care and public health activities; 3) examine issues raised by the integration of knowledge about genomics and gene-environment interactions into non-clinical settings; 4) explore ways in which genetic knowledge interacts with a variety of philosophical, theological, and ethical perspectives; and 5) explore how socioeconomic factors, gender, and concepts of race and ethnicity influence the use and interpretation of genetic information, the utilization of genetic services, and the development of policy.

Through its extramural and intramural research programs, NHGRI contributes to identification of genes involved in human disease and to the study of the functions of these genes and their products. HGP provides data, material resources, and technology that will improve the ability of scientists to conduct biological research rapidly, efficiently, and cost effectively. This infrastructure has already dramatically accelerated the study of human inherited disease. In the laboratories of the Division of Intramural Research, with the tools produced by the HGP, scientists are developing and using the most advanced techniques to study the fundamental mechanisms of inherited and acquired genetic disorders.

## National Institute of Allergy and Infectious Diseases

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

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

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

STDs are critical global and national health priorities because of the devastating impact on women and infants, and the interrelationships with HIV/AIDS. STDs and HIV are linked by biological interactions and infections occurring in the same populations. Infection with certain STDs can increase the risk of HIV acquisition and transmission, as well as alter the course of disease progression. Recent studies indicate that the more prevalent non-ulcerative STDs (chlamydial infection, gonorrhea, bacterial vaginosis, and trichomoniasis), as well as the ulcerative diseases (genital herpes, syphilis, and chancroid), increase the risk of HIV transmission by at least two- to fivefold. In addition, STDs can cause long-term health problems, particularly in women and infants. Some of the sequelae of STDs include:

- Pelvic inflammatory disease
- Infertility
- Fetal wastage
- Low birth weight
- Congenital/perinatal infection
- Chronic conditions, such as neurosyphilis, tubal, or ectopic pregnancy
- Cervical cancer
- Increased risk of HIV infection
- Perinatal or congenital infections in infants born to infected mothers

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

## NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

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

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

Osteoarthritis is the most common disease of the joints. As the number of older people in our population continues to grow, osteoarthritis can be expected to affect more Americans. To address the need for the identification of new disease targets and the development of tools for understanding how to measure clinically meaningful information, NIAMS has recently launched the Osteoarthritis Initiative (OAI). In cooperation with the National Institute on Aging and several other federal and non-federal components, the OAI will provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on biomarkers, x-rays, and outcome measures. In other research in osteoarthritis, NIAMS-supported researchers have examined a genetic link in inherited hand osteoarthritis.

Within the past two decades, there has been a major transformation in the treatments that are available to people with rheumatoid arthritis. Clinical studies in patients with early and established rheumatoid arthritis have broadened understanding of this pathogenesis and have fundamentally changed the therapeutic approach to this disease. Quantum leaps in therapy – including the use of early, aggressive therapy, combination therapy, and the introduction of anti-cytokine agents – have improved patients' quality of life, eased clinical symptoms, retarded the progression of joint destruction, and delayed disability. Not only are new treatment options being examined, but basic research is being conducted to understand disease development. NIAMS-supported researchers are examining several factors, such as enzyme expression, and genetic and non-genetic factors that may predict disease course and outcomes in minority populations.

Lupus is an autoimmune disease that mainly affects women of child-bearing age. Many health risks are associated with lupus disease activity and researchers have recently made advances in understanding the association between lupus and osteoporosis, the nervous system, and cardiovascular disease. Scientists are continuing to unveil information regarding potential genetic and ethnic links to disease manifestation, as well as how different ethnic groups cope with the disease. Additionally, researchers have determined that physicians appear to place more emphasis on laboratory features, while patients place more emphasis on function when evaluating disease activity.

Thanks to recent increases in the NIH budget, NIAMS has been able to expand its basic and clinical grant portfolio in scleroderma. In collaboration with the Office of Research on Women's Health (ORWH), ten new grants were recently awarded that will increase our understanding of the causes of scleroderma and bring us closer to finding treatments. NIAMS has also recently provided support for a Specialized Center of Research in Scleroderma which will investigate the possibility of both genetic and environmental causes of the disease.

Research suggests that temporomandibular joint (TMJ) disorders are more prevalent in women than men. These disorders are of interest to NIAMS since they can involve muscle pain, dislocation, and degeneration of the jaw

joint. In a joint effort with ORWH, NIAMS has provided support for a Specialized Center of Research which is investigating the sex differences associated with TMJ pain.

## NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest of the research institutes within the National Institutes of Health and was established by law in December 2000. NIBIB received its first appropriation and grant funding authority in FY 2002. As the NIBIB continues to grow and structure programs, new initiatives will be developed to support a variety of scientific areas, including programs aimed at fostering women's health research.

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

During FY 2002, NIBIB funded grant awards that were focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to new drug delivery systems designed specifically for women health diseases, disorders, and conditions such as breast cancer, osteoporosis, and temporomandibular joint diseases (TMJ). NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. NIBIB-supported researchers 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 researchers are working on novel drug delivery treatments that will promote bone resorption for women suffering from osteoporosis.

To identify advanced imaging technologies for specific biomedical applications, including TMJ research, NIBIB sponsored a workshop entitled "Thermographic Approaches to Medical Diagnosis and Therapy" with the Department of Energy in December 2001, and held a major international conference with the Institute of Electrical and Electronics Engineers in July 2002. NIBIB also conducted a biosensor symposium coordinated by the NIH's Bioengineering Consortium (BECON) (administered by NIBIB) to identify advanced biosensor technologies for biomedical research applications including mechanical sensing appropriate for TMJ research. In September 2002, NIBIB was also a cosponsor of the Medical Implant Information Performance and Policies workshop which promoted biomaterials development. Several initiatives addressing TMJ, as well as other medical implants, will be undertaken as a result of the recommendations from this workshop. In addition, NIBIB participates on the NIH Temporomandibular Disorders Interagency Working Group and will collaborate with the National Institute of Dental and Craniofacial Research on the initiative, Research Registries and Repositories for the Evaluation of the Temporomandibular Joint Implants and the upcoming conference on Joint and Muscle Dysfunction of the Temporomandibular Joint in May 2002.

NIBIB also participated in the National Institute of Child Health and Human Development's (NICHD) Small Grants Program that provides support for research in population science, reproductive science, pregnancy and birth, human growth and nutrition, normal and atypical development, pediatric, adolescent and maternal HIV/AIDS, genetics and teratology, developmental biology, and medical rehabilitation research. Through this partnership

with NICHD, NIBIB funded a project aimed at improving the resolution of an ultrasound imaging method for testicular perfusion in children, a condition that often causes infertility when not diagnosed early. This new methodology will offer a faster and more accurate diagnostic tool.

As NIBIB continues to grow, new multidisciplinary research and training programs will be developed which will bridge the fields of bioengineering and bioimaging. Consistent with these goals, NIBIB has conducted several meetings in areas relevant to the NIBIB mission and has plans for future meetings to request input from the extramural community on program directions. As programs are developed in response to the needs of the national community, they will include the needs of the female population and research areas, such as TMJ and breast cancer, that require a multidisciplinary approach.

## National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) has a broad research mission dedicated to understanding the processes governing the growth and development upon which the health of infants, children, youth, and families depends. Based on this mission, part of the institute's research portfolio is also dedicated to advancing women's health. NICHD is home to much of the nation's leading science related to reproductive processes, pregnancy and childbirth, and women with disabilities. As such, basic research and studies on health conditions such as endometriosis, uterine fibroids, premenstrual syndrome, menopause, polycystic ovary syndrome, premature ovarian failure, pelvic floor disorders, and HIV/AIDS are part of the institute's research portfolio.

## National Institute of Dental and Craniofacial Research

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

## NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

The research mission of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) includes the conduct and support of basic and clinical research on diabetes, endocrinology (including growth factors), and metabolic diseases (including fundamental research important to bone diseases such as osteoporosis); digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. In FY 2001 and 2002, the institute has made progress in the following areas of women's health, which are summarized in this report: diabetes, breast cancer, osteoporosis, irritable bowel syndrome, primary biliary cirrhosis, obesity and nutrition, lupus nephritis, end-stage renal disease, urinary tract infections, urinary incontinence, and interstitial cystitis.

An estimated 17 million Americans have diabetes, a disease which has a major impact on women's health. It is the leading cause of new-onset adult blindness, kidney failure, and non-traumatic lower-extremity amputations. It also increases the risk of stoke, heart attack, and premature death. Women, in particular, are at a much greater risk of heart disease due to diabetes, and older minority women are affected disproportionately by end-stage renal disease as a result of diabetes. Diabetes also disproportionately affects minorities. To address this major health problem, the institute is conducting several major clinical trials, both in type 1 and type 2 diabetes. The Office of Research on Women's Health has worked with NIDDK in supporting specific women's health studies in association with the institute's major trials aimed at preventing or delaying the onset of diabetes in populations at risk. At the same time, advances in basic research are providing clues to the underlying etiology and pathogenesis of both type 1 and type 2 diabetes, and may provide targets for intervention.

Obesity is increasing dramatically in the U.S. population and is now considered an epidemic. The problem is particularly severe for minority women. Obesity is a risk factor for cardiovascular disease, diabetes, stroke, gallstones, and certain forms of cancer. NIDDK is expanding its support for basic and clinical research to address this problem, and has established an Office of Obesity Research to coordinate efforts in this area. The institute, with support from ORWH and other ICs, has launched the Look AHEAD (Action for Health in Diabetes) clinical trial to examine the effects of weight loss in obese individuals with type 2 diabetes. The institute, ORWH, and other ICs are also supporting innovative studies in obesity prevention and intervention. Basic research supported by NIDDK is generating important discoveries about the underlying causes of obesity, and is leading to the identification of likely targets for development of pharmaceutical interventions for prevention and treatment.

Lack of knowledge of the urinary bladder has hampered insight into several major diseases affecting the bladder, including interstitial cystitis, urinary incontinence, and urinary tract infections, which are major health problems for women of all ages. NIDDK continues to support both basic and clinical research in these important areas of women's urologic health. In addition to NIDDK-led efforts, the institute has worked with ORWH to fund Specialized Centers of Research performing research on these diseases. The recently issued report from the NIDDK-established Bladder Research Progress Review Group, "Overcoming Bladder Disease: A Strategic Plan for Bladder Research," is guiding NIDDK as it plans new initiatives in basic and clinical research on the bladder and lower urinary tract.

## NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Environmental agents likely play a role in a number of important female-predominant diseases. These include breast cancer, osteoporosis, ovarian dysfunction (e.g., premature menopause, polycystic ovarian syndrome,

ovarian cancer) uterine fibroids, and autoimmune diseases. The National Institute of Environmental Health Sciences (NIEHS) approach is to define the underlying susceptibilities to these diseases, to investigate the role of estrogenic and other endocrine-active compounds (both natural and synthetic) in their etiology, to identify important environmental triggers for their development and important nutritional factors that can reduce risk, and to determine the importance of the timing of exposure on disease risk. As results of these studies become available, women can better determine how to alter lifestyle factors leading to these diseases and environmental health regulators can better define standards that protect women from environmental triggers of these diseases.

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

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

## National Institute of General Medical Sciences

The mission of the National Institute of General Medical Sciences (NIGMS) is to support research and research training in the areas of basic biomedical science. NIGMS supports research on cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus. The majority of the studies supported by NIGMS do not target any particular disease or condition but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, and genetics. In addition, NIGMS supports research in drug discovery, synthetic chemistry, and pharmacology, including studies in proteomics, glycomics, pharmacogenetics, and pharmacogenomics. These studies often have broad applicability to a wide variety of diseases or organ systems, including those specific to or which disproportionately effect women.

Knowledge of normal cell structure and function is necessary in order to understand the disease process. For example, major factors in the etiology of ovarian or breast cancer involve activation of cells by hormones, in particular estrogen, and by growth factors, such as epidermal growth factor, fibroblast growth factor, and insulin-like growth factor. Similarly, an understanding of invasion and metastasis of tumor cells relies on knowledge of normal cell adhesion and cell motility.

Natural plant and animal products are a major source of bioactive agents, including those with anti-tumor activity. The clinical exploitation of such agents depends on the ability to chemically purify and synthesize them. A prime example of this is taxol, derived from the bark of the yew tree. While very promising in the treatment of ovarian and breast cancer, only limited natural supplies were available. Improved approaches for isolation, purification, and synthesis have enabled widespread clinical trials of taxol and synthetic studies of 'second generation' taxoids hold promise for improved efficacy

with fewer side effects. Many other natural products are targets for synthesis and clinical testing.

Inter-individual drug responses depend on genetic variation, as well as modifying factors, such as environment, diet, age, and gender. NIGMS grants under program announcement PA-99-016, Mechanisms Underlying Individual Variations in Drug Response, supports investigations of critical candidate proteins and genes that may contribute to pharmacogenetic/pharmacogenomic variation in drug metabolism and clearance. In addition, a request for applications RFA-GM-99-004, Pharmacogenetic Research Network and Data Base, builds on this by supporting the formation of a coordinated Pharmacogenetic Research Network and Database. NIGMS participation in programs in tissue engineering (PA-99-024), nanoscience and nanotechnology (PAR-03-045), and bioengineering (PAR-02-010) hold promise for women's health. NIGMS also provides support for interdisciplinary research training at the pre- and postdoctoral levels that supplies the personnel for biomedical research.

## NATIONAL INSTITUTE OF MENTAL HEALTH

The epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on women's mental health. Overall, women and men do not differ in the likelihood that they will be diagnosed with a mental disorder, but they differ markedly in the prevalence and clinical course of different disorders. Starting in childhood, girls have higher rates of anxiety disorders than boys. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder. Such differences are not found for other serious disorders, such as schizophrenia and bipolar disorder, but men and women with these disorders differ in important clinical aspects. For instance, women with bipolar disorder have greatly increased recurrence risk in the postpartum period. In later life, because the majority of the older population is female, women's mental health is of particular concern.

One study has provided a clear public health context for the mental disorders. This study, "The Global Burden of Disease," provided a measure of lost years of healthy life due to premature death, as well as years lived with disability. For the first time, the burden of illnesses was shifted from an almost exclusive focus on premature mortality to one that included chronic illness. The study enabled a comparison of the burden of different illnesses. Based on 1990 data, depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder were among the top ten conditions accounting for years lived with disability in women. This public health burden stems from three aspects of the epidemiology of the disorders. First, the conditions are highly prevalent. For example, in a 1-year period, an estimated 12 percent of women meet criteria for depression and approximately the same percentage meet criteria for an anxiety disorder. Second, all four of the most disabling mental disorders in women and identified in the "Global Burden of Disease" study have an early onset and a recurrent or chronic course. Third, since these disorders rise markedly in incidence in adolescence and peak in incidence in young to middle adulthood, they can adversely impact educational and occupational attainment, as well as social and interpersonal functioning. The study did not consider the impact of maternal mental illness on children in assessing disability burden, but in other numerous studies, maternal mental illness has been associated with poorer child functioning. The best way to promote child mental health and enhance family functioning may be to reduce the burden of mental illness in women of childbearing age.

Through its research programs and related programmatic activities, the National Institute of Mental Health (NIMH) has increased

scientific understanding of the effects of sex and gender* differences in mental health and mental illness. Through crosscutting programs, such as the Women's Mental Health Research Consortium, NIMH has fostered interdisciplinary collaboration and the translation of basic findings into applications to improve diagnosis, treatment, services, and prevention. This 2001-2002 NIMH report highlights findings from areas of basic and clinical neuroscience, epidemiology and risk factors, and intervention development.

## National Institute of Neurological Disorders and Stroke

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease – a burden borne by every age group, by every segment of society, by people all over the world. To achieve this goal, NINDS supports research on the causes, diagnosis, treatment, and prevention of neurological and neuromuscular disorders.

Most neurological diseases and disorders affect men and women equally; however, there are several nervous system disorders that are more prevalent in, or are of special interest to, women. These include multiple sclerosis, pain (especially headache), and stroke. Also of interest are the effects of antiepileptic drugs on the fetus, and the role of hormonal cycles in seizure activity. Investigators are looking at the role of female hormones in pain and stroke, and are conducting studies to see if estrogen and progesterone protect neurons in degenerative disorders, such as Alzheimers or Parkinson's disease.

- *Multiple sclerosis (MS)* is an autoimmune disease that is characterized by inflammation and scarring of the thick sheath, called myelin, that encases the nerve fibers, resulting in a slowing or disruption of electrical impulses. It is one of the most common neurological disorders of young adults, and as in a number of autoimmune diseases, is overrepresented in women. There are 300,000 to 350,000 MS patients in the United States, with an estimated 200 new cases diagnosed each week. As published in *Multiple Sclerosis*, a 1998 survey by the Center for Health Policy Research and Education at Duke University, it is estimated that the cost of medical care, including patient rehabilitation and loss of productivity will represent an economic burden in excess of $6 billion annually to the United States.

- *Stroke* is the third leading cause of death in the United States, and a major cause of disability in both women and men. According to current estimates, Americans suffer about 700,000 strokes each year. About one-third of stroke victims die and another third face permanent disability. 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. Survivors are vulnerable to the acute effects of stroke and the long-term problems of permanent disability. The risk of stroke doubles each decade after age 50, and it is estimated that by the year 2050 there will be more than 70 million women over 50 years of age.

- *Migraine headaches* affect 16 to 18 million Americans, of whom nearly two-thirds are women. It is estimated that as many as 17 to 20 percent of all women will suffer moderate to severe migraines during their lifetime. Migraine accounts for an estimated 30 million days of lost productivity at a cost of $12 billion annually. Current research is aimed at discovering the etiology of migraine and fostering new treatments.

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

## NATIONAL INSTITUTE OF NURSING RESEARCH

The National Institute of Nursing Research (NINR) supports clinical and basic research to establish a scientific basis for the care of individuals across the life span – from management of patients during illness and recovery to the reduction of risks for disease and disability and the promotion of healthy lifestyles, promoting quality of life in those who suffer from chronic illness, and care for individuals at the end of life. This research may also include families within a community context. NINR's research extends to problems encountered by patients, families, and care givers, and emphasizes the special needs of at-risk and underserved populations, with an emphasis on health disparities. The research mission of NINR is available at *http://www.nih.gov/ninr/research/diversity/mission.html*

Studies focusing on women's health constitute a large component of the funded research at NINR and are central to the mission of NINR's extramural research activities. NINR-supported researchers are conducting a variety of studies related to the leading causes of morbidity and mortality among women. Findings from these studies are providing direction for improving the health and well being of American women.

Significant areas of research focus on promoting health among women across the life span, identifying and addressing the needs of women with chronic illnesses, exploring issues related to pregnancy and postpartum, and examining gender and sex differences in health status and outcomes. In the area of health promotion, several investigators are examining the role of exercise in improving the health and well being of women, from midlife to the elderly. Other investigators are exploring ways to prevent falls in elderly women. NINR researchers are identifying and addressing the unique needs of women living with chronic illness and are designing interventions that will assist these women to live more productive and healthier lifestyles, despite their chronic conditions. These studies are investigating such chronic disease issues as delays in seeking care for cardiovascular disease, symptom management for women with breast cancer, the health promotion needs of women with chronic illnesses, and prevention of osteoporosis.

Research on pregnancy and related issues is addressing a number of important areas, including interventions targeting high-risk pregnant women, postpartum stress and immunity, and support for mothers of premature infants. In addition, NINR supports research on women experiencing menopause. Several NINR researchers are examining aspects related to sex/gender differences in health status and health outcomes. For example, studies examining the mechanism of cardioprotective benefits of estrogen, the effects of estrogen in moderating pre- and post-ischemic platelet function, and sex differences in inflammatory pain and irritable bowel syndrome.

These diverse studies on women's health also illustrate NINR's long-standing commitment to research on health disparities and minority health. A large number of studies are devoted to addressing the needs of racial/ethnic minority women, which highlights the importance of examining psychosocial and cultural variables that influence health-seeking behaviors and health outcomes of these populations. Findings from these studies will add to the growing body of literature related to reducing the excess burden of illness borne by racial and ethnic minority women.

## NATIONAL INSTITUTE ON AGING

The National Institute on Aging (NIA) leads a national scientific effort to understand the mechanisms of aging and to extend the healthy, active years of life to all Americans. Many of the advances in knowledge about the biological, behavioral, and social changes that occur with aging have saved lives and prevented disabilities by contributing to improvements in public health and health care. Numerous findings have challenged stereotypes about the inevitability of decline

in old age, generating effective strategies that can maintain or even enhance both physical and cognitive abilities in old age. Other discoveries have provided exciting insights into the secrets of aging and longevity. These successes have the potential to benefit all generations and all women.

As baby boomers reach retirement age and medical breakthroughs, as well as more healthy lifestyles, continue to contribute to increasing life expectancy, the numbers of older Americans women, in particular, are projected to increase. "At her 120th birthday party, a journalist hesitantly told Mme. Calmet, well, I guess I'll see you next year. Instantly, she shot back, I don't see why not. You look to be in pretty good health to me!" Mme. Calmet lived longer than any other human in recorded history (NIA, 2002). Exceptional longevity is a wonder and a challenge to understand. Recent data from the census bureau statistics show that the numbers of those aged 65 and older have increased approximately 7 percent and now number 34 million, comprising about 13 percent of the general population. Projections for the middle of the century place those over age 65 at around 20 percent of the population.

Women make up a majority of the older population. In 1994, elderly women outnumbered elderly men 3 to 2 and numbered nearly 2 million. The combined factors of men generally being older than their spouses and higher life expectancy for women than men, contribute to the proportion of women living alone, the earlier institutionalization of women than men, disproportionately high level of poverty, and a need for special support (Bureau of the Census, 1996, 65+ in the United States). The death of a husband often marks the point of acute economic reversals for the surviving wife.

NIA supports a diverse portfolio of research on older women's health addressing health and wellness, basic biology of aging, neuroscience and neuropsychology of aging, diseases and conditions of older adults, and behavioral and social problems of older women. Thus, not only are the common age-related diseases under study (e.g., Alzheimers disease, Parkinson's disease, stroke, atherosclerosis, osteoarthritis, diabetes, cancer), but the determinants of healthy aging are also being defined. NIA research includes several long-term research projects that are in progress. The projects focus on physical disability, decline in function of older women, hormone therapy and menopause, hip fractures, osteoporosis and age-related muscle loss, memory, dementia and Alzheimers disease, care giver burden, and cancer in older-aged women.

One long-term intramural research program is the Women's Health and Aging Study (WHAS). Women make up a majority of the older population and report higher rates of physical disability, spend more years in the disabled state, make up a substantially larger proportion of the nursing home population, and have a greater need for formal and informal care than men. A number of important hypotheses related to disability and loss of independence in older women are being addressed by WHAS. It is a prospective study of a sample of 1,000 older, community-dwelling women with moderate to severe disability. Its unique aspect is the examination of women with disease and disability. The purpose is to understand the diseases and physiologic impairments underlying the disability, and then prospectively evaluate the course of disability and how the underlying conditions, such as health habits, psychological and social factors, and cognitive functioning, affect that course.

As life expectancy continues to increase, it has become important to understand factors that contribute to physical functioning, independence, and quality of life in persons reaching advanced old age. Although some disability in the older population is a result of catastrophic events, such as stroke and hip fracture, a large proportion of disability results from progressive decline in multiple physiologic systems that lead to gradual progression of functional limitations and onset of disability. Loss of muscle mass and muscle strength plays an important role in this progressive decline; interventions targeted at preserving muscle structure and function

could have a major impact on reducing age-related decrements in physical functioning. Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve physical function in patients with congestive heart failure, but these improvements have been attributed to beneficial effects of these drugs on the cardiovascular system. However, these drugs could also have a direct effect on skeletal muscle, as they influence the renin-angiotensin system, which has been associated with mechanical, metabolic, and biochemical changes in muscle. This study used data from WHAS, a longitudinal epidemiological study of the causes and course of disability in the one-third most disabled women living in the community. Women with hypertension were stratified into four groups according to type and duration of antihypertensive treatment over 3 years: continuous use of ACE inhibitors (n=61); intermittent use of ACE inhibitors (n=133); use of other drugs (n=301); and no drug use (n=146).

Knee extension strength and gait speed declined very slightly over 3 years in continuous users of ACE inhibitors and declined significantly more in the other antihypertensive treatment groups. These analyses were adjusted for many potential confounders of the relationship of antihypertensive drug use with strength and gait speed, including age, race, baseline systolic blood pressure, body mass index, diabetes, ischemic heart disease, and stroke.

ACE inhibitor use may slow the decline in muscle strength that is seen in aging and plays an important role in loss of functional abilities.

## NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports research on the biomedical and behavioral causes and consequences of alcohol use, abuse, and alcoholism, and on new and improved ways to prevent and treat these significant public health problems. Alcohol abusers, alcoholics, and their families – an estimated 98 million Americans – are the primary potential beneficiaries of this research. Society as a whole will also benefit from reductions in the high social, economic, and human costs of alcohol abuse and alcoholism to our society. These costs are estimated to be $185 billion and in excess of 100,000 deaths annually.

Of the 13.8 million alcohol-abusing or alcohol-dependent individuals in the United States, over one-third (approximately 4 million) are women. Women drink less alcohol and have fewer alcohol-related problems and dependence symptoms than men. However, among the heaviest drinkers, women equal or surpass men in the number of problems that result from their drinking. Further, the proportions of young men and women who begin drinking at age 13 are similar, and young people who begin drinking at this age are four times more likely to develop alcohol dependence sometime during their lifetimes than young people who begin drinking at age 21.

Our most comprehensive knowledge about alcohol use, abuse, and dependence among women comes from the 1992 NIAAA National Longitudinal Alcohol Epidemiologic Survey (NLAES). This survey collected data on alcohol consumption and alcohol problems and related disorders in a nationally representative sample of 42,862 adults 18 years of age and over. According to the NLAES findings, women are less likely to be drinkers than men (34 vs. 56 percent) and are more likely to be abstainers than men (45 vs. 22 percent). Women also were found to have started drinking about $1^1/_2$ years later than men, on average. The findings, both with regard to the percentage of women who drink and the percentage who abstain, are consistent with the findings from epidemiological studies over the past 30 years. A recent NIAAA-supported study, in fact, has found that this pattern of drinking is not only consistent across time, but across countries and cultures worldwide.

NIAAA continues to expand its research portfolio on the impact of alcohol and alcohol misuse on women. Collaboration with other federal agencies remains an important priority within this area of research, and has yielded important scientific advances in our understanding of the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women. In fiscal years 2001 and 2002, research on women and alcohol addressed five central themes: 1) psychosocial risk factors for the development of alcohol misuse in women; 2) the biological and behavioral correlates of alcohol abuse in women; 3) the impact of alcohol use and misuse on the physiology of women; 4) the consequences of drinking during pregnancy; and 5) effective approaches to the treatment of women with alcohol use disorders.

In the area of psychosocial determinants of alcohol misuse in women, significant findings include those from a 2001 study on sexual harassment, gender, and drinking. Study findings suggest that the distress caused by workplace harassment and generalized workplace abuse contributes to increased alcohol use and misuse. Generalized workplace abuse was predictive of psychological distress (depression, anxiety, and hostility) among women, while sexual harassment was predictive of psychological distress in both men and women. Furthermore, depression, anxiety, and hostility were positively correlated with nearly all alcohol outcomes, including higher frequency and quantity of drinking, heavy episodic drinking, and drinking to intoxication. Other studies during this period examined alcohol use in special populations of women. A comprehensive prevention study, involving four American Indian communities, found differential patterns of drinking among men and women. While most of the men and women who drank were typically binge drinkers, the women drank less frequently and in smaller quantities than the men, with the highest prevalence and heaviest drinking occurring among both women and men less than 30 years of age. The authors conclude that future research on prevention interventions among American Indians should target heavy-drinking young adults before drinking patterns become deeply entrenched. A second study examined drinking among women with comorbid eating disorders, which affect approximately 10 percent of women between the ages of 15 to 30 years and often co-occur with psychiatric disorders. Women with bulimia nervosa reported significantly more severe alcohol-related problems than non-eating disordered women. While eating-disordered women did not drink more frequently or in greater quantity than non-eating disorder women, they did report alcohol-related negative consequences up to twice the rate of non-eating disordered women. These findings suggest that prevention interventions offering coping skills for high-risk circumstances may benefit women with eating disorders.

Domestic violence, child abuse, homicide, and assault are among the most serious public health problems in the United States. For example, acts of domestic violence account for at least 20 percent of all emergency room visits and frequently result in physical injury and severe emotional distress. Two nationally conducted surveys in 1975 and 1985, involving a representative sample of approximately 6,663 American families, found that 16 percent of the men and women had been physically assaulted by their spouse or significant-other in the year prior to the survey. Federal Bureau of Investigation statistics indicate that 30 percent of all the women murdered in the United States are killed by their spouse or significant-other. Perpetrators with the highest chronic alcohol consumption were the most likely to be violent. NIAAA has thus continued to identify alcohol-related violence as a priority area within its programs of research. Ongoing analysis of data from a national household sample of couples (both married and unmarried) supports previous findings that problems

with alcohol and other drugs are associated with increased male to female inter-partner violence (MFIPV). Both male and female partner alcohol use problems independently predict MFIPV, but female compared to male alcohol and other substance use problems were each stronger predictors of MFIPV. One of the most exciting recent developments in this area of research is the finding that alcoholism treatment may have a significant positive impact on the incidence of domestic violence. In one study of male alcoholics treated in AA/12-step-oriented treatments, the prevalence of male-to-female overall violence in the year before treatment was four times the prevalence of such violence in a comparison community-based sample. At 1-year post-treatment, the prevalence of overall male-to-female violence was nearly identical to the comparison sample, and one-half the prevalence among relapsed patients.

Other research continues to substantiate the important role of alcohol in other types of male-to-female violence and in violent behavior committed by women. A comprehensive pilot study, testing an intervention to reduce abusive behavior in adolescent dating relationships, found that female adolescents who use alcohol are over three times more likely to be victimized than are their peers who abstain from alcohol use. Another study on the role of alcohol in women's victimization found that incidents involving *mutual* substance use were more likely to result in rape, take place outside the home, and involve perpetrators who were less well known to the victim, compared to incidents where the perpetrator was the only one drinking or where neither person was using substances. Study findings further suggest that a history of childhood sexual abuse contributes to poorer-quality intimate relationships, characterized by physical and sexual aggression in later life. While much of the research on alcohol-related aggression has focused on male-to-female violence, alcohol-induced aggression in women is a growing area of concern. Recent research suggests a causal relationship between brain serotonin function and aggression in women, and may inform effective approaches to identifying and intervening with women at risk for alcohol-related aggression.

Research in FY 2000 and 2001 also brought significant advances in our understanding of the mechanisms by which alcohol negatively impacts the physiology of women. Among the most notable studies is one which used cognitive and neuroimaging studies to examine brain changes resulting from chronic alcohol consumption in women and compared them to those previously found in men. In men, neuropsychological deficits were most pronounced on tests of executive and visuospatial ability and of functions of gait and balance. In alcoholic women, functions most severely affected were visuospatial and verbal and nonverbal working memory processes, as well as gait and balance. Areas of relative sparing in the women were executive functions, declarative memory, and upper limb strength and speed. Furthermore, total amount of lifetime alcohol consumption was a predictor of severity of cognitive impairment, suggesting a dose effect not seen in men. Other research using new imaging technology has identified abnormalities of the cerebral white matter in alcoholic women compared to control women, not detectable with conventional magnetic resonance imaging. These abnormalities are related to lifetime alcohol consumption and correlated with a specific neurologic deficit. In addition, another important line of research is elucidating the effects of alcohol on the cardiovascular system of women. In a prospective study of the association of moderate intake of alcohol (wine, beer, and liquor) and the risk of developing hypertension in women, light drinkers showed a modest decrease in risk compared with non-drinkers, and more regular heavy drinkers showed an increase

in risk. For all alcohol types, the risk of developing hypertension tended to increase with drinking more than one drink per day. A third area of continuing interest is the increased susceptibility of women to alcoholic liver disease (ALD). In an animal model of ALD, female rats had higher levels of plasma endotoxin and evidence of higher levels of oxidative stress and inflammation than male rats. Similar processes may be responsible for the increased susceptibility of women to alcohol-induced liver injury.

Given the wide range of potential adverse consequences of maternal alcohol consumption during pregnancy, NIAAA continues to expand its portfolio of research on fetal alcohol syndrome and on the entire spectrum of less severe abnormalities, collectively referred to as alcohol-related neurodevelopmental disorders and alcohol-related birth defects. Two long-range studies continue to uncover deleterious outcomes in cognitive and social functioning among individuals exposed to alcohol prenatally. Other research is focusing on the feasibility of and approach to screening pregnant women for alcohol use. In one such study, investigators found that the vast majority of participants attending certain general obstetrics clinics agreed to fill out a self-administered questionnaire regarding their use of alcohol and other substances while they waited for their medical appointments. Consistent with other studies, results indicated that approximately 15 percent of the participating women acknowledged drinking some alcohol during pregnancy. While most drank at very low levels, about 25 percent of those who consumed some alcohol were identified as high-risk drinkers (drinking greater than one drink per week and/or any binge drinking during pregnancy). A second study involving pregnant women receiving prenatal services in 12 Women, Infants and Children (WIC) clinics demonstrated decreased alcohol consumption among women who received brief interventions when compared to women who received screening only or the WIC standard of care. Similar results were seen in a study involving women receiving prenatal services in private OB/GYN clinics in Wisconsin, where women who received brief interventions for binge drinking during pregnancy demonstrated less alcohol use post-delivery than women in the control group.

There is recent research evidence that the need for universal screening for alcohol use and misuse among women receiving general medical and reproductive health services continues to go unmet. Results of an ongoing study of homeless women showed that women with a history of alcohol use and abuse were more likely to report being screened for alcohol problems than those without a comparable history. High rates of screening among alcohol-abusing and -dependent women stemmed from the fact that these women were more likely to have had contact with the health care delivery system through a recent hospitalization. These findings suggest that many women may be undergoing screening for alcohol use and misuse only late in their drinking career, well after they have begun to experience serious health and other problems related to their consumption of alcohol. On the other hand, there is a growing body evidence that early interventions are far more effective in preventing and alleviating the burden of alcohol-related illness than those initiated after serious alcohol-related problems have begun to develop.

Fiscal years 2000 and 2001 were exciting years for scientific research on gender-based differences in the causes, consequences, prevention, and treatment of alcohol use disorders. Cutting-edge genetics research is revealing differences at the molecular level which may help to explain gender differences in the rates of alcohol dependence and other psychiatric disorders. Such research may one day enable clinicians to identify and intervene with individuals at risk for alcohol use disorders, well before they develop alcohol-related problems. Studies evaluating approaches to preventing fetal alcohol spectrum disorders have demonstrated a high level of acceptance of alcohol screening among women attending obstetrics clinics, and a very favorable response to brief interventions delivered in those settings. Brief alcohol interventions

may also substantially reduce the incidence of domestic and other inter-partner violence. In coming years, it is expected that the convergence of new research technologies, and emerging trends in interdisciplinary and transcultural research, will greatly accelerate advancements in our understanding of the impact of alcohol use and misuse on women. At the same time, a growing body of translational research will help to assure that approaches to the prevention and treatment of alcohol use disorders, which work well under controlled experimental conditions, are effectively translated into clinical practice settings. Collaboration and translation are hallmarks of a shift in the alcohol research paradigm which, perhaps more than any others, hold the promise of significant improvements in the quality of life of millions of women and families affected by the misuse of alcohol.

## NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms, as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. NIDCD also conducts and supports research and research training related to disease prevention and health promotion.

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 NIDCD disproportionately affect women. Examples of significant research programs have been selected for inclusion in this report, including the latest research advances and plans for the future.

## NATIONAL INSTITUTE ON DRUG ABUSE

The National Institute on Drug Abuse (NIDA) supports over 85 percent of the world's research on the health aspects of drug abuse and addiction. NIDA-supported science addresses the most fundamental and essential questions about drug abuse, ranging from the molecule to managed care, and from DNA to community outreach research. Within this science, there is a major NIDA effort to investigate issues specific to women and to study sex and gender differences. Leadership for this effort is provided by NIDA's Women & Gender Research Coordinator and Deputy Coordinator, along with NIDA's Women & Gender Research Group, which has representation from all of NIDA's program branches, offices, and centers. The major goal of this effort is to infuse the study of sex and gender differences and issues specific to females in all areas of drug abuse research, and to disseminate research findings in this area.

As recently as a decade ago, NIDA supported virtually no gender-based research and very little research on women. Most of the research on women was from a pregnancy perspective and, in particular, the concern over the possible adverse effects on infants prenatally exposed to drugs and how to best treat drug-abusing pregnant women, topics that continue to be of great importance to NIDA today. In the early 1990s, however, NIDA began to have growing concerns about the lack of knowledge of other issues specific to women and whether there are important, but unidentifed, differences between males and females throughout the various aspects of drug abuse. To assess these issues and to identify research gaps, in 1994 NIDA held a conference, "Drug Addiction Research and the Health of Women." From that conference, three broad areas of gender-based drug abuse research needs were apparent: the need to study females of all ages, not just those of child-bearing age; the need to address issues

specific to females in all areas of drug abuse research; and the need to study sex and gender differences in all areas of drug abuse research.

Since that meeting, NIDA has been actively engaged in a number of efforts to fill these research gaps and the drug abuse research field has responded, as evidenced by a growing number of NIDA-supported research grants in this area. Today, NIDA supports gender-based research in all of its major program areas. From basic research on the biological underpinnings and consequences of drug abuse, to field research on etiology and consequences of drug abuse, to research on prevention and treatment, evidence for the importance and fruitfulness of taking a gender-based research approach and analyzing data separately for males and females is growing. NIDA-supported research is repeatedly showing that gender matters in drug abuse.

The research findings summarized below, published in 2001 or 2002, are representative of NIDA's research on women and gender differences. These research findings fall into five major research areas: Biological Mechanisms and Consequences, Nicotine, Adolescents, Treatment and Services, and HIV/AIDS. These findings strongly suggest that the identification and understanding of sex and gender differences can improve our understanding of the nature and etiology of drug abuse and have implications for tailoring prevention and treatment interventions to maximize outcomes for both males and females.

# *Summary of NIH Budgetary Expenditures on Women's Health*

## FY 2001 AND 2002

The amounts of funding NIH invested in research during Fiscal Years 2001 and 2002 specific to women, men, or applicable to both are presented in this budget summary. The budgetary figures presented in this report were provided and submitted by the budget officials at the individual institutes and centers, then were compiled by the Office of Financial Management and submitted to the ORWH for inclusion in this report.

It is obvious from data compiled that the greater part of NIH expenditures on research is on research that benefits men and women alike. In both Fiscal Years 2001 and 2002, an average 79 percent was spent on research that was not gender specific. The approach to data collection for this report is similar to that employed for reports since 1993-94, but different from that used in earlier NIH reports. In earlier years, the budgetary reporting on women's health expenditures focused on single-gender studies; studies to evaluate 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 in diseases, disorders, and conditions that are not unique to one gender, but for which there is documented evidence of greater prevalence in one gender by a ratio of at least 2:1, or for which a specific gender-related consideration exists.

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

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

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

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

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

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

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

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

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

## *Table 21*
## *DHHS–National Institutes of Health Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives* (Dollars in thousands)*

| | FY 2001 Actual | | | | FY 2002 Actual | | | |
|---|---|---|---|---|---|---|---|---|
| | *Women* | *Men* | *Both* | *Total* | *Women* | *Men* | *Both* | *Total* |
| **Cancer** | | | | | | | | |
| Breast cancer (Including mammography and other service) | $552,770 | $0 | $2,962 | $555,732 | $605,781 | $0 | $236 | $606,017 |
| Reproductive cancers: | | | | | | | | |
| cervical | 73,078 | 0 | 0 | 73,078 | 71,073 | 0 | 0 | 71,073 |
| ovarian | 88,552 | 0 | 0 | 88,552 | 107,645 | 0 | 0 | 107,645 |
| vaginal, uterine, and other | 35,936 | 0 | 0 | 35,936 | 61,303 | 0 | 0 | 61,303 |
| Lung cancer | 0 | 0 | 219,769 | 219,769 | 4 | 4 | 252,526 | 252,534 |
| Colorectal cancer | 0 | 0 | 222,126 | 222,126 | 20 | 60 | 262,731 | 262,811 |
| Prostate cancer | 0 | 317,427 | 29 | 317,456 | 0 | 336,910 | 0 | 336,910 |
| Testicular cancer | 0 | 6,675 | 0 | 6,675 | 0 | 5,865 | 0 | 5,865 |
| Penis and other male genital cancers | 0 | 11,533 | 0 | 11,533 | 0 | 5,274 | 0 | 5,274 |
| Head and neck cancer | 0 | 28,325 | 50,164 | 78,489 | 0 | 36,980 | 61,315 | 98,295 |
| Smokeless tobacco and oral cancer | 0 | 0 | 15,138 | 15,138 | 0 | 0 | 17,697 | 17,697 |
| Other neoplasms | 84,602 | 480 | 2,250,681 | 2,335,763 | 98,676 | 530 | 2,524,172 | 2,623,378 |
| **Subtotal** | **834,938** | **364,440** | **2,760,869** | **3,960,247** | **944,502** | **385,623** | **3,118,677** | **4,448,802** |
| **Cardiovascular and Pulmonary** | | | | | | | | |
| Blood diseases | 40,429 | 43,942 | 414,988 | 499,359 | 41,705 | 40,601 | 451,981 | 534,287 |
| Heart disease | 96,255 | 75,278 | 482,769 | 654,302 | 86,746 | 73,580 | 606,151 | 766,477 |
| Stroke | 11,967 | 11,611 | 177,698 | 201,276 | 14,394 | 11,620 | 207,872 | 233,886 |
| Other cardiovascular diseases and disorders | 112,416 | 79,711 | 436,037 | 628,164 | 99,281 | 73,647 | 575,138 | 748,066 |
| Pulmonary diseases | 92,503 | 85,661 | 380,433 | 558,597 | 82,580 | 86,401 | 466,512 | 635,493 |
| Hemophilia | 257 | 21,621 | 1,646 | 23,524 | 0 | 19,621 | 0 | 19,621 |
| Other | 29,480 | 4,020 | 77,311 | 110,811 | 378 | 0 | 129,722 | 130,100 |
| **Subtotal** | **383,307** | **321,844** | **1,970,882** | **2,676,033** | **325,084** | **305,470** | **2,437,376** | **3,067,930** |
| **Reproductive and Maternal, Child, and Adolescent Health** | | | | | | | | |
| Contraception | 26,299 | 2,263 | 0 | 28,562 | 37,277 | 2,610 | 0 | 39,887 |
| Infertility | 5,725 | 4,708 | 1,944 | 12,377 | 5,794 | 4,843 | 4,816 | 15,453 |
| Female reproductive physiology | 95,159 | 0 | 0 | 95,159 | 123,106 | 0 | 0 | 123,106 |
| Hysterectomy | 0 | 0 | 0 | 0 | 498 | 0 | 0 | 498 |
| Endometriosis and leiomyomas (fibroids) | 1,759 | 0 | 0 | 1,759 | 5,444 | 0 | 65 | 5,509 |
| Pregnancy, pregnancy prevention, and maternal health | 127,753 | 842 | 6,354 | 134,949 | 172,290 | 1,497 | 3,072 | 176,859 |
| Child health | 4,070 | 1,952 | 233,932 | 239,954 | 653 | 664 | 367,885 | 369,202 |
| Adolescent health | 1,780 | 2,044 | 82,198 | 86,022 | 446 | 601 | 139,669 | 140,716 |
| Diseases related to DES exposure | 1,482 | 0 | 0 | 1,482 | 5,334 | 0 | 0 | 5,334 |
| Male reproductive disorders | 0 | 35,396 | 0 | 35,396 | 0 | 36,902 | 0 | 36,902 |
| Mental retardation | 6,510 | 9,667 | 103,964 | 120,141 | 7,050 | 23,820 | 99,793 | 130,663 |
| Other | 8,302 | 0 | 367,786 | 376,088 | 8,563 | 0 | 412,507 | 421,070 |
| **Subtotal** | **278,839** | **56,872** | **796,178** | **1,131,889** | **366,455** | **70,937** | **1,027,807** | **1,465,199** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Aging** | | | | | | | | |
| Menopause | 22,794 | 0 | 0 | 22,794 | 30,453 | 0 | 0 | 30,453 |
| Hormone replacement therapy | 19,177 | 1,019 | 0 | 20,196 | 21,301 | 528 | 0 | 21,829 |
| Alzheimer's disease | 24,503 | 887 | 443,897 | 469,287 | 31,382 | 2,402 | 497,007 | 530,791 |
| Malnutrition in the elderly | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Incontinence | 9,335 | 0 | 488 | 9,823 | 8,705 | 50 | 412 | 9,167 |
| Osteoarthritis | 4,444 | 0 | 31,594 | 36,038 | 18,505 | 138 | 39,367 | 58,010 |
| Osteoporosis | 125,099 | 8,706 | 3,122 | 136,927 | 142,888 | 10,180 | 5,420 | 158,488 |
| Women's Health Initiative | 62,023 | 0 | 0 | 62,023 | 61,410 | 0 | 0 | 61,410 |
| Other | 51,083 | 6,919 | 426,363 | 484,365 | 37,377 | 7,940 | 505,957 | 551,274 |
| **Subtotal** | **318,458** | **17,531** | **905,464** | **1,241,453** | **352,021** | **21,238** | **1,048,163** | **1,421,422** |
| **Metabolism and Endocrinology** | | | | | | | | |
| Diabetes | $173,533 | $173,876 | $78,883 | $426,292 | $104,809 | $151,037 | $95,326 | $351,172 |
| Nutrition | 4,905 | 1,752 | 231,923 | 238,580 | 5,351 | 1,931 | 281,417 | 288,699 |
| Obesity | 68,955 | 36,750 | 21,438 | 127,143 | 100,772 | 53,597 | 25,503 | 179,872 |
| Hepatobiliary diseases | 1,800 | 0 | 98,572 | 100,372 | 59 | 114 | 11,586 | 11,759 |
| Thyroid diseases/conditions | 28,764 | 0 | 12 | 28,776 | 0 | 0 | 933 | 933 |
| Urolithiasis | 0 | 6,000 | 0 | 6,000 | 0 | 0 | 0 | 0 |
| **Subtotal** | **277,957** | **218,378** | **430,828** | **927,163** | **210,991** | **206,679** | **414,765** | **832,435** |
| **Substance Abuse** | | | | | | | | |
| Etiology (unspecified) | 1,647 | 1,423 | 27,408 | 30,478 | 1,955 | 324 | 24,106 | 26,385 |
| Epidemiology (unspecified) | 3,907 | 2,738 | 18,671 | 25,316 | 1,745 | 2,020 | 19,107 | 22,872 |
| Prevention (unspecified) | 3,375 | 3,099 | 16,648 | 23,122 | 1,463 | 1,370 | 21,373 | 24,206 |
| Treatment (unspecified) | 6,067 | 4,225 | 28,058 | 38,350 | 837 | 351 | 31,352 | 32,540 |
| Alcohol | 7,119 | 7,101 | 143,926 | 158,146 | 394 | 756 | 169,669 | 170,819 |
| Illegal drugs | 131,071 | 241,800 | 419,814 | 792,685 | 143,781 | 271,846 | 479,614 | 895,241 |
| Prescription drugs | 0 | 0 | 22 | 22 | 0 | 0 | 24 | 24 |
| Tobacco products | 191 | 191 | 13,835 | 14,217 | 52 | 0 | 20,462 | 20,514 |
| Other substances | 38 | 0 | 2,143 | 2,181 | 0 | 0 | 1,356 | 1,356 |
| Co-occurring substance abuse & mental disorders | 684 | 664 | 4,811 | 6,159 | 86 | 36 | 4,035 | 4,157 |
| **Subtotal** | **154,099** | **261,241** | **675,336** | **1,090,676** | **150,313** | **276,703** | **771,098** | **1,198,114** |
| **Behavioral Studies and Programs** | | | | | | | | |
| Violence (Includes domestic, abused women, spousal abuse) | 6,898 | 3,762 | 14,922 | 25,582 | 7,980 | 3,976 | 25,023 | 36,979 |
| Behavior change/ risk-taking behavior | 5,678 | 1,500 | 151,420 | 158,598 | 4,442 | 568 | 157,876 | 162,886 |
| Cultural/lifestyle factors | 1,914 | 2,256 | 2,460 | 6,630 | 1,042 | 133 | 3,793 | 4,968 |
| Women as caregivers | 4,736 | 0 | 0 | 4,736 | 3,784 | 0 | 0 | 3,784 |
| Other | 14,310 | 1,943 | 247,712 | 263,965 | 14,902 | 1,663 | 289,595 | 306,160 |
| **Subtotal** | **33,536** | **9,461** | **416,514** | **459,511** | **32,150** | **6,340** | **476,287** | **514,777** |
| **Mental Health** | | | | | | | | |
| Etiology (unspecified) | 0 | 0 | 4,816 | 4,816 | 0 | 0 | 6,348 | 6,348 |
| Epidemiology (unspecified) | 0 | 0 | 0 | 0 | 0 | 0 | 35 | 35 |
| Prevention (unspecified) | 0 | 0 | 590 | 590 | 50 | 0 | 1,615 | 1,665 |
| Treatment (unspecified) | 0 | 0 | 372 | 372 | 0 | 28 | 1,143 | 1,171 |
| Depression/mood disorders | 17,522 | 1,046 | 127,522 | 146,090 | 13,622 | 663 | 134,597 | 148,882 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Mental Health** *(continued)* | | | | | | | | |
| Suicide | 72 | 459 | 8,746 | 9,277 | 0 | 564 | 13,904 | 14,468 |
| Schizophrenia | 2,075 | 0 | 96,706 | 98,781 | 2,081 | 0 | 108,348 | 110,429 |
| Anxiety disorders | 391 | 37 | 21,063 | 21,491 | 326 | 0 | 21,214 | 21,540 |
| Eating disorders | 4,402 | 0 | 2,290 | 6,692 | 6,022 | 98 | 4,889 | 11,009 |
| Psychosocial stress | 5,228 | 926 | 35,895 | 42,049 | 6,206 | 954 | 32,662 | 39,822 |
| Post traumatic stress disorder (PTSD) | 3,053 | 227 | 6,387 | 9,667 | 2,627 | 753 | 11,327 | 14,707 |
| Other mental disorders (excluding Alzheimer's) | 8,985 | 3,533 | 454,627 | 467,145 | 7,509 | 6,032 | 457,543 | 471,084 |
| **Subtotal** | **41,728** | **6,228** | **759,014** | **806,970** | **38,443** | **9,092** | **793,625** | **841,160** |
| **Infectious Diseases** | | | | | | | | |
| AIDS/HIV | 207,186 | 62,015 | 1,469,603 | 1,738,804 | 226,189 | 66,692 | 1,653,171 | 1,946,052 |
| Tuberculosis | 2,707 | 218 | 60,773 | 63,698 | 1,567 | 1,498 | 68,244 | 71,309 |
| Sexually transmitted diseases (STD) | 42,264 | 4,230 | 68,378 | 114,872 | 46,955 | 5,501 | 97,886 | 150,342 |
| Topical microbicides | 36,295 | 582 | 6,269 | 43,146 | 45,063 | 481 | 7,843 | 53,387 |
| Toxic shock syndrome | 0 | 0 | 452 | 452 | 0 | 0 | 467 | 467 |
| Chronic fatigue syndrome | 1,140 | 0 | 3,103 | 4,243 | 1,985 | 0 | 2,905 | 4,890 |
| tropical diseases | 4,439 | 0 | 200,972 | 204,411 | 5,589 | 1,560 | 204,623 | 211,772 |
| Urinary tract infections | 7,050 | 0 | 3,474 | 10,524 | 7,968 | 145 | 3,619 | 11,732 |
| Other | 5,906 | 1,751 | 343,872 | 351,529 | 2,600 | 237 | 405,737 | 408,574 |
| **Subtotal** | **306,987** | **68,796** | **2,156,896** | **2,531,679** | **337,916** | **76,114** | **2,444,495** | **2,858,525** |
| **Immune Disorders** | | | | | | | | |
| Arthritis | $25,836 | $3,576 | $190,641 | $220,053 | $29,218 | $4,550 | $241,026 | $274,794 |
| Lupus erythematosus | 41,219 | 630 | 20,127 | 61,976 | 56,147 | 1,507 | 21,235 | 78,889 |
| Multiple sclerosis | 35,180 | 0 | 30,595 | 65,775 | 52,646 | 0 | 33,617 | 86,263 |
| Myasthenia gravis | 1,065 | 0 | 2,416 | 3,481 | 2,151 | 0 | 1,684 | 3,835 |
| Scleroderma | 8,845 | 0 | 2,814 | 11,659 | 10,487 | 0 | 1,643 | 12,130 |
| Sjogren's syndrome | 262 | 0 | 142 | 404 | 370 | 0 | 394 | 764 |
| Takayasu disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 70,421 | 49,010 | 94,196 | 213,627 | 6,767 | 58,258 | 171,496 | 236,521 |
| **Subtotal** | **182,828** | **53,216** | **340,931** | **576,975** | **157,786** | **64,315** | **471,095** | **693,196** |
| **Neurologic, Muscular, and Bone** | | | | | | | | |
| Trauma research | 709 | 38 | 107,488 | 108,235 | 3,723 | 0 | 149,382 | 153,105 |
| Muscular dystrophy | 148 | 15,233 | 3,287 | 18,668 | 475 | 18,540 | 5,600 | 24,615 |
| Chronic pain conditions | 1,478 | 309 | 66,373 | 68,160 | 2,029 | 1,201 | 68,162 | 71,392 |
| Temporomandibular disorders | 0 | 0 | 1,145 | 1,145 | 688 | 459 | 5 | 1,152 |
| Fibromyalgia and eosinophilic myalgia | 7,015 | 32 | 816 | 7,863 | 8,231 | 0 | 275 | 8,506 |
| Migraine | 698 | 0 | 4,908 | 5,606 | 4,230 | 0 | 1,410 | 5,640 |
| Sleep disorders | 655 | 190 | 30,806 | 31,651 | 1,000 | 120 | 46,979 | 48,099 |
| Paget's disease | 0 | 0 | 2,065 | 2,065 | 0 | 0 | 1,353 | 1,353 |
| Post-traumatic epilepsy | 0 | 0 | 2,153 | 2,153 | 0 | 0 | 0 | 0 |
| Amyotrophic lateral sclerosis | 0 | 0 | 24,001 | 24,001 | 138 | 138 | 27,664 | 27,940 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Neurologic, Muscular, and Bone** *(continued)* | | | | | | | | |
| Autism | 155 | 5,300 | 16,787 | 22,242 | 423 | 6,761 | 22,251 | 29,435 |
| Head injury | 0 | 45,439 | 12,859 | 58,298 | 0 | 35,951 | 12,738 | 48,689 |
| Spinal cord injury | 0 | 40,893 | 12,714 | 53,607 | 0 | 42,849 | 14,320 | 57,169 |
| Other | 7,087 | 5,553 | 701,666 | 714,306 | 11,106 | 5,434 | 753,687 | 770,227 |
| **Subtotal** | **17,945** | **112,987** | **987,068** | **1,118,000** | **32,043** | **111,453** | **1,103,826** | **1,247,322** |
| **Ophthalmic, Otolaryngologic, and Oral Health** | | | | | | | | |
| Eye diseases & disorders | 14,427 | 12,131 | 499,429 | 525,987 | 14,834 | 12,511 | 573,131 | 600,476 |
| Ear diseases & disorders | 9,516 | 65 | 254,985 | 264,566 | 11,142 | 340 | 288,945 | 300,427 |
| Caries & periodontal disease | 0 | 0 | 5,380 | 5,380 | 197 | 131 | 9,396 | 9,724 |
| Other | 18,999 | 2,424 | 224,061 | 245,484 | 24,182 | 2,500 | 238,609 | 265,291 |
| **Subtotal** | **42,942** | **14,620** | **983,855** | **1,041,417** | **50,355** | **15,482** | **1,110,081** | **1,175,918** |
| **Health Effects of the Environment** | | | | | | | | |
| Environmental estrogens | 21,057 | 0 | 1,515 | 22,572 | 16,612 | 380 | 3,116 | 20,108 |
| Health effects of toxic exposure (excluding cancer) | 0 | 0 | 85,411 | 85,411 | 0 | 0 | 88,144 | 88,144 |
| Toxicological research & testing program | 0 | 0 | 115,514 | 115,514 | 0 | 0 | 133,846 | 133,846 |
| Chemical/biological warfare agents | 0 | 0 | 3,625 | 3,625 | 0 | 0 | 11,554 | 11,554 |
| Other | 0 | 0 | 38,732 | 38,732 | 0 | 0 | 42,811 | 42,811 |
| **Subtotal** | **21,057** | **0** | **244,797** | **265,854** | **16,612** | **380** | **279,471** | **296,463** |
| **Cross-Cutting Categories and Special Initiatives** | | | | | | | | |
| Treatment, prevention & services | 3,592 | 3,119 | 189,440 | 196,151 | 3,344 | 2,642 | 203,885 | 209,871 |
| Access to health care & financing | 352 | 352 | 3,235 | 3,939 | 286 | 0 | 2,927 | 3,213 |
| Education & training for health care providers | 379 | 0 | 21,121 | 21,500 | 754 | 27 | 22,702 | 23,483 |
| Education & training for consumers | 609 | 284 | 5,296 | 6,189 | 33 | 0 | 13,752 | 13,785 |
| Bilingual & cross-cultural approaches | 87 | 0 | 1,448 | 1,535 | 0 | 0 | 1,775 | 1,775 |
| Disability research & services | 488 | 4,187 | 42,046 | 46,721 | 818 | 9,127 | 47,428 | 57,373 |
| Female genital mutilation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Homeless women | 577 | 141 | 0 | 718 | 561 | 0 | 838 | 1,399 |
| Health statistics & data collection | 0 | 0 | 8,115 | 8,115 | 169 | 0 | 6,428 | 6,597 |
| Office of Women's Health | 22,046 | 0 | 0 | 22,046 | 37,243 | 0 | 0 | 37,243 |
| Other cross-cutting | 310 | 0 | 1,763,304 | 1,763,614 | 610 | 300 | 2,086,588 | 2,087,498 |
| **Subtotal** | **28,440** | **8,083** | **2,034,005** | **2,070,528** | **43,818** | **12,096** | **2,386,323** | **2,442,237** |
| **Women's and Men's Health TOTAL** | **$2,923,061** | **$1,513,697** | **$15,462,637** | **$19,898,395** | **$3,058,489** | **$1,561,922** | **$17,883,089** | **$22,503,500** |

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

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

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

*Table 22*

***NIH Research Budget Summary by Gender, FY 2001 and 2002*** *(Dollars in thousands)*

| | Women | | Men | | Both* | | Total | |
|---|---|---|---|---|---|---|---|---|
| FY | Dollars | Percent | Dollars | Percent | Dollars | Percent | Dollars | Percent |
| 2001 | $2,923,061 | 14.7 | $1,513,697 | 7.6 | $15,462,637 | 77.7 | $19,898,395 | |
| 2002 | 3,058,489 | 13.6 | 1,561,922 | 6.9 | 17,883,089 | 79.5 | 22,503,500 | |

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

differences, and clinical research on diseases, disorders, and conditions that affect both women and men.

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

Table 21 lists the overall NIH expenditures in Fiscal Years 2001 and 2002 for specific diseases, disorders, and conditions. The health categories and subcategories in Table 21 were developed to accommodate all agencies in PHS. Certain subcategories are not applicable to the NIH mission; for those subcategories, the table shows a "0" across all columns. In some cases, however, a "0" is shown even when the subcategory is appropriate. This occurs because each budget allocation may be listed only once, even though conceptually it applies to more than one category. For example, expenditures for research on infertility are listed under "female reproductive physiology" and "male reproductive disorders."

As shown in Table 22, for Fiscal Years 2001 and 2002, approximately 78 and 79 percent respectively of the NIH budget supported research that benefits both women and men. The total actual dollars in the research budget expended on both women's and men's health, as interpreted by the specific parameters for this data collection, increased from Fiscal Year 2001 to Fiscal Year 2002, although the percent of total research dollars remained the same for both.

# *Reports of the Institutes and Centers*

## FOGARTY INTERNATIONAL CENTER

The Fogarty International Center (FIC) promotes and supports scientific research and training internationally to reduce disparities in global health. In particular, FIC supports international research training and capacity building in the developing world. FIC's research and training programs address a wide range of topics, including infectious diseases, maternal and childhood conditions that contribute to maternal and infant mortality and morbidity, population dynamics, environmental and occupational health, bioethics, and biodiversity.

As part of its effort to reduce global health disparities, FIC supports a number of research training programs that address women's health conditions. In particular, the FIC International Research and Training Program in Population and Health supports research training in reproductive processes; contraceptive development; and demographic studies of population health issues, including rapid societal changes, societies under stress, and aging. The FIC International Maternal and Child Health Research and Training Program addresses the continued high levels of maternal, perinatal, and infant mortality and morbidity in many countries. The FIC AIDS International Training and Research Program funds training that supports research to address issues of HIV infection that have particular relevance for women: stigma associated with HIV/AIDS, perinatal transmission of HIV, HIV transmission through breast feeding, female-controlled methods to reduce sexual transmission of HIV (including microbicides, biomedical interventions, and behavioral interventions), and interventions appropriate for adolescent girls. The Fogarty International Research Collaboration Award (FIRCA), a small grants program that fosters international research partnerships between NIH-supported U.S. scientists and their collaborators in the developing world, provides the opportunity for a wide spectrum of research on women's health problems and issues. Some examples of research supported by the FIRCA program include pre-eclampsia, fetal intrauterine growth restriction, ovarian cancer, and breast cancer.

In FY 2002, FIC launched the Stigma and Global Health Research Program in partnership with several other NIH Institutes and with the ORWH. The first awards under this program, to be made in FY 2003, will address the role of stigma in health, and on how to intervene to prevent or mitigate its negative effects on the health and welfare of individuals, groups and societies worldwide. Applications are expected on research projects to study how stigma associated with specific health conditions interacts with individual or group characteristics (such as gender, race, religion, sexual orientation and nationality.) It is expected that some projects will explore the linkages between gender and stigma and how these linkages impact health-seeking behavior of individuals, families and groups, among other topics.

### Accomplishments

#### *Youth is the Major Risk Factor for Malaria Infection in Pregnant Women*

It is well documented that pregnant women are more susceptible to malaria infection than non-pregnant women. This is due to the natural suppression of the mother's immune system during the second trimester. Pregnant women living in malaria endemic regions are four times more susceptible to malaria then non-pregnant women. Through the FIC Maternal and Child Health Research and Training Program, researchers from the United States and Cameroon examined the risk factors for malaria infection in pregnant women attending prenatal clinics in Yaounde

and a rural village as part of a larger, long-term study of antimalarial immunity during pregnancy. Rural pregnant women, on average, were younger, fewer took antimalarial drugs to prevent infection and, overall, displayed a higher prevalence of malaria infection. Age (less than 20 years old) was identified as the major risk factor for malaria infection in both populations after adjusting for the number of pregnancies experienced, self-reported use of prophylactic drugs (more than 50 percent used chloroquine), and season of malaria transmission and conception. In developing country settings where there is limited access to health resources, it is critical to identify pregnant women at most risk to malaria infection and design strategies to provide prophylactic antimalarial drug treatment to prevent adverse pregnancy outcomes. The authors suggest that the lack of impact for self-reported prophylaxis may be partially explained by the increasing level of drug resistance being observed in Cameroon. It is recommended that Fansidar, an antimalarial drug that is effective against certain strains of malaria that are resistant to chloroquine, would be more effective based upon a previous study conducted on the use of prophylaxis by pregnant women in Malawi.

### *Spousal Communication and Family Planning Behavior*

The poor performance in the 1980s of most family planning and reproductive health programs in sub-Saharan Africa generated significant concern among researchers and health planners. One of the major factors identified as inhibiting the success of these programs was the alienation of men from participating in family planning and reproductive health programs, which have typically been focused on women. The role of men, however, cannot be underestimated in most of sub-Saharan Africa, where most societies are patriarchal. Research conducted through the FIC Maternal and Child Health Research and Training Program shows that improved communication between spouses does indeed promote contraceptive use. The call for male involvement in family planning and reproductive health programs, as spelled out in the International Conference on Population and Development program of action, requires more dialogue or communication between spouses on these issues.

### *Prevention of Mother-to-Child HIV Transmission: Preferences of Zambian Women*

Prevention of HIV transmission from infected mothers to their babies has been simplified with the introduction of an effective drug, Nevirapine, given to the mother once during labor and once to her newborn. Prior to administering the regimen, however, one key requirement is knowledge of the woman's HIV status. In Lusaka, about $5 per patient per year is allocated for obstetrical care and no funds are allocated to support VCT. One controversial, cost-effective strategy under these conditions is treatment of all women during labor and their newborns, especially when HIV rates of infection among pregnant women are high; one such setting is Lusaka, Zambia, where nearly one-third of the pregnant women are estimated to be HIV infected. However, before introducing a strategy of this nature, it is important to understand how acceptable this approach would be to the pregnant women themselves. Researchers from the Zambian Ministry of Health and University of Alabama, supported by the FIC AIDS International Training and Research Program, conducted a questionnaire among pregnant women attending an antenatal clinic. Among the participants, over one-third had already had a delivery during which a child had died. Less than 1 percent of the women surveyed had undergone HIV testing, although almost nearly one-third acknowledged their own risk of HIV infection as moderate or high. Approximately 75 percent of women preferred the option of "test me for HIV and give me the treatment only if I am infected." Women who acknowledged their risk of HIV infection to be moderate or high were more likely than those with no or low perceived risk to choose mass therapy as the preferred option. This research demonstrates that women's preferences should be considered as program policies are developed in Africa and elsewhere.

### *Breast or Formula Feeds for Newborns of HIV-infected Mothers*

The lack of concrete data to elucidate the risks and benefits of breastfeeding by HIV-infected women in low-resource countries has contributed to the continuing controversy surrounding this issue and has hampered the development of useful recommendations for policymakers and women in these settings. Although HIV infection can be transmitted by breastfeeding, the risk of not doing so in resource-poor settings is well known to contribute to other causes of increased infant death, ill health, and poor growth. Evidence is required to suggest safe alternatives to breastfeeding in these settings with poor infrastructure. The risk of maternal mortality has been found to be three times higher among mothers who breastfed, compared to those who provided formula. There was no difference in the 2-year mortality risk for their babies. Researchers from the FIC AIDS International Training and Research Program from Nairobi and the University of Washington conducted a study to better describe mortality and any morbidity risks associated with formula feeding in this same population. Infants who were HIV-infected were nine times more likely to die by 2 years of age than infants who remained HIV uninfected. However, after taking HIV-infection status into account, infants born to mothers who were HIV-infected and were formula fed had similar 2-year mortality risk (20 percent) to those who were breast fed (24 percent). The formula-fed infants did not have increased episodes of pneumonia, diarrhea, or other recorded illnesses during the first 2 years of life. The breastfed babies tended to have better nutritional status over the 2 years, especially in the first 6 months of life, than the formula-fed babies. These results, while encouraging, cannot be generalized to all women in resource-poor countries, since the participants had access to services that are not the norm. The study does, however, demonstrate that with safe water, adequate supplies of formula, good counseling, followup and care, formula-fed babies do not suffer from increased morbidity. However, these data continue to highlight the need to increase acceptance and availability of voluntary HIV counseling and testing, to increase services to address the complex needs of all women and babies in these resource-poor countries.

### *Premature Ovarian Failure*

Autoimmune ovarian disease (AOD) occurs when a woman's immune system abnormally reacts against her own ovarian tissue. This condition may cause premature ovarian failure in which egg maturation permanently stops in a woman's ovaries before the normal age of menopause. The immunological basis of premature loss of ovarian function is poorly understood, in part because the early stages of the disease produce no clinical symptoms in women. The advanced stages of the disease show no signs of active inflammation that are usually found in autoimmunity, and studies of human antibodies that react with ovarian or placental tissue have given inconsistent results. In the past, scientists have investigated the mechanisms underlying autoimmune ovarian disease using mice as a laboratory model animal; however, monkeys are also becoming an important primary laboratory model for human reproductive biology and contraceptive research. Irreversible infertility and varying levels of ovarian dysfunction have been reported as complications of some contraceptive vaccines (specifically zona pellucida [ZP] vaccination) in macaque monkeys. These vaccinated monkeys may provide information related to the autoimmune basis of premature ovarian failure. A study conducted by scientists from India and the University of Virginia, through the FIC International Population and Health Research Training Program, established that ZP peptide vaccination in primates can cause a condition similar to AOD in mice. This model will also help scientists understand and prevent complications from contraceptive vaccines.

## Initiatives

*Request for Applications (RFAs)*

- **Stigma and Global Health Research Program**

  This RFA, issued in FY 2002, will support research studies to better understand the causes and consequences of stigma. Gender and women's health issues are an area of emphasis in the RFA, whose first awards will be made in FY 2003. ORWH is a cosponsor of this RFA.

- FIC, ORWH, and the NIH Office of Intramural Research convened a consultation at NIH in 2002 with representatives from across NIH and with a special guest, Dr. Carola Eisenberg, Harvard University. The purpose of the consultation was to explore issues related to career development of women scientists in the developing world. A follow-on and expanded consultation, with representation from key developing countries, will take place in FY 2003.

- In FY 2002, FIC and ORWH began working with counterparts at the Canadian Institutes of Health Research, and its Institute on Gender and Health specifically, to organize a series of consultations that would lead to the development of a research agenda on sex, gender, and global health. These activities are ongoing.

- In FY 2002, FIC embarked on a major new 3-year effort to assess disease control priorities in the developing world and to produce science-based analyses and resource materials to inform health policymaking in developing countries. The *Disease Control Priorities Project* (DCPP) is a joint project of FIC, the World Health Organization, and The World Bank, with support from The Bill & Melinda Gates Foundation. DCPP will develop material specific to women's health and gender issues, and disseminate the findings through technical workshops involving experts and policymakers from developed and developing countries. ORWH is working with FIC to identify experts who could contribute to the development of gender-related and women's health materials for DCPP.

### *Plans for Future Activities*

FIC will continue to work with ORWH, the Canadian Institutes of Health Research, other components of NIH, and other science funding agencies to develop research priorities on sex, gender, and global health. This activity will conclude in FY 2003.

FIC, working closely with ORWH, will convene a 1-day consultation in FY 2003 of scientists from the United States and developing countries to consider challenges facing women in science in resource-poor countries. It is expected that best practices that assist women's career development in these countries will be identified.

## National Cancer Institute

The National Cancer Institute's (NCI's) research programs in fiscal years 2001 and 2002 addressed cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, and lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

*Please note:* Incidence and mortality statistics reported for 2003 will be age-adjusted to the 2000 U.S. population standard. Previous statistics based on the 1970 population standard should not be compared to new data generated from 2000 age-adjusted population standard. Additionally, some of the rates, particularly for different racial/ethnic groups, will be changed as the new statistics are calculated.

Cancer continues to take a devastating toll on American women. By the end of 2003, an estimated 658,800 women will have been diagnosed with cancer, and approximately 270,600 women will have died of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer. In the 1990s, cancer incidence rates for all cancer decreased for men and remained relatively

stable for women. Cancer mortality rates for both women and men declined through the 1990s. However, lung cancer mortality rates for women have been increasing. Breast cancer incidence rates showed little change in the 1990s, but death rates have declined by about 3 percent per year since 1995. Statistics also show that more people are living with cancer. As of January 1999, there were 8.9 million people, or 3 percent of the U.S. population, who were cancer survivors, and 56 percent of these survivors were women.

NCI is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. In 2000, NCI formally established an Office of Women's Health. Organizationally located within the Office of Science Planning and Assessment, the Office of Women's Health is responsible for assisting in planning, evaluating, and coordinating activities related to cancers in women. Among the other programs and activities in NCI that focus on women's cancers are the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the multidisciplinary Breast Cancer and Gynecologic Malignancies Faculties of NCI intramural researchers. NCI staff participate in multiple, diverse relevant scientific partnerships and collaborative activities with other federal and non-federal scientists.

NCI supports a number of broad-based research programs that apply to all types of cancer in both women and men. Through its strategic planning process, NCI has identified many of the questions that need to be answered, areas of research and care that need to be further addressed, and infrastructure that needs to be strengthened to advance our knowledge in the study of cancer. By focusing research on areas with high potential, we have the opportunity to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application. The strategies are outlined in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004 (http://plan2004.cancer.gov/budget/2004.htm)*. As part of the planning process, NCI convenes Progress Review Groups (PRGs) to assist in setting priorities for organ site-specific research. Between 1998 and 2002, ten PRG reports were completed for cancers including breast, colorectal, lung, and gynecologic. Following release of the reports, NCI develops strategic plans for implementing PRG recommendations. Reports for all completed PRGs, strategic plans, and additional information are available at *http://prg.nci.nih.gov*.

## Initiatives

### *Trends In Cancer*

Accurate information on the incidence and impact of the disease is critical to decision making in science and public health. For this reason, NCI has established a number of programs and initiatives to provide infrastructure, track trends, and report cancer statistics. In the 1990s, NCI's surveillance efforts were expanded to cover a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country. These include:

- The Surveillance Research Program
  *http://surveillance.cancer.gov/*
- Surveillance, Epidemiology, and End Results (SEER) Program
  *http://seer.cancer.gov*
- Atlas of Cancer Mortality in the United States, 1950–94
  *http://www3.cancer.gov/atlasplus/*
- Cancer Intervention and Surveillance Modeling Network (CISNET)
  *http://cisnet.cancer.gov*

### *Cancer Biology and Genetics*

Basic research studies exploring the science of how cancer develops form the foundation of cancer research. Identifying, at the molecular and cellular level, the fundamental processes that underlie a cell's normal development and transformation, from normal to premalignant to malignant, can lead to new prevention, detection, and treatment approaches. NCI has established a number of initiatives to provide infrastructure and

stimulate interdisciplinary research in order to make progress. These include:

- Specialized Programs of Research Excellence (SPOREs) (including nine in breast cancer and four in ovarian cancer) *http://spores.nci.nih.gov*
- The Cancer Genetics Network (CGN) *http://epi.grants.cancer.gov/CGN/*
- The Cancer Family Registries (CFRs) *http://epi.grants.cancer.gov/CFR/*
- Cancer Genome Anatomy Project (CGAP) *http://cgap.nci.nih.gov*
- Early Detection Research Network *http://edrn.nci.nih.gov*
- Director's Challenge: Toward a Molecular Classification of Tumors *http://dc.nci.nih.gov*
- Clinical Proteomics Program *http://clinicalproteomics.steem.com/index.php*
- Tissue Array Resource Program (TARP) *http://resre.nci.nih.gov/tarp/*
- Mouse Models of Human Cancer Consortium (MMHCC) *http://emice.nci.nih.gov/*
- Specimen Resource Locator *http://pluto3.nci.nih.gov/tissue/*

### *Patient-oriented Research*

Clinical trials to evaluate improved and novel prevention, detection, and treatment strategies are carried out within the National Clinical Trials Program in Treatment and Prevention infrastructure that includes NCI Cancer Centers, Cooperative Groups, SPOREs, the CCOP, and minority-based CCOPs. In addition to supporting clinical trials, NCI supports a broad range of clinical research to develop new agents and novel approaches for the prevention, early detection, and treatment of cancer. Programs and initiatives that support clinical research include:

- Cancer Therapy Evaluation Program (CTEP) *http://ctep.cancer.gov/index.html*
- Cancer Trials Support Unit (CTSU) *http://www.ctsu.org/*
- Program for the Assessment of Clinical Cancer Test (PACCT) *http://www.cancerdiagnosis.nci.nih.gov/assessment*
- Physician Data Query Database *http://www.cancer.gov/clinicaltrials/*
- The Biomedical Imaging Program (BIP) *http://www3.cancer.gov/dip/*
- *In vivo* Cellular and Molecular Imaging Center (ICMIC) *http://www3.cancer.gov/bip/ICMICs.htm*
- Rapid Access to Intervention Development (RAID) *http://dtp.nci.nih.gov/docs/raid/raid_index.html*
- Rapid Access to NCI Discovery Resources (RAND) *http://dtp.nci.nih.gov/docs/rand/rand_index.html*
- Rapid Access to Prevention Intervention Development (RAPID) *http://www3.cancer.gov/prevention/rapid/*

### *Cancer Control and Outcomes*

NCI supports patient-oriented research that includes intervention, nutrition, chemoprevention, biobehavioral influences on disease, cancer screening, pain and symptom management, quality of life, ethics, confidentiality, and understanding health disparities. A number of initiatives address ways to improve the quality of cancer care and include:

- The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) (lung and colorectal cancer) *http://healthservices.cancer.gov/cancors/*
- The HMO Cancer Research Network *http://healthservices.cancer.gov/hmo/*
- The Patterns of Care/Quality of Care Initiative *http://healthservices.cancer.gov/surveys/poc/*

- SEER–Medicare-Linked Database
  *http://healthservices.cancer.gov/seermedicare/*

### *Addressing Health Disparities*

NCI has identified cancer health disparities as an area of public health emphasis in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004*. Disparities are widespread and decentralized, encompassed by the broad scope of research supported by NCI. The challenges are to understand what causes disparity, develop potent interventions, and implement them.

In 2000, NCI established the Center to Reduce Cancer Health Disparities (*http://crchd.nci.nih.gov/*) to function as an organizational locus for the critical tasks needed to translate discovery into delivery. NCI supports a number of partnerships, collaborations, initiatives, and programs that focus on reducing cancer health disparities. For example, Partnerships between NCI, the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration, and other federal and nonfederal agencies are working together to develop and improve interventions to increase screening and followup for breast, cervical, and colorectal cancers in underserved and historically underscreened women. Other activities include:

- The Special Populations Network
  *http://crchd.nci.nih.gov/spn/about.html*

- Center for Population Health and Health Disparities, to begin in 2003, in collaboration with the National Institute of Environmental Health Sciences, the National Institute of Aging, and the National Institutes of Health Office of Behavioral and Social Sciences Research.

- The Cooperative Planning Grant for Cancer Disparities Research Partnerships will support the expansion of radiation oncology clinical trials in three institutions that serve populations of Native Americans, African Americans, Hispanics, and rural Appalachians.

- The California Health Interview Survey (CHIS)
  *http://appliedresearch.cancer.gov/surveys/chis/*

- Network for Cancer Control Research Among Native American/Alaska Native Populations
  *http://www.mayo.edu/nativecircle/networkres.html*

### *Cancer Information and Education*

NCI provides information about women's health to cancer patients, health and research professionals, and the public in a variety of formats. The most recent, complete, and reliable information is available to assist cancer patients, their families, and their health care providers in making decisions about cancer prevention, detection, treatment, and followup care through NCI's website at *http://cancer.gov*. This site features LiveHelp, a web-based instant messaging service.

NCI's website links to a gateway to information and education about ongoing research programs and activities through NCI's Cancer Information Service (CIS). Printed publications and audiovisual material are available for a range of cultural and literacy levels and can be accessed directly via *http://cis.nci.nih.gov* or toll-free number, 800-4-CANCER. Through its Partnership Program, CIS provides technical assistance and materials to aid local, regional, and state partner organizations to reach and educate minority and medically underserved women with limited access to health and cancer information. In 2002, CIS, partnering with local organizations, completed four "digital divide" projects, whose goal was to increase information technology use for cancer information among underserved population.

NCI disseminates information through press releases and television, supplemented with in-depth background information through the BenchMarks website and accessible via *http://cancer.gov*. 2002 BenchMarks issues featured the results of the Women's Health Initiative study on postmenopausal hormone use, August 2002, and cervical cancer screening, April 2002.

NCI's Office of Education and Special Initiatives (OESI) has developed the Clinical Trials Education Series, a group of mixed media about participating in cancer clinical trials. The series includes workbooks, booklets, brochures, videos, slide programs, and a web-based course. OESI has also developed the *Facing Forward Survivor Series*, publications about the issues that survivors face after treatment. This series includes Spanish language adaptations.

The *Cancer Progress Report 2001*, *http://progressreport.cancer.gov*, is the first in a new series of NCI reports to describe the Nation's research progress against cancer through research and related efforts. The report is based on the most recent data from NCI, CDC, other federal agencies, professional groups, and cancer researchers. The report was designed to help policymakers review past efforts and plan future ones; to help the public better understand the nature and results of strategies to fight cancer; and to inform researchers, clinicians, and public health providers of the research gaps and opportunities that will pave the way for future progress.

## *Breast Cancer*

Despite significant advances in detection, diagnosis, treatment, and prevention, breast cancer continues to have a devastating impact on American women. By the end of 2003, an estimated 211,300 women are expected to be diagnosed with breast cancer and nearly 39,800 will die of the disease. An estimated 2 million women in the United States have either survived breast cancer or are living with breast cancer today.

SEER data indicate that breast cancer is responsible for the highest number of new, invasive cancer cases among women each year and, after lung cancer, the second leading cause of cancer deaths in women. The increase in breast cancer incidence that began in the early 1980s continues today, although this increase has slowed dramatically since 1987. Despite this improvement, recent years have shown an increased incidence in women over the age of 50. Overall, breast cancer mortality rates also have shown an encouraging downward trend, dropping 1.4 percent per year from 1989 to 1995, and 3.2 percent per year thereafter. This trend suggests that improved breast cancer management, from early detection to treatment, is having a beneficial effect. The largest decrease in mortality occurred in young, white and African American women. Currently, white women exhibit greater incidence than African American women, but lower mortality rates.

NCI's Breast Cancer Progress Review Group released a report in 1998 that evaluated the current state of breast cancer research, identified research gaps and resource needs, and developed recommendations for future research priorities to move the field ahead. In 2003, an internal working group at NCI will begin a review of the progress of the National Breast Cancer Research Program over the last 5 years by looking at disease trends; new FDA-approved interventions; clinical trials, both new and ongoing; advances in scientific knowledge; and NCI-supported research activities.

## *Biology and Genetics*

### Molecular Profiling

DNA array technology is being used to establish molecular profiles of gene expression in a series of breast cancer specimens and normal, at-risk breast. The analysis results in an easily visualized clustering of specimens that have similar patterns of gene expression and provides a relative measure of the similarity of the expression patterns between any two specimens. Identification of clusters of genes that are expressed in different cell types or are associated with cell proliferation have demonstrated that this technology will allow exploration of potentially important interactions between different cell types in tumors.

### Mouse Models

NCI sponsors a number of projects, such as the MMHCC, to develop, analyze, and apply mouse cancer models. Significant improvements in the technology of modeling human breast cancer in mice have

resulted in models that more accurately mimic the human situation in which genetic alterations occur in a subset of somatic cells. Mouse models have facilitated the investigation of distinct pathways involved in breast cancer, important for cancer prevention and therapeutic studies and for target validation in cancer drug discovery (*http://emice.nci.nih.gov/*).

**Estrogen Receptors**

Estrogens influence the growth, differentiation, and function of the human reproductive system and stimulate the proliferation and metastatic activity of nearly 40 percent of breast tumors. Estrogen receptor (ER) expression seems to correlate with prognosis and may provide targets for therapy. Treatments, such as tamoxifen and raloxifene, which block ERs, do not seem to affect ER-negative tumors, found in 20 to 30 percent of all breast tumors, and more prevalently in women under age 50, in black women at all ages, and in women at risk due to alterations in the *BRCA1* gene. Animal models of ER-negative breast cancer may lead to strategies for preventing ER-negative disease. Other studies are examining possible correlations between tumor cell characteristics, age, race, reproductive status, and lifestyle issues and ER status.

**Cyclin E**

Cyclin E, a key cell cycle regulator involved in the control of the initiation of both DNA replication and centrosome duplication, is often overexpressed in a variety of malignant tumors, including breast, gastric, and ovarian, and appears to correlate with a more aggressive breast cancer phenotype and a poorer patient outcome. Recent studies in cell lines show that cyclin E overexpression leads to chromosomal instability and polyploidy, and along with patient analyses, suggest that cyclin E expression may be a powerful prognostic indicator for survival for patients with breast cancer.

**Gene Mutations**

Fifteen to 20 percent of familial breast cancers can be accounted for by germ-line mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2*. Estimates of the lifetime risk of breast cancer among women with *BRCA1* or *BRCA2* vary from 56 percent to as high as 80 to 85 percent (as opposed to a 12 percent lifetime risk for most women). These women have an increased risk of ovarian cancer as well. Studies in Ashkenazi Jewish women diagnosed with breast cancer, 7 percent of whom carry mutations in *BRCA1* and *BRCA2*, have found that early birth in women with *BRCA* mutations does not confer protection against later breast cancer. Investigators in NCI's Cancer Genetics Network (CGN) (*http://epi.grants.cancer.gov/CGN/*) are examining whether hormonal factors and genes involved in hormone metabolism, carcinogen metabolism, and DNA repair modify risk for cancer in women with *BRCA1* and *2* mutations.

Rare germ-line mutations in p53 and CHK2 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), and the serine threonine kinase STK11/LKB1 (Peutz-Jegher syndrome) account for another small fraction of the familial cases. Genes for the remaining familial clusters are unknown and may be caused by low-penetrance susceptibility genes. Causes for sporadic cancers are not clear, but many genes that contribute to growth and apoptosis have been found to be deregulated in sporadic breast cancer.

The Cancer Genome Anatomy Project (CGAP)(*http://cgap.nci.nih.gov/*) coordinates data and reagents that will support advances in molecular detection and diagnosis with the goal of providing a complete picture of all major molecular changes that occur during cancer development. CGAP currently has information on nearly 20,000 cDNA sequences for normal and malignant breast, which include 400 genes unique to breast.

**Specimen Resources**

NCI Cooperative Breast Cancer Tissue Resource provides researchers with access to approximately 9,000 cases of formalin-fixed, paraffin-embedded breast cancer tissue samples with associated pathology and clinical data, particularly well suited to validation studies of diagnostic and prognostic markers (*http://www.cbctr.ims.nci.nih.gov*).

## *Risk Factors*

### Genetic Factors

The Breast and Ovarian Cancer Family Registries include information and laboratory specimens from over 6,000 families at risk and support investigations in genetic epidemiology, including the identification and characterization of genes, gene-gene interactions, and gene-environment interactions (*http://epi.grants.cancer.gov/BCFR/index.html*). The CGN, a group of collaborative clinical centers of excellence in cancer genetics, participate in the development and testing of interventions to better prevent, detect, and treat breast cancer among individuals at high risk (*http://epi.grants.cancer.gov/*).

### Diet

It has been hypothesized that estrogen-like compounds in soy foods influence the risk of breast cancer. A population-based, case-control study among women in China found that soy food consumption appears to lower the risk of breast cancer. High soy and dietary folate intake during adolescence were associated with reduced risk of breast cancer later in life. This effect appeared to be strengthened by increased dietary intake of methionine, vitamin $B_{12}$, and vitamin $B_6$. There is conflicting data on the association between dietary fat and breast cancer risk. Studies are ongoing, although a recent analysis showed no overall association.

### Obesity

Before menopause, obese women are at a decreased risk for breast cancer. Post menopause, the same obese women have an increased risk for breast cancer, which is ameliorated by hormone therapy. The roles of caloric intake and energy balance are under investigation. Limited studies in African American women have shown reduced obesity-associated risks for breast cancer. The Four Corners Breast and Endometrial Cancer Study is investigating obesity and weight change effects on breast and endometrial cancer among minority women, while the Black Women's Health Study is focusing on risk factors for breast cancer that include obesity.

### Breast Changes

Case-control studies have shown that increased mammographic breast density, atypical hyperplasia, and nonproliferative benign disease increase the risk for breast cancer. Women who have breast fed one or more children have a slightly reduced risk of breast cancer compared with parous women who have not breast fed.

### Other Lifestyle Factors

The Health, Eating, Activity, and Lifestyle (HEAL) study, begun in 1996, is designed to explore the associations among physical activity, eating habits, weight patterns, diet, hormones, prognostic factors, and the differences in these associations among various racial and ethnic groups in relation to risk for breast cancer (*http://appliedresearch.cancer.gov/surveys/heal/*).

### Diethylstilbestrol

Women given diethylstilbestrol (DES) during pregnancy showed a modest, but statistically significant increase in breast cancer risk which was not exacerbated by family history, use of oral contraceptives, or hormone therapy. A study of DES-exposed daughters showed a slight, not statistically significant, increase in risk for invasive breast cancer, and also for ER-positive tumors in women over 40, but not in younger women.

### Hormones

Estrogen, essential for the normal growth and development of the breast and reproductive tissues, childbearing, and regulation of the menstrual cycle, may play a role in carcinogenesis. Lifetime exposure to estrogen has been linked to an increased risk for breast cancer. Progestins, acting with estrogen, bring about mammary gland proliferation. The role of progestins in breast cancer etiology has been examined in the context of oral contraceptives and postmenopausal hormone use. Prolactin, a polypeptide hormone essential for the development of mammary glands and for lactation, enhances the rates at which mammary tumors develop in animals. A population-based, case-control study of breast cancer in Asian women living in the United States found that endogenous

hormone levels varied with differences in degree of westernization and that aspects of hormone metabolism may play a role in population differences in breast cancer incidence. Other studies of endogenous sex hormones have shown strong correlations between increased levels and increased risk for breast cancer in postmenopausal women.

**Postmenopausal Hormone Use**

Recent studies on postmenopausal hormone use and breast cancer have suggested that length of use and the type of postmenopausal hormone therapy – estrogen alone versus an estrogen/progestin combination – may be important factors. A recent reanalysis of data from more than 50 studies on breast cancer showed an increased risk of breast cancer in women who used postmenopausal hormone therapy (estrogen only) for longer than 5 years. Risk increases with the length of hormone use but decreases after a woman stops taking hormones.

After estrogen alone was linked with an increased risk for endometrial cancer, many women began using estrogen plus progestin combination therapy. In July 2002, NIH stopped early the Women's Health Initiative multicenter clinical trial of estrogen plus progestin in 16,608 healthy menopausal women who had not had a hysterectomy. Mid-trial results showed adverse health effects, including a 26 percent increase in breast cancer risk (or eight additional breast cancers per 100,000 women); and a higher risk for developing heart attacks, strokes, and blood clots in the legs and lungs. Although the estrogen plus progestin therapy yielded benefits, including fewer cases of hip fractures and colon cancer, on balance the harm was greater than the benefit. Increased breast cancer risk has not been found in the ongoing study of estrogen-only (in women who already had a hysterectomy before joining the study) (*http://cancer.gov/clinicaltrials/digest-postmenopausal-hormone-use*).

**Oral Contraceptives**

The Women's Contraceptive and Reproductive Experiences (Women's CARE) study, a population-based, case-control study involving over 9,000 women ages 35 to 64, found that oral contraceptive use was not associated with a significant increase in risk of breast cancer. A 2002 study concluded that women with *BRCA1* mutations, who had used oral contraceptives for 5 or more years, had a 33 percent increased risk of breast cancer. Those women in the study who used oral contraceptives before the age of 30, who had been diagnosed with breast cancer before age 40, or who used early types of oral contraceptives (before 1975), had a higher risk of breast cancer. Carriers of *BRCA2* mutations did not show the increased risk with oral contraceptive use. Other studies have suggested that long-term use of oral contraceptives before first pregnancy increases risk.

**Environmental Factors**

NCI research programs are investigating the links between breast cancer and exposures to pesticides, air pollution, drinking water contaminants, electromagnetic and ionizing radiation, and lifestyle and other factors. A major thrust of current research work is focused on biomarker approaches (genetic, molecular, cellular, and tissue or organ specific) as one way to assess internal dose. Research is being conducted to measure the estrogenicity of environmental chemical exposures. Markers of exposure are being developed and validated. Current research includes identification of geographic areas with increased breast cancer incidence, morbidity and mortality, and potential contributions of local environmental factors. Of particular concern has been the relationship to risk of organochlorine products, which are established endocrine disrupters. Investigators in the Division of Cancer Epidemiology and Genetics (DCEG) have undertaken several studies in populations uniquely exposed, including a study in India, where DDT is still used, and in occupational groups such as farmers, dry cleaners, and formaldehyde workers.

The Long Island Breast Cancer Study Project (LIBCSP) is an NCI and NIEHS multistudy effort to investigate whether environmental factors are responsible for

breast cancer in specific counties in New York and Connecticut. Scientists have found no evidence supporting an association between organochlorines, including the pesticide DDT, its metabolite DDE, and industrial compounds known as PCBs, and heightened risk of breast cancer. Exposure to air-polluting polycyclic aromatic hydrocarbons in the environment appears to elevate women's risk of breast cancer, but women with a higher ratio of 2-hydroxyestrone had decreased risk of breast cancer by a modest 50 percent. Further analyses and a followup study are in progress. A case-control study is investigating the possible association between electromagnetic fields and increased risk for breast cancer. Findings from this study are expected in mid to late 2003. In 2001, NCI completed development of a prototype health-related geographic information system (GIS-H) for Long Island that provides researchers with a new advanced tool to investigate relationships between breast cancer and the environment on Long Island (*http://epi.grants.cancer.gov/LIBCSP*).

Recently, a joint NCI, NIEHS, and CDC task force developed several strategies to address the high breast cancer rates in Marin County, California, including recalculating and comparing breast cancer rates for Marin County and all of California, enhancing existing GIS in California, completing epidemiologic studies on breast cancer in Marin County, and partnering with the CDC to explore opportunities and technologies for measuring environmental exposures.

#### Radiation

Current research in the Radiation Epidemiology Branch focuses on the specific effects of diagnostic, therapeutic, and occupational exposure to ionizing radiation, a known risk factor for breast cancer, in established cohorts such as x-ray technologists, ataxia-telangiectasia carriers, and A-bomb survivors. Multidisciplinary investigations are focusing on genetic susceptibility to radiation carcinogenesis and the interactions of radiation dose, hormonal factors, and genetic factors. Scientists have found that women with scoliosis (abnormal curvature of the spine), who were exposed to multiple diagnostic x-rays during childhood and adolescence, have a 70 percent higher risk of breast cancer than women in general. Nonionizing radiation (electromagnetic-field) exposure has been hypothesized to affect breast cancer risk through changes in melatonin levels that affect estrogen secretion. Current research is measuring electromagnetic-field exposure in several cohorts, including teachers in California, nurses, and x-ray technologists, who have the potential for cumulative exposures up to as much as 0.2 Gy, and radiation technologists.

### *Prevention*

#### Chemoprevention

Many breast cancer prevention studies are testing the effectiveness of selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene.

One of the largest breast cancer prevention studies ever undertaken, the Study of Tamoxifen and Raloxifene (STAR), has enrolled 15,000 of a planned 19,000 participants through more than 500 centers across the United States, Puerto Rico, and Canada. The study will determine whether the drug raloxifene, which is used for osteoporosis prevention and treatment and previously shown to reduce breast cancer incidence, is as effective as tamoxifen in reducing the risk of breast cancer. The long-term safety of both drugs will be studied. Thirty percent more minority women have joined the study than in the preceding Breast Cancer Prevention Trial of tamoxifen (*http://www.cancer.gov/clinicaltrials/digestpage/STAR*). The Capital Area SERM Study is evaluating the safety of raloxifene in premenopausal women who are at increased risk for breast cancer.

Women at high risk for breast cancer, especially premenopausal women who took the drug tamoxifen, were less likely to be diagnosed with benign breast conditions, such as atypical hyperplasia, than women at equal risk who took a placebo. The results of the 2001 study are part of the followup for the Breast Cancer Prevention Trial.

### Prophylactic Surgery

Studies published in 1999 found that prophylactic mastectomy was associated with a reduction in incidence of breast cancer of at least 90 percent among women with a family history of the disease. Similarly, other recent studies have found that prophylactic mastectomy, salpingo oophorectomy (removal of the ovaries and fallopian tubes), or oophorectomy (removal of the ovaries) reduced the number of cases of breast cancer in women with alterations in *BRCA1* or 2. A study of breast cancer among Swedish women who had breast reduction surgery found that removal of greater amounts of tissue reduced breast cancer risk dramatically.

## *Early Detection, Diagnosis, and Prognosis*

### Imaging Technologies

NCI is funding research on a variety of technologies for breast imaging, including digital mammography, elastography, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, ultrasound techniques, positron emission tomography (PET), single-photon emission computed tomography (SPECT), and thermography. Projects studying PET and SPECT involve the development of imaging agents designed to look at molecular, biological, or metabolic characteristics, such as radiolabeled estrogen-like compounds, to indicate the overexpression or location of estrogen receptors. Optical-imaging techniques provide information about the presence and amount of various chemicals in tissue. Optical technologies, using the near-infrared region of the spectrum combined with MRI, may allow sensitive and specific detection of breast abnormalities. Thermography (digital infrared imaging) can detect the increase in regional breast temperature resulting from increased chemical and blood vessel activity in both precancerous tissue and the area surrounding a developing breast cancer.

### Mammography

NCI is funding research to reduce the already low radiation dosage of mammography; enhance mammogram image quality; develop statistical techniques for computer-assisted interpretation of images; enable long-distance, electronic image transmission technology (telemammography/teleradiology) for clinical consultations; and improve image-guided techniques to assist with breast biopsies. Computer-enhanced images in digital mammography can detect suspicious areas that human review might miss. In 2001, NCI and the American College of Radiology Imaging Network launched the Digital Mammographic Imaging Screening Trial (DMIST) to compare digital mammography to standard film mammography (*http://www.dmist.org*).

### Magnetic Resonance Imaging

Several large studies are examining the application of MRI in the detection of breast cancer to reduce the number of false-positive x-ray mammograms that lead to biopsy. MRI, in combination with near-infrared optical imaging, is being evaluated for heightened sensitivity and specificity in breast abnormality detection.

### Other Imaging Initiatives

Ongoing studies of the NCI-supported American College of Radiology Imaging Network include a study of breast MRI to assess response to chemotherapy prior to surgery, and a study partially supported by the Avon cosmetics company to study ultrasound for screening. The Small Animal Imaging Resource Program supports studies to develop and apply a wide variety of functional, quantitative imaging modalities through partnerships with industry (*http://www3.cancer.gov/dip/sairp_abs.htm*).

### Gene Expression Profiles

Studies in the Director's Challenge Program (*http://dc.nci.nih.gov*) have distinguished five subsets of breast cancers, previously unidentified by morphology. Two of the subsets, HER2/neu overexpressing and basal cell tumors, correspond to poor prognosis.

**Population-based Breast Screening**

The Breast Cancer Surveillance Consortium works to reduce breast cancer mortality by enhancing current understanding of breast cancer-screening practices and fostering collaborative research in the hope of improving the practice of community-based mammography screening (*http://breastscreening.cancer.gov/*).

The International Breast Cancer Screening Network (IBSN), a consortium of 25 countries that have active population-based screening mammography programs, is dedicated to collaborative research aimed at identifying and fostering efficient and effective approaches to breast cancer control worldwide through population-based screening mammography (*http://appliedresearch.cancer.gov/ibsn/*).

NCI, in partnership with the Centers for Medicare and Medicaid Services, the National Asian Women's Health Organizations, CIS, and Asian community organization, recently released educational brochures in English, Chinese, Vietnamese, and Tagalog to encourage Asian-American/Pacific Islander women in their 40s and older to get mammograms every 1 to 2 years using Medicare benefits for screening.

**Sentinel Node Biopsy**

The status of lymph node involvement is likely to gain increased clinical significance in the future as improved imaging techniques detect growing numbers of women who have small tumors. NCI is sponsoring two large trials comparing long-term survival for patients assessed using the less invasive technique of sentinel node biopsy with those having complete axillary lymph node dissection, which has a number of associated serious, long-term side effects. The studies will also compare the postsurgical side effects between the two groups.

## *Treatment*

**Proteomics**

A new clinical proteomics program investigates new methods to diagnose cancer earlier and monitor the protein status of a patient before, during, and after treatment for cancer by generating a protein "fingerprint." Potential benefits include developing individualized therapies using targeted treatments, preclinical assessment of the toxic and beneficial effects of treatments, earlier diagnosis, and improving the understanding of tumors at the protein level to develop more effective treatments.

### *Adjuvant Therapy*

**Tamoxifen**

In October 2002, investigators with the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported that women with very small breast tumors who received both radiation therapy and the drug tamoxifen after surgery had fewer recurrences of cancer in the same breast than women who received either radiation therapy or tamoxifen, but not both. This supports treating most women with early breast cancers with radiation therapy following conservative surgery. Additionally, women with ER-positive tumors benefit from tamoxifen treatment, suggesting that tumor size, as well as tumor type, hormone sensitivity, and the woman's general health, need to be considered when making treatment decisions.

**Fulvestrant**

The drug tamoxifen is effective against breast cancer by binding to estrogen receptors, but not in all tumors and for a limited time in others. High levels of the proteins HER-2 and AIB1, in combination, seem to make tumors in some women more resistant to tamoxifen. Fulvestrant, effective against tamoxifen-resistant tumors, attaches to the ER but, unlike tamoxifen, destroys the receptor, thereby blocking all estrogen activity. The FDA recently approved fulvestrant for treatment of tamoxifen-resistant, ER-positive breast cancers. Fulvestrant was recently shown to be as effective as anastrozole, an aromatase inhibitor, in treating postmenopausal women with advanced, previously treated breast cancers. It is not yet known whether fulvestrant is effective in premenopausal women.

**Aromatase Inhibitors**

A new class of drugs, aromatase inhibitors (AIs), have been shown to be effective in treating advanced, ER and progesterone receptor-positive breast cancer, and also show promise as adjuvant therapy for early breast cancer. The FDA has approved anastrozole (Arimidex®) for adjuvant treatment of breast cancer based on the results of the Arimidex, Tamoxifen, alone or in combination trial of early breast cancer, which compared 5 years of treatment with tamoxifen alone, anastrozole alone, or the two drugs together, after initial surgery. Anastrozole has been shown to be as effective as tamoxifen as a first-line treatment for advanced breast cancer, extending length of time to disease progression, with fewer side effects. Another AI, letrozole (Femara®), has also received FDA approval for treatment of postmenopausal women with hormone-sensitive advanced breast cancer.

**Combination Therapy**

PACCT has developed a trial to identify patients with low-risk and early-stage disease who will not benefit from systemic adjuvant chemotherapy. Intermediate and high-risk participants with node-negative, hormone receptor-positive tumors between 1 to 3 cm will be treated with endocrine therapy plus or minus systemic chemotherapy.

**"Dose Dense" Chemotherapy**

Commonly used drugs in breast cancer treatment, when administered under a dose dense regime with increased frequency and the addition of filgrastim to prevent neutropenia, showed decreased disease recurrence and significant survival benefits for patients in a study of node-positive women. Side effects were not found to be more severe in the dose dense groups.

**Herceptin®**

Trastuzumab (Herceptin®) with standard chemotherapy, shown to be effective for the treatment of metastatic breast tumors that overexpress the HER2/neu protein, is now being studied in earlier stages of breast cancer. Several new Phase 3 clinical trials, which should have results in 2006 or 2007, are testing the addition of Herceptin® to the postsurgery treatment of earlier-stage breast cancer with standard chemotherapy agents (Adriamycin® and Cytoxan®) and Taxol®. Herceptin's® effect on the heart is being assessed, since earlier studies suggested that it could cause problems in some women.

**High-dose Chemotherapy with Stem Cell Transplant**

The final analysis of data from one of the major U.S. trials of high-dose chemotherapy with stem cell transplant for breast cancer shows that it holds no survival advantage over intermediate-dose therapy. Early results from two other trials add to the growing evidence that high-dose regimens do not increase breast cancer survival. Several large, randomized trials are still ongoing. The current recommendation is that women should receive high-dose chemotherapy with transplant only as part of a high-priority clinical trial so that they can be followed for several years after treatment.

**Effectiveness of Shorter Radiation Treatment**

Results of a new study among node-negative, lumpectomy-treated women shows that reducing daily radiation therapy from 5 to 3 weeks is equally effective in preventing cancer recurrence. Shortened radiation schedules lessen the overall burden for these patients in terms of personal costs, travel, and time off work, and for the health care system by reducing costs and freeing resources for use by more patients. The results of the study can only be applied to the subgroup of women in the trial.

**Effectiveness of Lumpectomy Compared to Mastectomy**

Two longitudinal studies, one initiated in the 70s and the other in the 80s, report that women with early breast cancers, treated with breast-conserving surgery plus radiation therapy, were as likely to be alive and disease-free 20 years later as women treated with mastectomy.

**Other Research**

Other ongoing therapeutic research includes studies of gene therapy strategies that target key stages of the cell cycle, such as programmed cell death by using adenoviral vectors to transfer specific genes; use of angiogenesis inhibitors; chemoprotection by making drug-resistant bone marrow cells to reduce potential bone marrow toxicities; immunotherapies designed to stimulate antitumor responses; and complementary and alternative medicine.

### *Cancer Control, Survivorship, and Outcomes Research*

NCI's Office of Cancer Survivorship (OCS) (*http://dccps.nci.nih.gov/ocs/healthdisp.html*) conducts and supports research that both examines and addresses the long- and short-term physical, psychological, social, and economic effects of cancer and its treatment among survivors of cancer and their families. For example, we know that patients exposed to systemic chemotherapy are at increased risk for problems with cognitive functioning (e.g., memory, concentration, executive capacity) and some may be genetically more susceptible to this chronic effect of treatment.

**Treatment Decisions**

NCI's Office of Education and Special Initiatives and the Office of Women's Health have partnered with the National Center for Policy Research for Women and Families, the Agency for Health Research Quality, the Office of Women's Health, the Department of Health of Human Services, and the Office of Research on Women's Health, NIH, to develop education and communication materials to assist women with early-stage breast cancers and their health care providers to make informed treatment decisions. Information provided will describe the standard surgical options of mastectomy and lumpectomy plus radiation, and the factors that can be considered when making treatment choices.

OCS supports development of tailored print and interactive health communications, such as the Comprehensive Health Enhancement Support System, which provides a computer-based system of integrated services designed to help individuals cope with a health crisis or medical concern. This system has resulted in several important outcomes, including reduced hospital days.

**Pain, Depression, and Fatigue**

These were the focus of a July 2002 NIH State-of-the-Science meeting, Symptom Management in Cancer, examining the current state of knowledge on the management of pain, depression, and fatigue in individuals with cancer, and identified directions for future research. The final statement of the conference is available at *http://consensus.nih.gov/ta/022/022_intro.htm*.

**Health Disparities and Cancer Survivors**

NCI is supporting projects, three of which are on breast cancer, in Cancer Centers to promote research in cancer survivorship among minorities and underserved populations in their communities after the completion of initial treatment, and/or the families of such patients; to strengthen linkages between researchers and community representatives; and to disseminate research findings to targeted community and members of the Cancer Center. NCI is also funding projects on issues such as menopausal symptom relief in breast cancer patients, breast cancer and function in aging women, and quality of life in long-term cancer survivors.

## Cervical Cancer

An estimated 12,200 cases of invasive cervical cancer are expected to be diagnosed in American women in 2003, with about 4,100 deaths from the disease. The overall incidence and mortality rates in the United States have declined by approximately 80 percent since 1950. This dramatic decrease is largely due to screening programs using the Papanicolaou test (Pap smear), implemented in the last 50 years. Throughout the world, the incidence of cervical cancer is second only to breast cancer as the leading, invasive cancer among women, although in some developing nations, cervical cancer is more prevalent. The 471,000 new cases diagnosed annually

worldwide are predominantly among the economically disadvantaged in both developing and industrialized nations.

Women in America have not benefitted equally from the overall cervical cancer mortality reductions noted above. African American women have more than twice the death rate compared with white women. Native Americans of the northern plains; Native Alaskans; and Vietnamese, Korean, and Hispanic women have higher than average cervical cancer mortality rates. Also of note, the incidence rate among Hispanic women declined by 4.3 percent per year between 1992 and 1999, though this rate remains higher than average. Many factors may interact to create and perpetuate discrepancies, including biology, sociocultural factors, economics, and provider issues.

The NCI Center to Reduce Cancer Health Disparities (CRCHD) held a series of three meetings in 2001 and 2002 on cervical cancer disparities in the United States. The first two meetings examined, in detail, the geographic patterns of cervical cancer mortality in the United States and explored social, cultural, and system barriers that could be contributing to the disparities in the United States. A working hypothesis was developed of cervical cancer as an index disease that highlights the complex health care issues facing women in the Deep South and Appalachia, regions which also have high rates of other life-threatening, chronic illnesses, as well as chronic living conditions of poverty. The third meeting in October 2002 brought together health care leaders from these regions to address what is known about cervical cancer rates, the health care available to medically underserved women who live there, and information, access, and cultural issues affecting that care. Using currently available research and medical information, participants are developing recommendations in the areas of communication and education, advocacy and partnerships, outreach and services, and research. Regional and race-specific programs to study cervical cancer disparities are supported through the CRCHD's Special Populations Network.

The *Report of the Gynecologic Cancers Progress Review Group* in 2001 described research priorities and the resources needed to bridge gaps in understanding and overcoming barriers to progress. The Progress Review Group (PRG) stressed the importance of developing an effective prophylactic and therapeutic human papillomavirus (HPV) vaccine, which could have the potential to nearly eradicate cervical cancer globally, as well as reduce the cost of screening. Additional recommendations specific to cervical cancer included developing better screening and prevention strategies, developing treatment approaches to reduce sexual dysfunction and improved fertility outcomes, and understanding the mechanisms and efficacy of combination therapies. High-impact priorities of the PRG applicable to all gynecologic cancers included a virtual shared specimen resource (VSSR) and research to understand and improve quality of life and reduce or eliminate disparities related to care. The report is available at *http://prg.nci.nih.gov/gyno/finalreport.html*.

## *Risk Factors*

### Human Papillomavirus

Studies have shown that approximately 90 percent of cervical cancers and cervical hyperplasias are associated with HPV, primarily types 16, 18, 31, and 45. HPV type 16 is found in 50 percent of cancers and their precursors, high-grade squamous intraepithelial lesions, and various degrees of association with the development of cervical neoplasias. A case-control study of Costa Rican women, less than 50 years old, found that cervical inflammation may be associated with high-grade lesions and may be an etiologic cofactor in women infected with oncogenic HPV, suggesting that HPV infection is a primary cause of cervical neoplasia and supporting the clinical applications of HPV DNA testing and primary prevention of cervical cancer by vaccination.

### Cofactors

Women who have never had a Pap test or who have not had one for several years have a three- to tenfold increased risk of developing cervical cancer compared to women who have been tested. Women who first had sexual intercourse at an early age or who have had many sexual partners have a higher-than-average risk of developing cervical cancer due to the risk of infection with HPV. Oral contraceptive use was associated with HSIL/CA among women with fewer than three pregnancies. Another cofactor for cervical cancer, herpes simplex virus-2 (HSV-2), was identified following meta-analysis of seven case-controlled studies.

Investigators are looking at the interactions between immune system functioning, smoking, nutritional and hormonal factors, and the presence of other sexually transmitted diseases in a large study of cervical cancer cofactors. New diagnostic technologies are also being evaluated.

### Tobacco

Studies show an increased amount of tobacco-specific, cancer-causing agents in the cervical lining of smokers. Active cigarette smokers have been shown to have a twofold greater risk of developing cervical cancer. The risk appears to be dose dependent with women who smoked approximately 20 cigarettes per day associated with high-grade disease. Nonsmokers exposed to environmental tobacco smoke lasting for at least 3 hours per day have three times the risk over unexposed nonsmokers. Risk for HSIL or cancer in HPV-positive women increased with the number of live births and was almost three times greater among women who smoked more than six cigarettes a day. Current use of barrier contraceptives reduced the risk. Increased incidence of squamous carcinomas has been associated with smoking, with an inverse risk association for adenocarcinoma.

### HIV

The Centers for Disease Control and Prevention (CDC) has designated invasive cervical cancer as an AIDS-defining cancer. Sixty-three percent of HIV-infected women in a study of the Women's Interagency HIV Study (WIHS) were HPV antibody positive at last screen compared to 28 percent of HIV-uninfected women. An association has been found between low amounts of serum retinol and risk of cervical dysplasia in HIV-infected women but not in high-risk uninfected women. HIV-infected women were nearly twice as likely to have high-risk subtypes of HPV infection and had higher rates of high-grade squamous intraepithelial lesions. Anal HPV infection was more common than cervical HPV infection in both HIV-infected and -uninfected women. It is still unclear whether treatment by highly active antiviral therapy for HIV leads to real regression of HPV-associated ano-genital lesions.

### Diethylstilbestrol

The drug diethylstilbestrol, given to pregnant women in the United States and Europe between 1938 and the early 1970s to prevent miscarriage or premature delivery, has been linked to the development of clear cell adenocarcinoma, a rare cancer of the vagina and cervix. A study of exposed daughters followed for diagnosis of high-grade disease showed a two- to threefold increase in risk, depending on timing of exposure. Results of the NCI DES Follow-up Study, which has been following over 15,000 exposed men and women since 1992, are anticipated in Spring of 2003.

NCI has partnered with the CDC since 1999 to build a national education campaign on the potential health effects of DES exposure. Information in various formats was developed and tested for a broad range of health care professionals and consumers with and without known DES exposure. The CDC will begin information dissemination in early 2003, including the DES website (*http://www.cdc.gov/des/*) and will also convene five teleconferences on topics pertinent to known-exposed persons.

## *Prevention*

### HPV Vaccine

Several candidate vaccines have undergone preclinical evaluation, and a small number have been approved for clinical trials. One of these vaccines developed at NCI, HPV-16 L1 virus-like particle (VLP), was shown to be safe and effective at stimulating production of HPV antibodies in a Phase 1 trial. A larger scale, double-blind, placebo-controlled efficacy trial of this vaccine was conducted in 2,400 women. All of the women treated with a full course of the vaccine were free of HPV-16 at the end of the trial, while in those treated with a placebo, 41 developed persistent HPV-16 infections, of which nine progressed to HPV-16-related cervical intraepithelial neoplasia. NCI plans to do a large efficacy trial in Costa Rica involving 10,000 to 15,000 women. Two additional NCI-supported trials were conducted for another VLP vaccine, HPV-16 E7 VLP and a recombinant vaccinia virus containing HPV-16/18 E6 and E7 (TA-HPV). Phase 1 trials have been completed for HPV-16 E7 VLP, and Phases 1 and 2 are completed for HPV-16/18 E6 and E7.

### Diet

Previous research has shown decreased risk of cervical cancer development with dietary intake of beta-carotene and vitamin A. NCI is supporting continued research in this area.

## *Early Detection, Diagnosis, and Prognosis*

### Pap Test Screening

Data from the 1994 National Health Interview Survey show that about one fifth of women ages 18 to 64 had not had a Pap test in the preceding 3 years, and about half of women with newly diagnosed invasive cervical cancer had not had a Pap test in the past 5 years. The largest groups of unscreened populations include the uninsured; ethnic minorities, especially Hispanics; elderly African American women; poor women, particularly those in rural areas; and older women, who do not see it as a risk. NCI has initiated an information dissemination project to improve screening in women over age 65, alerting them to their need for Pap smears. Collaborative research is also underway to find a more accessible and cost-effective alternative to Pap tests.

Certain Asian, Hispanic/Latina, and Southeast Asian women have greater risk than white women for cervical cancer, while mortality rates are highest among African American women. Low screening rates could account for these trends. Ongoing studies in the Applied Cancer Screening Research Branch (*http://dccps.nci.nih.gov/acsrb/*) include novel methods to target the older population, as well as ethnic and racial minorities for cervical cancer screening. An NCI-supported study among Chinese Americans in the Seattle area resulted in an increase in cervical cancer screening when culturally and linguistically appropriate educational materials were developed, distributed, and followed up with home visits.

The American Cancer Society (ACS) and the U.S. Preventive Services Task Force, in partnership with NCI, have recently published new guidelines for cervical cancer screening (*http://cancer.gov/newscenter/pressreleases/cervicalscreen*). The guidelines recommend cervical screens 3 years after sexual intercourse is initiated or by age 21, to be repeated every 3 years through age 65 to 70. Women should consult medical advice for screening initiation, frequency, and termination, especially if they are at an increased risk for cervical cancer.

The 2001 Bethesda System (*http://cancer.gov/newscenter/bethesda2001*), developed by an NCI-sponsored workshop, is used by the majority of diagnostic laboratories in the United States. It serves as the basis for guidelines for communicating cervical cancer screening results to physicians, published by The American Society for Colposcopy and Cervical Pathology (ASCCP) in 2002.

#### HPV Testing

An NCI-supported study in Costa Rica indicated that testing for HPV DNA can accurately identify many precancerous changes in the cervix and may be a useful screening tool for cervical cancer in some populations. The HPV test was more sensitive but less specific than conventional Pap testing.

The ASCUS/LSIL Triage Study (ALTS), sponsored by NCI, was designed to help physicians and women decide what to do about ASCUS and LSIL Pap test results. HPV testing, followed by ASCUS results, proved to be highly sensitive in detecting lesions needing immediate attention. However, HPV testing in women with LSIL is limited because of the high prevalence (82.9 percent) of HPV infection in these women. It was concluded that testing for HPV DNA in women with ASCUS is a more sensitive and specific detector for cervical intraepithelial neoplasia grade 3 (CIN3) or above, compared to a single additional cytologic test. These studies were the partial basis for the ACS/NCI guidelines published in 2002.

Studies of HPV and cervical cancer found that increased viral loads were positively associated with greater risk of an abnormal Pap test within 5 years. Other studies in HPV-positive women were assessed for viral clearance and cytologic regression by HPV DNA testing and thin-layer cytology for 2 years. HPV DNA detection persisted longer than related cytologic abnormalities. It appears that the natural history of HPV can be detected before and after cytologic abnormalities by a more sensitive HPV DNA method.

### *Treatment*

Five large randomized clinical trials found that chemotherapy administered with radiation therapy decreased the risk of death from cervical cancer by 30 to 50 percent, supporting concomitant chemotherapy with radiotherapy for advanced disease. There are currently 29 new or ongoing treatment clinical trials, with most investigating the differences between types and combinations of chemotherapy drugs for the treatment of cervical cancer.

### *Cancer Control, Survivorship, and Outcomes Research*

#### Psychological Issues

The Cognitive Behavioral Stress Management (CBSM) study is exploring the impact of group-based interventions for distress, quality of life, and cervical cellular atypia level. Another study is looking at behavioral and immunologic components that correlate to psychological distress and coping in women diagnosed with mild dysplasia of the cervix caused by HPV infection.

#### Sexuality Issues

Several studies are under way to track the sexual function and general quality of life for women receiving treatment for different stages of cervical cancer.

#### Treatment-related Side Effects

Studies in progress are examining the efficacy of drugs to alleviate or prevent side effects of cervical cancer treatment, including treatment-induced anemia and quality-of-life changes.

## Ovarian Cancer

In 2003, approximately 25,400 women in the United States are expected to be diagnosed with ovarian cancer, and approximately 14,300 are expected to die of the disease. Incidence rates decreased by 0.7 percent per year between 1989 and 1999. Ovarian cancer is responsible for the highest mortality rates of all gynecologic cancers. Incidence and mortality rates are highest in white women compared to other racial and ethnic groups.

When detected early, ovarian cancer is highly treatable, with a 5-year survival rate of 95 percent. Ovarian cancer is often asymptomatic in its early stages, and symptoms that do occur are often not of the type that would alert most women or their health care providers. Thus, most diagnoses occur at advanced stages of disease, when survival rates are 81 percent for regionally advanced stages and 31 percent for stages with distant metastases.

The *Report of the Gynecologic Cancers Progress Review Group* in 2001 described research priorities and the resources needed to bridge gaps in understanding and overcoming barriers to progress. Recommendations specific to ovarian cancer included: early detection and prevention strategy development, proteomic technology development, and elucidation of mechanisms of tumorigenesis and metastasis, as well as clinical trial optimization for new agents and surrogate markers. The PRG deemed a VSSR essential for all three gynecologic cancers for the support of studies in cancer biology, identification of genetic and molecular signature, specific molecular pathways, and surrogate biomarkers in precursor lesions, metastatic, and recurrent tumors. The PRG also designated research in quality-of-life issues and disparity reduction and elimination as a high-impact priority for gynecologic cancers. The report is available at *http://prg.nci.nih.gov/gyno/finalreport.html*.

## *Risk Factors*

The lifetime risk of ovarian cancer is 1.8 percent, and its annual incidence is about 61.8 per 100,000 women who reach ages 75 to 79. The causes of ovarian cancer are unclear. One theory suggests that constant, uninterrupted ovulation increases the risk of ovarian cancer. This could explain why pregnancy, breast feeding, and oral contraceptive use are associated with a decreased risk of ovarian cancer. Other theories speculate that increased pituitary gonadotropin levels contribute to an increased risk of the disease or that alterations in ovarian blood flow or the transtubal transportation of carcinogens may be involved in the initiation of ovarian cancers.

### Exogenous Hormones

Follow up after 20 years of participants in the Breast Cancer Detection Demonstration Project who used estrogen-only menopausal hormone therapy showed a significantly greater risk, dependent on duration of use, for developing ovarian cancer. Women on estrogen-progestin hormone therapy did not demonstrate a change in risk, but this arm of the study was a small sample size and therapy was of relatively short duration.

### Inherited Risk Factors

Three inherited ovarian cancer susceptibility syndromes have been described: 1) familial site-specific ovarian cancer, 2) familial breast/ovarian cancer, and 3) Lynch II syndrome (combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancers). It is believed that 5 to 10 percent of ovarian cancers are caused by inherited mutations in the *BRCA1* or *BRCA2* genes.

### *BRCA1* and *BRCA2* Mutations

There are large variations in risk for ovarian cancer in carriers of *BRCA1* mutations, indicating that other factors play a role. Recent NCI-funded studies have found that the risk for developing ovarian cancer increases to between 16 and 60 percent with a *BRCA1* mutation and between 15 and 25 percent with a *BRCA2* mutation. Despite these risks for developing ovarian cancer, patients with *BRCA* mutations were found to survive 20 months longer than patients without the mutation, possibly caused by differences in disease pattern due to the mutation, rather than early detection.

### Registries

A Family Registry for Ovarian Cancer (FROC) is being established using histories of families that are positive and negative for ovarian cancer. The variables of interest include race/ethnicity, invasiveness and type of tumor, age at diagnosis, and *BRCA1* prevalence. The Breast and Ovarian Family Cancer Registry collected information and specimens from over 6,000 families with the diseases, potentially valuable in the study of the cooperative effects between genetics, the environment, and lifestyle (*http://epi.grants.cancer.gov/BCFR/index.html*).

### Diet

Analyses of questionnaires from women, enrolled in the Nurses' Health Study (NHS) showed a link between ovarian cancer and frequent egg consumption, but no change

in risk with antioxidant vitamin consumption from foods or foods and supplements. Women who consumed 2.5 servings of fruits and vegetables per day during adolescence decreased ovarian carcinoma risk by 46 percent, suggesting that antioxidant vitamins are protective when consumed earlier in life.

**Genetic Polymorphisms**

Scientists supported by NCI are investigating the effects of polymorphisms in genes regulating steroid metabolism, catecholestrogen formation, and detoxification of oxidative damage. A study with population-based controls found that deficiencies in a metabolic enzyme that cause galactose to accumulate in the ovary were not related to ovarian cancer development.

**Other Risk Factors**

A multicentered, nested case-control study found a direct relationship between circulating levels of IGF-I and an inverse relationship between BMI and risk for ovarian cancer. A different study found a decreased risk with cigarette smoking, alcohol consumption, and complex carbohydrates; and increased risk with upper body obesity, inactivity, and higher intake of fat.

## *Prevention*

**Oral Contraceptives**

Previous studies have shown that the risk of ovarian cancer is decreased by 40 to 50 percent in women who take oral contraceptives, regardless of whether they had children, a family history of ovarian cancer, or hereditary ovarian cancer syndrome. This effect increases with time, ranging from a 10 to 12 percent decrease in risk after 1 year of use to a 50 percent decrease after 5 years and persisting for 10 to 15 years after use is discontinued. A study in 840 Israeli women found that additional births were protective in *BRCA1/2* mutation carriers; however, only noncarriers had decreased risk with oral contraceptive use.

**Fertility Drugs**

Women who had never given birth, or had used fertility drugs, even when used for over 12 months, were not at increased risk for ovarian cancer. Increased risks were associated with endometriosis and other unknown causes of infertility. An NCI-funded study is examining medical records of women in Denmark who have received ovulation-stimulating drugs to identify medical conditions that may increase risk of ovarian cancer.

**Prophylactic Oophorectomy**

Oophorectomy after childbearing in *BRCA1/2* mutation carriers decreased risk of ovarian cancer by 96 percent. Side effects of premature menopause are treated medically, and with diet and exercise, but there is little data on risks of premature menopause. NCI Gynecological Oncology Group and CGN are collaborating on a national, prospective followup study that will investigate precursor lesions, incidence of cancer prior to ovary removal, and effects on quality of life. Women who don't have surgery will be monitored using a novel CA-125 measure that follows levels over time to assess alterations in the ovaries.

## *Early Detection, Diagnosis, and Prognosis*

**Proteomics**

The FDA/NCI Clinical Proteomics Program, in collaboration with Correlogic Systems Inc., have developed a procedure to distinguish patterns of protein expression in blood samples from unaffected women and those with ovarian cancer. A blinded set of test samples correctly identified 50 of 50 bloods from women with cancer and 63 of 66 samples from unaffected women. This technology was able to recognize a cancer signature in the blood of all stage I ovarian cancer cases, albeit in a small sample size. A pilot diagnostic study is following women currently in ovarian cancer remission and archiving serial samples of blood through relapse or continued remission from which to identify changes in proteomic profiles that are indicative of disease recurrence and to compare these results against the results of the existing marker, CA-125. Trials are under way at NCI to evaluate proteomics both alone and in combination with current screening methods for ovarian cancer.

**Gene Expression Profiles**

Studies in the Director's Challenge program (*http://dc.nci.nih.gov/*) have developed profiles in ovarian cancer cells that can distinguish between morphologic subtypes, high- versus low-grade tumors, and alterations in *BRCA1* and *BRCA2*.

**Microarray Technology**

Scientists participating in NCI investigator-initiated research have been testing the feasibility of a cDNA microarray technology to identify the overexpression of the biomarker osteopontin. The technology found significant differences between healthy and cancerous cells, tissue, and plasma, evidencing an association between osteopontin and ovarian cancer.

**Prognostic Indicators**

Studies by the Gynecologic Oncology Group have found that age, tumor grade and size, and residual lesions are prognostic indicators after cytoreductive surgery. This was determined by retrospective chart review of 282 women with stage III and IV carcinomas. Eighteen clinical variables were evaluated for significance.

**Early Detection Research Network**

In 1999 NCI initiated the Early Detection Research Network (EDRN), a multi-institutional network, to develop sensitive and specific biomarkers for the early detection of cancer. Protein profiling studies initiated in ovarian cancer indicate promising results for early detection. This technology is being further investigated in breast, prostate, and lung cancers. More information on the EDRN can be found at *http://edrn.nci.nih.gov*.

**Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial**

Screening for ovarian cancers, one component of the PLCO trial, includes a physical examination of the ovaries, a blood test for the tumor marker CA-125, and transvaginal ultrasound in healthy women, ages 55 to 74 (*http://dcp.nci.nih.gov/plco*).

**Three-dimensional Power Doppler Ultrasound**

In a comparison with two-dimensional (2D) imaging, 3D Doppler Ultrasound both allowed for correct identification of all malignancies. Specificity and positive predictive value improved with 3D use, indicating the possibility of clinical advantages for detection.

**National Ovarian Cancer Early Detection Program**

The program is assessing the detection of precancerous lesions and early changes of the ovaries using a less invasive in-office laparoscopy technique for ovary visualization and tissue sample collection, the "ovarian pap test." The program is currently enrolling 6,000 high-risk, asymptomatic women and women with confirmed or suspected ovarian cancer.

**Cancer Genome Anatomy Project**

Molecular markers for the detection of ovarian cancer are a high priority of this gene discovery effort. Ovarian cDNA sequences in the CGAP database now number more than 300,000. These sequencing efforts have identified two known unique ovarian-specific sequences and nearly 1,000 unknown ovarian-unique sequences.

## *Treatment*

**New Drug Strategies**

The use of drug combinations holds promise in overcoming the resistance to platinum-based drugs that develop in many ovarian cancers after initial treatment. The drugs oxaliplatin, epirubicin, liposomal doxorubicin, topotecan, oral etoposide, gemcitabine, and vinorelbine have produced responses in ovarian cancer patients when used alone and are now being tested in two- and three-drug combinations. Also promising in early studies is the use of a second or consolidation round of standard-dose chemotherapy for patients whose tumors have responded well to the first round. Data from two large trials has indicated that intraperitoneal therapy may

have more side effects but may offer some disease-free and overall survival advantages over intravenous therapy for selected patient populations. Innovative approaches to the treatment of advanced ovarian cancer in development or in early trials include therapeutic vaccines, gene therapy, and antiangiogenic agents.

## Endometrial Cancer

Cancer of the corpus uteri, or endometrium, is the fourth most common invasive cancer among women in the United States. An estimated 40,100 American women will be diagnosed with uterine cancer in 2003, and approximately 6,800 will die from the disease. The incidence of endometrial cancer declined during the 1970s and 1980s; however, from 1988 to 1999 there has been an 0.6 percent increase per year. Average incidence rates for white women were 26 per 100,000 from 1992 to 1999, while African American incidence rates were significantly less at 17.7 per 100,000. Average mortality rates are opposite, with the mortality rate for white women at 3.9 per 100,000, and mortality rates for African Americans nearly double that at 7.0 per 100,000.

The *Report of the Gynecologic Cancers Progress Review* Group in 2001 described research priorities and the resources needed to bridge gaps in understanding and overcoming barriers to progress. Recommendations specific to endometrial cancer included: developing animal models and imaging methods, and conducting clinical studies for detection and prevention. The PRG identified a VSSR as essential to all of the gynecological cancers for support of studies in cancer biology, identification of genetic and molecular signature, specific molecular pathways, and surrogate biomarkers in percursor lesions, metastatic, and recurrent tumors. The PRG also designated research in quality-of-life issues and disparity reduction and elimination as high-impact priorities for gynecologic cancers. The report is available at *http://prg.nci.nih.gov/gyno/finalreport.html*.

### *Biology*

#### The Cancer Genome Anatomy Project

CGAP currently includes about 84,000 cDNA sequences of normal endometrium and malignant endometrial tumors with three known and 3,857 unknown unique genes.

#### Microsatellite Instability

Approximately 20 percent of endometrial cancers demonstrate MSI, which is the abnormal expansion or contraction of small repetitive DNA sequences due to defects in the DNA mismatch repair pathway. MSI is a common feature of hereditary nonpolyposis colorectal cancer (HNPCC). Among HNPCC families, endometrial cancers are the second most common tumors. In hereditary cases of endometrial cancer, mutation of the MSH2 or MLH1 mismatch repair gene is causative of HNPCC and the MSI phenotype. However, most endometrial cancers with MSI are the result of somatic inactivation of the hMLH1 gene by promoter hypermethylation. Findings of recent studies are helping scientists understand the initiation of tumors through methylation, a primary cause of MSI in endometrial tumors, and to distinguish pathways of endometrial cancer development. Several other studies in endometrial cancer have examined genes that are inactivated by promoter methylation, including the APC tumor suppressor and the progesterone receptor. MSI and mutations of the gene PTEN I occur in complex atypical hyperplasia, the precursor to endometrial cancer. Recently, it was discovered that some normal endometrial glands lack PTEN. These PTEN-deficient glands reappear through repeated menstrual cycles. These important insights into the initiation of endometrial cancer may help in the development of targeted therapies that will benefit patients with this disease.

#### Gene Expression Profiling

Recent gene expression profiling studies of endometrial cancers have shown a number of expression differences between the different histologic types of endometrial cancers, and also with normal endometrium.

### Stromal Interactions

Researchers are currently investigating whether alterations in stromal cells, extracellular matrix (ECM), as well as changes within the cell itself, initiate or affect tumor development. Experiments with endometrial adenocarcinoma cells showed that introduction of stromal factors and appropriate ECM-induced differentiation of more normal cells and that basement membrane proteins exert effects on the regulatory function of stromal cells.

### Tumor Suppressor Genes

NCI is also supporting efforts to isolate a novel tumor suppressor gene that is involved in the development of uterine papillary serous carcinoma (UPSC), the most aggressive type of endometrial cancer. The research has identified a specific mutation in approximately 65 percent of UPSCs.

## *Risk Factors*

An increased risk for endometrial cancer has been associated with estrogen-only hormone therapy, diabetes, obesity, age, lack of physical activity, HNPCC, and other medical conditions, but possible mechanisms remain obscure. Cigarette smoking and high intake of complex carbohydrates appear to reduce risk. Ongoing research in cancer etiology is looking into contributing factors, including specific medical conditions, and linkage to subsequent risk for endometrial and other cancers.

### Obesity

Recent increases in endometrial cancer incidence may be linked to the increase in obesity in Americans. Risk can be increased two- to fourfold in obese women compared to women of healthy weight. NCI is sponsoring two studies on obesity and endometrial cancer-associated risk. The Four Corners Breast and Endometrial Cancer Study is investigating the effects of obesity and weight changes in Hispanic, Native American, and non-Hispanic white women. Another study is looking at the effects of phytoestrogen consumption on endometrial cancer risk in obese white, African American, and Latino women.

### Exogenous Hormones

A woman's risk for endometrial cancer is increased by exposure to estrogen unopposed by progesterone, either endogenous or exogenous. Risk factors related to endogenous estrogenic effect include obesity, high fat diet, nulliparity, early menarche, and late menopause. NCI's Estrogen Replacement Therapy Study is a high-priority Phase 3 clinical trial designed to resolve the debate over whether women who have had early-stage endometrial cancer should take estrogen replacement.

### Tamoxifen

The SERM, tamoxifen, used to treat ER-positive breast cancer and for the prevention of breast cancer in women at high risk, has been linked with an increased risk of endometrial cancer. New drugs that can be used alone or in combination therapy with tamoxifen for treatment of hormone-dependent tumors are being investigated. Alternate-substituted alkyl PCDFs are a new mechanism-based class of antiestrogens that block estrogen-induced mammary and endometrial cell/tumor growth via crosstalk between the ER and Ah receptor signaling pathways. These compounds have been shown to be relatively nontoxic, inhibit ER-positive and -negative mammary tumor growth, and synergize with tamoxifen to inhibit breast cancer growth and block tamoxifen-induced estrogenic activity in the uterus. Preliminary studies also indicate that selective androgen hormone receptor modulators (SahRMs) that inhibit prostate cancer cell growth may provide a new approach for treating women with breast cancer in combination with tamoxifen and SERMs.

### History of Breast Cancer

Six hundred forty-eight of 37,583 women participating in the Breast Cancer Detection and Demonstration Project developed endometrial cancer during the average 13.8 years of followup. Women with a personal history of breast cancer were more likely to develop endometrial cancer, yet a family history of breast cancer did not increase that risk.

**HNPCC**

HNPCC, responsible for 5 percent of all colon cancers, increases a woman's risk for endometrial cancer to 60 percent by age 70. Average risk is about 1.5 percent.

**Other Factors**

Since other medical conditions have been implicated as risks for endometrial cancer, a case-cohort study is being conducted in Denmark that will allow access to medical records for the precise diagnoses of conditions prior to development of endometrial cancer.

### *Prevention*

NCI prevention studies are focusing on altering the effects of hormones necessary for prevention or therapy through route of administration; alternative, less harmful hormones or additionally regimented attenuating hormones; and new chemopreventions. A Phase 2 randomized study comparing medroxyprogesterone and ethinyl estradiol and norgestrel is ongoing for the prevention of endometrial cancer in HNPCC patients. Multiple studies are investigating phytoestrogens. Research includes attenuating risk associated with obesity or endometrial cancer incidence. Other NCI studies are looking at nutrition in terms of epidemiology and genetics and cancer.

### *Early Detection, Diagnosis, and Prognosis*

A study conducted in 101 women compared two endometrial biopsy techniques, Tao Brush and Pipelle, using both techniques during the same office visit. Sensitivity for Tao Brush was 95.5 percent, and 86 percent for Pipelle's. Both have specificities and positive predictive values of 100 percent and negative predictive values of 98 percent. Using both biopsy devices increased positive and negative predictive values to 100 percent and reduced costs.

### *Treatment*

The standard treatment for endometrial cancer is surgery – hysterectomy and bilateral salpingo-oophorectomy. In women who have not completed childbearing, alternative treatments that address fertility issues are being investigated, such as hormonal therapy, chemotherapy, radiotherapy, and adjuvant therapies.

**Hormonal Therapies**

A Phase 2 trial is comparing an estrogen blocker and receptor modulator in patients with recurrent, metastatic endometrial cancer. An NSABP study found that progesterone exerts molecular effects in cancerous endometrial cells, including cyclin p21 and p27 induction, decreasing proliferation, and inhibiting invasion. In progesterone receptor B expressing cells, it induces a secretory phenotype. Array analysis also showed inhibition of a number of cellular adhesion molecules. Another study showed that in poorly differentiated endometrial cancer cells, the introduction of progesterone receptors A and B allowed progestin to re-exert regulatory effects on proliferation.

**Targeted Therapies**

NCI treatment studies focus on comparison of different chemotherapies, alone or in combination, and with or without radiotherapy. Most trials are in Phase 1 or 1/2. Side effects of therapy and quality-control issues in radiation equipment are also being investigated. The more aggressive endometrial cancer, type 2, is a HER/neu-overexpressing tumor that should theoretically respond to Herceptin® treatment. Several studies, one in combination with traditional chemotherapy, are in progress. Erlotinib, an epidermal growth factor receptor inhibitor, and flavopiridol, another kinase inhibitor, are being tested in Phase 1 and 2 studies for advanced endometrial cancers.

## Lung and Other Tobacco-related Cancers

Lung cancer is the leading cause of cancer death for men and women in the United States, claiming the lives of an estimated 157,200 people in this country each year. The average annual rate of invasive lung and bronchus cancer among American women between 1995 and 1999 was

51.4 per 100,000. It is estimated that lung cancer will affect 80,100 women in 2003, and approximately 68,800 will die from lung cancer. Although incidence and mortality rates in men have been declining since the late 1980s, these rates for women continued to increase into the 1990s, leveling off since 1991 for incidence and 1995 for mortality. Since 1987, more women have died each year of lung cancer than of breast cancer, which until that year had been the major cause of cancer death in women for more than 40 years. High lung cancer mortality rates reflect our limited ability to detect lung cancer at an early and potentially more curable stage. Through the use of available detection methods, most people are diagnosed in advanced stages of the disease, and only 15 percent survive for 5 years. Survival improves dramatically, to 49 percent, when the disease is identified and treated early.

Smoking, a preventable factor, has been implicated in many cancers of concern to women including: lung, cervical, breast, endometrial, and ovarian. NCI has taken the lead in a public/private partnership effort to address the high rate of tobacco-related cancers in women. A meeting held in February 2003, Women, Tobacco, and Cancer: An Agenda for the 21st Century, assembled researchers, clinicians, and members of the advocacy community to identify gaps and research priorities, and to identify and prioritize needs in dissemination and application. Recommendations from that meeting will provide the basis for the development of action plans to increase our understanding of the sex-based differences in women's smoking behaviors, susceptibility to tobacco addiction and tobacco-related cancers, and translation of current knowledge to effective prevention and treatment interventions.

NCI's Lung Cancer PRG released a report in August 2001 that assessed the state of the science and recommended future research-related priorities for lung cancer. The PRG recommended the implementation of interdisciplinary, multi-institutional consortia; emphasized the need for continued research on the genetic, social, and biobehavioral aspects of tobacco control; and the need to better elucidate the contributions of injury, inflammation, and infection on lung cancer development. The report is available at *http://prg.nci.nih.gov/lung/finalreport.html*.

### *Transdisciplinary Tobacco Use Research Centers*

Launched in 1999 under the joint sponsorship of NCI, the National Institute on Drug Abuse, and the Robert Wood Johnson Foundation, Transdisciplinary Tobacco Use Research Centers (TTURCs) are helping to provide the needed infrastructure for tobacco research across many disciplines. TTURC researchers are tackling a wide range of topics, including genetic susceptibility, animal models of behavior, sociocultural factors, innovative treatments, and research on health care policy and the bioethical implications of tobacco control. The Centers will accelerate the development of interventions to control tobacco use, speed the transfer of these approaches to communities nationwide, and train a new generation of tobacco-control researchers.

### *Lung Cancer SPOREs*

NCI currently funds seven lung cancer SPOREs. The Lung SPORE at the University of Pittsburgh Cancer Institute is studying the mechanisms for increased susceptibility to lung cancer in women.

### *Tobacco-related Cancers*

While lung cancer is the leading tobacco-related cancer, the following cancers in women are also associated or linked with exposure to tobacco smoke.

#### Endometrial Cancer

Some research suggests that female smokers have half the risk of nonsmokers for developing endometrial cancer. Though the precise mechanism is unknown, nicotine has been shown to decrease the levels of estrogen, which might decrease the growth of estrogen-sensitive tumors, such as endometrial cancer and some breast cancers.

### Colon Cancer

The PLCO Cancer Trial, sponsored by NCI, has reported an association between smoking, polyps, and colorectal cancer. Previous studies have shown that smoking increased the risk by twofold of colon cancers that display MSI, seen in 15 percent of colon cancers. MSI increased with the amount of cigarettes smoked, the duration of smoking, and the age of smoking initiation. The time from smoking initiation to colon cancer diagnosis could be 35 years, which could explain how colon cancer rates during the 1990s increased subsequent to smoking increases in the 1970s.

### Cervical Cancer

Active cigarette smokers were identified as having a twofold greater risk of developing cervical cancer. Risk appears to be dose dependent for smokers and nonsmokers exposed to environmental tobacco smoke. The findings of increased amount of tobacco-specific cancer-causing agents in the cervical lining of smokers may provide the mechanism for initiation of disease.

## *Biology*

### Molecular Characterization

The MMHCC developed a mouse model for lung adenocarcinoma, commonly found in tobacco users. The model has been instrumental in identifying a pathway for tumorigenesis. Researchers have recently reported the ability to discern patterns of gene expression for squamous cell carcinoma and adenocarcinoma, two common types of non-small cell lung cancers (NSCLC) that account for 80 percent of lung cancers.

Although nicotine is not considered a carcinogen, recently published data suggests that it plays a role in making cells resistant to apoptosis, allowing them to survive longer and undergo cancerous transformation. These findings provide evidence for treatments directed toward inhibiting survival pathway initiation and imply that nicotine replacement therapy is not without hazards, though their use to quit smoking would outweigh cost of continued tobacco use.

## *Risk Factors*

### Smoking

Some research has shown that smoking increases the risk for tobacco-related cancers more in women than in men. Current research is looking at the differences between how men and women metabolize tobacco carcinogens, express related genes, and repair DNA.

Lung cancer mortality is about 13 times higher among current female smokers than among women who have never smoked, and former smokers who retain a heightened cancer risk for the remainder of their lives. Despite these facts, many women continue to smoke and many young girls start smoking. As smoking in adult women began to decline, rates in teenage girls rose sharply. In 2000, almost 30 percent of high school senior girls reported smoking a cigarette within the last 30 days, a decrease from 1999 when tobacco use peaked at 35 percent among teenage girls. Between the mid-1970s and the early 1990s, smoking rates in African American girls declined substantially while rates among white girls only experienced a small decline. Currently, African American girls are less likely to be smokers than white girls. The *2001 Surgeon General's Report on Women and Smoking* describes prevalence rates in U.S. females. Rates were highest among Native Americans and Alaskan Natives (34.5 percent); white women were next (23.5 percent), followed by African American women (21.9 percent). Hispanic and Asian/Pacific Islander women have rates of 13.8 and 11.2 percent, respectively. During pregnancy, women will stop smoking, either with assistance or spontaneously, but 12 months after delivering, 67 percent will have resumed smoking. By educational level, smoking prevalence is nearly three times higher among women with 9 to 11 years of education than among women with 16 or more years of education.

**Environmental Tobacco Smoke**

Each year about 3,000 nonsmoking adults die of lung cancer as a result of breathing second-hand smoke. Recent epidemiologic studies of nonsmoking women exposed to tobacco smoke in the home estimate that there is about a 20 percent higher risk for lung cancer in these women than in unexposed women. Three hours of second-hand smoke per day increases cervical cancer risk by threefold. A study of nonsmoking women in China found an association between levels of exposure to home fuel in poorly ventilated homes and development of lung cancer.

**Genetic Epidemiology of Lung Cancer and Smoking Study**

NCI will support an interdisciplinary case-controlled study on how tobacco and genes influence both lung cancer and smoking by incorporating the study of siblings and an extensive biospecimen collection. Another study in Italy, exploring the genetic determinants of lung cancer and smoking, will also look at gene-environment interactions.

**Cancer Survivors**

An NCI study reported that people who received chemotherapy, radiotherapy, or both for the treatment of Hodgkin's disease are at increased risk for developing lung cancer. Those who also smoke increase their risk about fivefold. Survivors of childhood cancer were less likely to smoke than the general population; however, those diagnosed during late childhood, those with lower income, and those with less education became smokers more often than their opposing counterparts. Survivors who began smoking were more likely to continue the habit if they began smoking after the age of 13, were less educated, or developed brain cancer that required radiation treatment. Analysis of these patterns is important for smoking prevention and cessation efforts in high-risk groups.

## *Prevention and Control*

NCI, through public and private partnerships, promotes research and interventions in tobacco surveillance, prevention, and control in all populations. Some of these efforts include state and community tobacco control intervention, youth prevention and cessation research, and monitoring progress in tobacco control. Resources, such as the Tobacco Intervention Research Clinic, the Smoking Cessation Service, and the Smoking and Tobacco Control Monograph series, are available to researchers and the public through the Tobacco Control Research Branch (*http://dccps.nci.nih.gov/tcrb/*). Current NCI activities include:

- **Studies on Tobacco Use and Addiction in Women**

  Studies on reducing tobacco use by pregnant women are focused on helping low-income women quit, testing the ability of women's partners to assist them in quitting, and preventing relapse after delivery. Another study examines the relationship between smoking and major depressive disorder, a problem that disproportionately affects women. NCI also is funding a major study of African American women's health that includes an examination of smoking behavior.

- **Smoking Cessation during Pregnancy**

  A study sponsored by NCI's Tobacco Control Research Branch includes partner-assisted intervention for pregnant smokers, acceleration of progress in smoking cessation in pregnancy, and motivational enhancement therapy for pregnant smokers.

- **Efficacy of Exercise as an Aid for Smoking Cessation**

  Researchers at the Miriam Hospital and Brown University School of Medicine studied whether sedentary female smokers in a behavioral smoking cessation program would benefit from vigorous exercise.

This study demonstrates that vigorous exercise, used in conjunction with a comprehensive cognitive-behavioral smoking cessation program, leads to improved rates of smoking abstinence.

- **Nicotine Addiction**

  An NCI study demonstrated that variations in the two genes that regulate dopamine are related to the age at which a person started smoking, the likelihood of being a current smoker, and the length of periods of smoking abstinence. Scientists continue to investigate whether a specific variation in the dopamine receptor gene will make an individual less likely to smoke or, if they smoke, if it would make them less likely to become addicted. Complementary studies conducted by Transdisciplinary Tobacco Use Research Center investigators have found regulator genes for dopamine activity that contribute to identifying which smokers will be able to quit. These genes do not appear to affect the success of a cessation treatment drug, bupropion, to aid in cessation. Prenatal exposure to nicotine was found to increase the probability of progressing to regular use. Other NCI-supported studies in teenagers attempting to quit smoking found nicotine withdrawal symptoms as soon as 1 month after smoking initiation.

### *Early Detection, Diagnosis, and Prognosis*

The National Lung Screening Trial was recently initiated to determine whether spiral computerized tomography (CT) or chest x-ray will reduce lung cancer mortality prior to symptom onset. The 50,000 patient, 30-site study is being coordinated by NCI through two established networks, PLCO and the American College of Radiology Imaging Network. Blood, sputum, and urine samples have been obtained for future biomarker research.

The American College of Surgeons Oncology Group, an NCI-sponsored network, is evaluating position emission tomography (PET) for lung cancer staging. Another program, Novel Imaging Technologies, facilitates new imaging technology through collaborative efforts between academia, industry, and foreign institutes. A group of NCI-supported investigators are working on the next-generation PET/CT scanner for greater localization and evaluation in difficult cancers.

Studies in the Director's Challenge Program (*http://dc.nci.nih.gov/*) have developed methods in gene expression profiles to evaluate survival prognosis, after surgery, in patients with early-stage NSCLC.

### *Cancer Control, Survivorship, and Outcomes Research*

Quality-of-life (QOL) issues associated with lung cancer are being investigated by NCI-supported scientists through self reporting by 5-year survivors of NSLC. The evaluation was designed to look into pulmonary function, depression and anxiety, tobacco use, social and spiritual well being, and demographics as they affect QOL. Depression was strongly associated with lower QOL, while comorbid conditions were weakly indicative of QOL. It was noted that non-white participants assessed at higher QOL and mental health than whites. African Americans diagnosed with advanced NSCLCs, and treated with systemic chemotherapy, were found to present with poor performance and greater weight loss. Findings of the studies suggest that socioeconomic status may play an important role in QOL.

## Colorectal Cancer

The incidence and mortality rates of colorectal cancer in both women and men have declined modestly or remained the same over the past decade. It is estimated that 74,700 women in the United States will be diagnosed with cancer of the colon or rectum in 2003, and an estimated 28,800 women will die of the disease by the end of the year, making colorectal cancer the third leading cause of cancer death among women in the United States. Native Alaskan women have the highest incidence and mortality rates due to colorectal cancer, followed by African

American women, while Native Americans of New Mexico have the lowest rates. It is estimated that deaths due to colorectal cancer could be reduced as much as 50 percent if current screening techniques were implemented as recommended.

In April 2000, NCI released the report of the Colorectal Cancer Progress Review Group (PRG). The national agenda identified an expansion of the current fundamentals through cooperation, collaboration, and new technologies as vital to advancement. The complete report, *Conquering Colorectal Cancer: A Blueprint for the Future* is available at *http://prg.nci.nih.gov/colorectal/finalreport.html*. NCI will be preparing and issuing a progress report on the implementation of the PRG's recommendations in 2004.

## *Biology*

There is evidence that the addition of methyl groups to stretches of DNA where the C and G nucleotide pairing is repeated can lead to inactivation of genes involved in DNA repair and tumor initiation and progression. Additional research has discovered a connection between gene methylation and MSI, which may elucidate pathways for colorectal cancer development.

## *Risk Factors*

A number of studies are currently investigating risk factors associated with colorectal cancer, including the role of IGF-1 and its binding proteins; insulin; diet; nutrient levels, such as folate, vitamin D, and antioxidants; postmenopausal hormones; smoking behaviors; body mass index (BMI); physical activity; and energy fibers.

### Obesity

Reports have shown that men with a high BMI are at increased risk for colon cancer. The relationship between BMI and colon cancer in women is more complex. Obesity is associated with increased risk of colon cancer in premenopausal women, but not in postmenopausal women. Risk may be modified by high levels of physical activity and is opposite to the relationship found in obesity and breast cancer where postmenopausal obesity increases risk.

### Diet and Exercise

The roles of diet, energy balance, and physical activity in the etiology of colorectal cancer remain unclear. In animal studies, both saturated and polyunsaturated fatty acids from vegetable sources increased cancer risk, while diets lower in calories and high in dietary fiber, fruits, and vegetables reduce risk. The most consistent epidemiological findings for lowering risk are maintenance of a healthy body weight, exercise, and vegetable consumption. Increased colon cancer risks are seen in those with low intakes of folate, calcium, and vitamin D. Investigators in the recently completed Polyp Prevention Trial found no evidence, after 4 years of followup, that adopting a low-fat, high-fiber, fruit- and vegetable-enriched eating plan reduced the recurrence of colorectal polyps, frequently a precursor of colorectal cancer. Continued followup of these patients may lead to further understanding of the long-term impact of diet on neoplasia. Alcohol consumption and a sedentary lifestyle have been associated in some, but not all, studies with an increased risk of colorectal cancer.

### Polyp Biomarkers Study

In collaboration with the Veterans Administration (VA), NCI is establishing a biological specimen bank within an ongoing VA Cooperative Study to examine characteristics of and risk factors for the presence of large and small polyps.

### Colon Cancer Family Registries

NCI currently supports six primary registries of familial colon cancer located throughout the world. These registries, established in 1997, assemble and maintain comprehensive lists of families with histories of colon cancer, including those resulting from familial adenomatous polyposis (FAP) syndromes and HNPCC. The registries bank blood samples and tumor biopsies for research purposes and include information on race and ethnicity, diet, and lifestyle information.

**CGN, SEER Colon CFRS**

Eight hundred pairs of siblings or close relatives, where one individual has been diagnosed with colon cancer, are being recruited to identify genetic loci significant to the disease. The investigations will be conducted in individuals where there is no known HNPCC or FAP in hope of identifying cancer susceptibility regions (*http://epi.grants.cancer.gov/CCFR/index.html*).

## *Early Detection, Diagnosis, and Prognosis*

**Cancer-screening Practices**

New efforts are under way to increase awareness of screening benefits and treatment for colon cancer, including the CDC-led, broad-based educational campaign "Screen for Life." NCI has launched a study to understand how screening for colorectal cancer is being conducted in the United States and to help identify barriers to screening and appropriate followup. Investigators from NCI, CDC, and HCFA are collaborating on a study designed to obtain nationally representative data on the physician and health system factors that may affect the use of screening and diagnostic followup related to early detection of colorectal cancer in community practice. NCI also has a formal working relationship with the CDC on colorectal cancer-screening awareness programs.

Disparity issues for colorectal cancer exist, in part, because of low screening rates among low-income and minority populations. NCI is funding numerous studies related to increasing detection and diagnosis in racial and ethnic minorities, and in those historically underscreened, by making health communications culturally friendly and studying community-based primary care for future intervention approaches.

Noninvasive diagnosis, detection, and screening methods for colorectal cancer are being developed and tested. A team of NCI-supported investigators have been testing for tumor-associated alterations in cancer cells shed in stool samples. Studies are under way to determine the specificity of these markers in symptomless patients.

**PLCO Trial**

Flexible sigmoidoscopy for colorectal cancer screening and followup will continue for 14 years following enrollment in PLCO. The study results will help to determine whether screening tests will reduce the number of deaths from colorectal, lung, prostate, and ovarian cancers. An etiologic component of the trial will collect biospecimens from a subset of participants to identify risk factors for colorectal adenoma and cancers.

**Prognostic Indicators**

Current prognostic indicator assessment relies on diagnostic pathology methods. Recent research on molecular markers has identified allelic imbalance, when chromosome pairs are different from one another, as a potential prognostic marker. Digital single nucleotide polymorphism analysis, a technology developed in SPOREs, has been able to accurately and reliably identify allelic imbalance in the two colorectal cancer-relevant chromosomes, 8 and 18. This technology has shown that 42 percent of patients with allelic imbalance in both chromosomes had recurrence within 5 years, while 26 percent of patients with allelic imbalance in one chromosome had recurrence within 5 years. Gene expression profile studies in the Director's Challenge Program (*http://dc.nci.nih.gov/*) are under way to determine profiles that discern those cancers that will recur after surgery, when metastasis will occur, and response to chemotherapy. Results, so far, indicate that the expression of gene clusters predict cancer cell behavior.

## *Prevention*

**Nonsteroidal Anti-inflammatory Drugs**

Nonsteroidal anti-inflammatory drugs block the COX-1 enzyme, required for healthy mucosal lining, and the COX-2 enzyme, which is produced in response to inflammation and precancerous tissue, such as polyps. Celecoxib (Celebrex), a selective COX-2 inhibitor, has been approved by the FDA for the treatment of osteoarthritis and adult rheumatoid arthritis. NSAID studies

noted lower incidences of colorectal polyps, colorectal cancer, and death by colorectal cancer, which spurred further investigation and sponsorship of celecoxib studies by NCI. Ongoing clinical trials are investigating efficacy of celecoxib in reducing polyp occurrence, as well as its effect on cellular and molecular biomarkers in rectal mucosa. Other studies are in progress to identify biological markers for cancer progression for noncancerous polyps. NCI studies have found that, in persons with surgically removed precancerous polyps, a baby aspirin (80 mg of aspirin) can reduce the risk of recurrence by 19 percent, and by 40 percent in persons with advanced adenomas. Larger doses did not show significant changes in either polyps or advanced adenomas.

**Diet**

NCI is supporting studies in women of Shanghai, looking at potential protective effects of low fat diet against colorectal cancer. Investigators using data from the Nurses' Health Study, the Health Professional Follow-up Study, and the Physician's Health Study have found strong evidence that consuming about 700 mg of calcium per day can reduce the risk of developing colon cancer in both men and women. Other results have shown that multivitamins with folate, diets rich in both folate and methionine, and alcohol consumption lower than moderate to heavy, may decrease colon cancer risk in women with family histories of the disease.

## *Treatment*

**FOLFOX4**

Oxaliplatin is an investigational drug used in conjunction with two routine cancer drugs in an experimental regimen, FOLFOX4. In a large, randomized clinical trial, patients on FOLFOX4 showed significant improvement outcomes, including longer life span, longer time to tumor progression, better response rate, and fewer severe side effects.

**Saltz Regimen**

This multidrug treatment – composed of irinotecan, 5-fluorouracil, and leucovorin – was approved by the FDA in April 2000 and has since become standard therapy for metastatic colorectal cancer. Two Phase 3 clinical trials studying the Saltz regimen were suspended in April 2001 because deaths due to toxic side effects occurred at rates higher than expected. The trials reopened in July 2001 with decreased doses and increased patient monitoring.

**Gleevec**

Originally approved in May 2001 for the treatment of chronic myelogenous leukemia, NCI has launched clinical trials for the safety and efficacy of this monoclonal antibody for the treatment of gastrointestinal stromal tumors (GIST) since researchers found evidence of its success in treating this rare form of cancer. Results showed dramatic reduction of tumor size in 53 percent of patients and decreased growth rates in another 28 percent of patients. Despite development of drug resistance, 88 percent of patients were living 1 year after treatment initiation.

## *Quality of Life*

Laparoscopic surgery for colon cancer resulted in slightly shorter hospital stays and less postoperative pain medication while in the hospital, compared to standard surgery patients. However, quality-of-life measures and symptom management within the first 2 months after surgery are similar for both procedures. These studies were conducted in 428 men and women with colon cancer already enrolled in the Clinical Outcomes of Surgical Therapy trial, which is being conducted in 37 centers in the United States and Canada.

## AIDS-associated Malignancies

### *Prevalence*

AIDS and HIV infection continue to be major public health concerns. From 1981 to 2001, 816,149 cases of AIDS were reported to the CDC, 18 percent of which were in women. Heterosexual transmission of HIV increased from 3 percent in 1985 to 28 percent in 2001. Sixty-five percent of HIV-positive women are infected by this route. Approximately 506,154 persons are currently living with HIV infection or AIDS in the United States. Of those, 141,048 adults and adolescent women are living with AIDS, and 49,226 are living with HIV infection. In 2001, 41,744 new cases of AIDS were reported to the CDC; one third were in women. There were also 35,051 new cases of HIV infection reported; however, this is likely an underestimate since not all states report new cases.

While the numbers of deaths per year in the United States due to AIDS has decreased in the era of highly active antiretroviral therapy (HAART), the numbers of persons living with the disease has increased. The longer life expectancy of HIV-positive people with access to HAART may increase their cumulative risk of developing cancer to rates similar to solid organ transplant recipients whose lifetime risk of cancer is increased due to iatrogenic immune suppression.

### *AIDS Malignancy Program*

The long-term risks of developing cancer for HIV-positive/AIDS patients are not yet known. Malignancies occur in more than 30 to 40 percent of HIV-positive patients during the course of their disease and include: non-Hodgkin's lymphoma (NHL), cervical cancer, anal cancer, and Kaposi's sarcoma (KS). Although KS is extremely rare among women, NHL currently ranks sixth in overall female cancer incidence and mortality. In addition, there is an increased incidence of NHL in women from the pre-HAART to HAART period. The risk of cervical neoplasia is five times higher in women with HIV infection than in uninfected women, due to the extraordinarily high prevalence of oncogenic HPV infection among HIV-seropositive women. Cervical HPV rates in HIV-infected women are 43 percent, versus 24 percent in uninfected women. Rates for anal HPV in HIV-infected women are 79 percent, compared to uninfected women whose rates are 53 percent.

### *Women's Interagency HIV Study*

Since 1995, NCI has provided supplemental funds to support malignancy studies in the NIAID/NICHD/NIDA/NIDCR-funded WIHS, the largest U.S. study of HIV infection in women. HIV-infected women have increased incidence rates for Kaposi sarcoma (>200-fold), non-Hodgkin's lymphoma (23-fold), and lung cancer (tenfold) when compared to SEER rates. No significant increases have been detected among HIV-infected and high-risk uninfected WIHS women for lung cancer after adjusting for cigarette smoking. Only one confirmed case of invasive cervical cancer has occurred, to date, in an HIV-infected woman. Despite concerns to the contrary, no increased risk of breast cancer or unusual types of breast tumors have been detected in over 5,000 woman, after years of followup. HIV-infected women who initiated highly active antiretroviral therapy against HIV experienced significant reductions in overall cancer risks. WIHS women have high rates of infection with oncogenic tumor viruses, including hepatitis C and human herpes virus 8.

### *Treatment*

#### AIDS Malignancy Program

NCI developed a multi-component AIDS Malignancy Program (AMP) (*http://ctep.cancer.gov/resources/aids.html*) to assist the research community in studying the interplay of viruses, immune dysfunction, aberrant growth factor expression, and the development of cancer in AIDS patients – the goal being the development of more effective treatment regimens. The main components of the program are the AIDS-associated Malignancies Clinical (AMC) Trials Consortium (*http://www.amc.uab.edu*) and the AIDS and Cancer Specimen Resource

(ACSR) (*http://acsr.ucsf.edu*). The ACSR contains or provides access to over 100,000 specimens collected from cohort studies, clinical trials, and other research.

The AMC unites 15 main member sites that conduct innovative treatment trials for AIDS-associated malignancies, providing access to tissue specimens and clinical data from patients. Important clinical information from completed AMC trials includes: Oral 9-cis-retinoic acid was shown to be an active anti-tumor drug for AIDS-related KS with an overall response rate of 37 percent; CHOP, or a modified dosage of CHOP chemotherapy, is an effective and tolerable treatment for NHL in HIV-positive patients on HAART; IFN-2 administered to HIV-positive KS patients on protease inhibitors was well tolerated with overall response of 39 percent; in a phase I trial, Oral COL-3 administered once daily to HIV-positive KS patients, is well tolerated with overall response of 44 percent; and a phase III study indicated that IM862 is ineffective against AIDS-KS, in contrast to earlier phase I and II trials.

**EPOCH**

An NCI study of dose-adjusted EPOCH (etopside, prednisone, vincristine, cyclophosphamide, and doxorubicin) chemotherapy with HAART suspension for untreated AIDS-related Non-Hodgkin's lymphoma (ARL) patients showed disease-free and overall survival of 92 and 60 percent, respectively, at 53 months median followup. Results seemed to correlate with high MIB-1 and possible upward CD4 risk migrations and providing emphasis for the importance of tumor biology in treatment outcomes. The results also suggest that by forestalling immune depletion, HAART has shifted tumor pathogenesis and confers no specific benefit during chemotherapy treatment.

A European–U.S. study showed a reduction in HIV transmission in pregnant women treated with antiretroviral therapy, caesarian section, with greater birthweight babies, and higher CD4 cell count.

## Initiatives

*Requests for Applications (RFAs)*

- **Complementary and Alternative Medicine at the End of Life for Cancer and/or HIV/AIDS**

  NCI joins the National Center for Complementary and Alternative Medicine in inviting applications to generate scientific knowledge on complementary and alternative medicine therapies that alone, or in combination with conventional treatment modalities, have the potential to improve the quality of life for persons with cancer or HIV/AIDS who are at the end of life. (NCCAM, NCI, NIAID, NIMH, NINR) (RFA-AT-01-002)

- **Cancer Care Outcomes Research and Surveillance Consortium**

  This RFA, focusing on lung and colorectal cancer, will support the development of a system for obtaining details about cancer care beyond the initial diagnosis and limited treatment data that are now routinely collected in high-quality, population-based cancer registries. This research will help build the information base needed for measuring and improving the quality of cancer care in the United States, including an examination of disparities in cancer care and outcomes and identifying ways to lessen those disparities. (RFA-CA-01-013)

- **Tissue and Biological Fluids Banks of HIV-related Malignancies**

  NCI invites applications from consortia of institutions for cooperative agreements to bank tissue and biological fluids and to maintain associated clinical data from patients with HIV-associated malignancies to be utilized for research, by the research community at large, on the pathogenesis of HIV-associated malignancies and development of more effective therapies. (RFA-CA-02-001)

- **Chemoprevention of Estrogen Receptor-negative Breast Cancer Preclinical Studies**

  The purpose of this initiative is to support the preclinical development and evaluation of chemopreventive strategies that could be rapidly translated to clinical studies and are applicable to women at high-risk for development of estrogen receptor-negative breast cancer. (RFA-CA-03-005)

- **Comprehensive Minority Institution/ Cancer Center Partnership**

  The purpose of this project is to increase the cancer research capabilities at the minority-serving institutions; to increase the number of minority scientists engaged in cancer research and other related cancer activities; and to improve the effectiveness of NCI-designated cancer centers in developing and sustaining activities focused on the disproportionate incidence, mortality, and morbidity in minority populations in the region the cancer center serves. (RFA-CA-03-010)

- **Minority-based Community Clinical Oncology Program**

  The Community Oncology and Prevention Trials Research Group (COPTRG), Division of Cancer Prevention, will support domestic institutions with the capability and intent to serve new cancer patients, largely from minority populations, through cooperative agreements to support cancer clinical trials, to expand the cancer prevention and control research effort using the minority-based Community Clinical Oncology Program (CCOP) network, and to evaluate minority-based CCOP performance and its impact in the community. (RFA-CA-03-012)

- ***In Vivo* Cellular and Molecular Imaging Centers**

  This initiative is designed to capitalize on the extraordinary opportunity for studying cancer noninvasively and, in many cases, quantitatively due to recent advances in molecular imaging modalities, as well as molecular and cellular biology, with an emphasis on multidisciplinary approaches to discover and develop new projects. (RFA-CA-03-015)

- **Diet, DNA Methylation and Other Epigenetic Events, and Cancer Prevention: Competing Supplements**

  NCI and the Office of Dietary Supplements, NIH, will support new and existing projects to encourage collaborative research leading to the elucidation of mechanism(s) by which dietary factors influence epigenetic processes, as well as increasing the understanding of these processes in cancer prevention and tumor incidence and behavior. (RFA-CA-03-016; RFA-CA-03-016)

- **Cooperative Planning Grant for Cancer Disparities Research Partnership Program**

  Grants funded by this RFA will support the planning, development, and conduct of radiation oncology clinical research trials in institutions that care for a disproportionate number of medically underserved, low-income, ethnic, and minority populations but have not been traditionally involved in NCI-sponsored research. These grants will similarly support nurturing partnerships between applicant institutions and committed and experienced institutions actively involved in NCI-sponsored cancer research. (RFA-CA-03-018)

- **Breast Cancer and the Environment Research Centers**

  NCI joins the National Institute of Environmental Health Sciences in inviting applications to create a network of research centers in which multidisciplinary teams of scientists, clinicians, and breast cancer advocates focus on how chemical, physical, biological, and social factors in the environment work together with genetic factors in normal breast and reproductive system growth and development and in the cause of breast cancer. (RFA-ES-03-001)

- **Pathways Linking Education to Health**

  The goal of this RFA is to increase the level and diversity of research directed at elucidating the causal pathways and mechanisms that may underlie the association of general education experiences to health-related behaviors, decisions, and outcomes. (OBSSR, NIA, NCI, NICHD) (RFA-OB-03-001)

- **Endocrine Disruptors: Epidemiologic Approaches**

  This interagency program by NIOSH, the Environmental Protection Agency, NIEHS, and NCI will support research on the relationship between exposure to endocrine disruptors and adverse health effects in humans, particularly reproductive and developmental, with a focus on epidemiologic approaches. (NIOSH, NCER, NIEHS, NCI) (RFA-OH-01-001)

*Program Announcements (PA)*

- **Defining and Validating Biomarkers of Risk for Cervical Cancer**

  The purpose of this PA is to collect and store cervical tissue specimens that will be used for DNA and RNA analyses in women representative of the four natural history categories in cervical neoplasia: normal, HPV-positive, precancer, and cancer. The main focus of the research is to identify and validate biomarkers at different stages of cervical neoplasia that may be predictive of disease. (N02-CP-21005-50)

- **Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses**

  This PA provides a flexible system within the Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs to accommodate special needs of the complex drug discovery and development process, from basic discovery through proof-of-principle demonstration in clinical trials, allowing for projects to be presented at all stages of the drug discovery and development process. (PA-01-091)

- **Exploratory Grants for Behavioral Research in Cancer Control**

  The objective of this PA is to conduct creative, novel research in the behavioral aspects of the cancer control continuum from prevention to end-of-life care and to increase scientific knowledge about health behaviors and health care practitioners' behaviors. (PA-02-001)

- **Clinical Cancer Therapy Research**

  The overall aims of this initiative are twofold: 1) to stimulate development of innovative therapeutic clinical trials with or without laboratory correlations, and 2) to support innovative correlative laboratory studies linked to therapeutic clinical trials to foster the development of interactions between basic science laboratories and clinicians performing the clinical trials. (PA-02-002)

- **Economic Studies in Cancer Prevention, Screening, and Care**

  Through this PA, NCI and the Agency for Health Care Research and Quality

(AHRQ) will support research to generate new economic knowledge that will promote the optimal design of cancer prevention and control trial studies and interventions, to facilitate the formulation of effective health care policy related to cancer prevention and control, and to increase the overall understanding of economic aspects of cancer prevention, screening, and care. (PA-02-005)

- **Social and Cultural Dimensions of Health**

  NCI joins other NIH offices and institutes to support research to: 1) elucidate basic social and cultural constructs and processes used in health research; 2) clarify social and cultural factors in the etiology and consequences of health and illness; 3) link basic research to practice for improving prevention, treatment, health services, and dissemination; and 4) explore ethical issues in social and cultural research. (PA-02-043)

- **Integrating Aging and Cancer Research**

  The National Institute on Aging and NCI will support studies directed at understanding aging and age-related aspects of cancer in older persons, with research spanning the scientific spectrum of cancer control for early detection, diagnosis, prevention, treatment, prognosis, and survivorship. (PA-02-169)

- **Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis**

  The major goals of this PA are to promote the initial evaluation of new molecular or cellular characteristics of premalignant cells or tumors to identify new biomarkers; the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis; and the evaluation of assays through translational studies to decide whether potential clinical utility justifies further investment. (PA-03-003)

- **Molecular Targets for Cancer Drug Discovery (SBIR/STTR)**

  The objective is to support young, start-up biotechnology companies and more established firms to conduct preclinical studies toward developing novel drugs for cancer treatment and prevention, with a focus on new molecular targets and agents that modulate them. (PA-03-021)

- **Molecular Epidemiology of Cancers Associated with Acquired Immunodeficiency**

  The purpose of this project is to better understand the molecular epidemiology and role of cofactors in the etiology and pathogenesis of preneoplastic conditions and cancers occurring among persons infected with human immunodeficiency virus, specifically cancers associated with viruses such as human papillomavirus, Epstein Barr virus, human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus, and hepatitis B and C. (NCI, NIAAA, NIDA, NICHD) (PA-03-024)

- **Development of Novel Technologies for *In Vivo* Imaging (PIA and SBIR/STTR)**

  These initiatives are primarily intended to facilitate the development of novel imaging technologies for early detection, screening, diagnosis, or image-guided treatment of cancer, and to facilitate clinical evaluation studies of the development that are specifically limited to proof of concept. (NCI; NCI, NIEHS) (PAR-01-101; PAR-01-102)

- **Small Grants Program for Behavioral Research in Cancer Control**

  This program is designed to conduct behavioral research investigations in cancer prevention and control. The following program areas focused on behavior and cancer may be supported:

screening and early detection, health promotion research, tobacco control research, applications research, health communications and informatics research, basic biobehavioral research, applied surveillance, survivorship, and health disparities. (PAR-02-037)

- **Colorectal Cancer Screening in Primary Care Practice**

  NCI and AHRQ will promote research to develop the capability for gathering patient, provider, practice, and clinical data and/or conducting interventions to assess and enhance colorectal cancer screening delivery, utilization, and outcomes. (PAR-02-042)

- **Specialized Programs of Research Excellence in Human Cancer for the Year 2003**

  NCI supports Specialized Programs of Research Excellence (SPOREs) in organ-specific cancers. Applicant institutions must be able to conduct the highest-quality, balanced, translational research on the prevention, etiology, screening, diagnosis, and treatment of a specific organ-site cancer. A new Ovarian Cancer SPORE will be awarded in 2003. (PAR-02-126)

- **Quick Trials for Novel Cancer Therapies**

  The focus of this PA is on rapidly ushering translational research through pilot, Phase 1, and Phase 2 clinical trials to ensure timely exploitation of cancer therapeutic approaches, including the development of new cancer prevention agents. (PAR-03-005)

*Workshops and Meetings*

The following workshops and meeting were cosponsored by NCI:

- **The National Conference on Tobacco and Health Disparities**
  **December 11-13, 2002**
  Palm Harbor, Florida

- **2002 National Conference on Tobacco or Health**
  **November 19-21, 2002**
  San Francisco, California

- **Symposium for Nurses: How Clinical Trials at NCI Can Increase Options for Your Patients**
  **November 15, 2002**
  Bethesda, Maryland

- **Workshop on Vaccine Development in Breast Cancer**
  **September 30, 2002**
  Bethesda, Maryland

- **Post-translational Protein Modification: Novel Technologies and Implications for Cancer Prevention**
  **August 28-29, 2002**
  Bethesda, Maryland

- **Applications of Bioinformatics in Cancer Detection Workshop**
  **August 6-7, 2002**
  Bethesda, Maryland

- **Fifth Annual Breast Cancer Faculty Intramural Retreat**
  **July 17-18, 2002**
  Baltimore, Maryland

- **NIH State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue**
  **July 15-17, 2002**
  Bethesda, Maryland

- **Cancer Health Disparities Summit 2002**
  **July 15-17, 2002**
  Washington, DC

- **Cancer Survivorship: Resilience Across the Lifespan**
  **June 2, 2002**
  Washington, DC

- **6th International Conference on Malignancies in AIDS and Other Immunodeficiencies: Basic, Epidemiologic, and Clinical Research**

**April 22-24, 2002**
Bethesda, Maryland

- **2nd International Conference on Cervical Cancer**
  **April 11-14, 2002**
  Houston, Texas

- **United States–Japan Cooperative Cancer Research Program Symposium on Tobacco-related Cancers**
  **February 25-26, 2002**
  Bethesda, Maryland

- **Epigenetics in Cancer Prevention: Early Detection and Risk Assessment Workshop**
  **December 3-4, 2001**
  Bethesda, Maryland

- **2001 National Conference on Tobacco or Health**
  **November 27-29, 2001**
  New Orleans, Louisiana

- **Comprehensive Cancer Care: Integrating Complementary and Alternative Therapies**
  **October 19-21, 2001**
  Arlington, Virginia

- **Breast Cancer Think Tank 2001 Retreat**
  **July 19-20, 2001**
  Chantilly, Virginia

- **Bethesda 2001 Workshop – Bethesda System for Reporting Results of Cervicovaginal Cytologic Diagnoses**
  **April 30-May 2, 2001**
  Bethesda, Maryland

- **Fifth International AIDS Malignancy Conference**
  **April 23-25, 2001**
  Bethesda, Maryland

- **Workshop on Colorectal Cancer Screening for Persons of Average Risk**
  **March 1-2, 2001**
  Bethesda, Maryland

- **Second 5 A Day International Symposium for Better Health**
  **January 7-9, 2001**
  Washington, DC

- **Nanotechnology in Early Detection of Cancer Workshop**
  **August 30, 2001**
  Gaithersburg, Maryland

- **Trans-HHS Workshop: Diet, DNA Methylation Processes, and Health**
  **August 6, 2001**
  Bethesda, Maryland

## The National Center for Complementary and Alternative Medicine

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

The 1999 National Health Interview Survey found that 28.9 percent of the 30,801 respondents had used at least one CAM

therapy in the past year and that CAM use was higher among women (33.4 percent) than men (24 percent). Rates of CAM use were highest among 45- to 54-year-old females (40 percent) and women with 16 or more years of education (42.6 percent). In this survey, the CAM therapies most commonly used were spiritual healing or prayer, herbal medicine, and chiropractic therapies. However, many other CAM practices within the five aforementioned domains are also used. CAM therapies are used to treat a broad range of health conditions by both men and women, including back and neck problems, allergies, fatigue, arthritis, headaches, diabetes, and cardiovascular disease. CAM therapies for women treat a variety of conditions such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and urinary tract problems. Thus, NCCAM's research portfolio includes investigations focused on a variety of diseases, using a myriad of CAM therapeutic interventions.

## Accomplishments

### *Menopause*

In 2002, the Women's Health Initiative (WHI) found increased risk for cardiovascular disease, blood clots, and breast cancer among women receiving estrogen plus progestin to treat menopausal symptoms. NCCAM has a strong interest in menopausal health since women use alternative therapies, such as red clover and black cohosh, to treat hot flashes and other symptoms; in the wake of WHI, use is likely to increase. A 1999 survey found that women in the United States spent $600 million on products thought to be helpful for menopause. Moreover, alternatives to hormone-based therapies are needed for women with a history of breast cancer whose tumors may be hormone dependent. There are several CAM therapies used for menopausal symptoms, including botanicals or herbs (i.e., black cohosh, dong quai, ginseng) and dietary phytoestrogens (PE). PE products consist of plant-derived nonsteroidal compounds (isoflavones and lignans) with estrogen-like biologic activity. Black cohosh (*Actaea racemosa*) is the most widely used herb for the treatment of menopause symptoms. Use within the United States originated in indigenous Native American cultures and persists today. Several small studies have indicated that black cohosh may decrease menopausal symptoms, including hot flashes. A German Commission recommended the use of black cohosh for menopausal symptoms but indicated that use should be limited to 6 months. Further work is needed to verify the efficacy of black cohosh in the treatment of menopausal symptoms. Other herbs, such as dong quai (*Angelica sinensis*), ginseng (*Panex ginseng*), and red clover (*Trifilium pratense*) are also used, although their effectiveness for menopause has not yet been thoroughly studied. There are epidemiological studies that have found fewer cardiac events and hot flashes in postmenopausal populations with high soy consumption. A small number of clinical studies have also shown lower blood pressure and cholesterol levels in those with increased soy intake (25 g soy protein per day). However, findings are equivocal regarding effects on hot flash frequency and severity.

NCCAM supports a range of research projects on menopause, including several research centers. Ongoing research on menopause targets several CAM botanical therapies, including black cohosh, red clover, soy, and other phytoestrogens, as well as the use of non-botanical treatments (e.g., therapeutic touch, macrobiotic diet) to deal with a range of symptoms associated with menopause, such as hot flashes, osteoporosis, and cognitive and affective problems. Some of these projects will generate fundamental information on the active ingredients and *in vivo* characteristics of botanicals used to treat menopausal symptoms. Others will generate clinical information on their safety and efficacy.

The NCCAM-funded Center for CAM Research in Aging and Women's Health at Columbia University in New York is investigating several therapies hypothesized

to effect women's health in menopause. Studies include: macrobiotic diet and flax seed effects on estrogens, phytoestrogens and fibrinolytic factors, dietary phytoestrogens and bone metabolism, and the effects of black cohosh on menopausal hot flashes. In addition, the Center on Botanical Dietary Supplements for Women's Health in Chicago, supported by the Office of Dietary Supplements (ODS) and NCCAM, is studying the clinical safety and efficacy of botanicals used to treat women's health with particular emphasis on therapies for menopause. Projects include pharmacognosy to standardize botanical dietary supplements, the use of bioassay-guided fractionation to isolate active compounds for structure elucidation, and biochemical studies to determine the mechanism(s) of several botanicals used for women's health (*Vitex agnus-castus* [VACS], black cohosh, and red clover). In addition, Phase I and Phase II clinical trials are under way to determine the efficacy of black cohosh and red clover to decrease the frequency and intensity of hot flashes in healthy menopausal women. Secondary end points will determine (i) the efficacy of black cohosh and red clover for the relief of somatic symptoms (e.g., insomnia, joint pain, fatigue) in healthy menopausal women; (ii) the efficacy of black cohosh and red clover for the relief of sexual dysfunction (e.g., vaginal dryness, pain during sex, libido, difficulty in achieving orgasm); (iii) the longer-term (1 year) effects and possible risks associated with the use of black cohosh and red clover; and (iv) the biochemical markers (e.g., lipids, bone turnover, effects on the endometrium) of black cohosh and red clover. A third ODS/NCCAM-funded center, the Botanical Center for Age-related Diseases in Indiana, focuses on characterizing active ingredients in botanicals. The emphasis is on polyphenolics and determining their efficacy in reducing risk of age-related diseases including osteoporosis, cancer, cardiovascular disease, and neurodegeneration. Specific projects will study isoflavones and bone resorption in postmenopausal women; the effects of soy isoflavones on the prostate, breast, and bone; and soy and estrogen interactions on breast and endometrium markers.

### *Arthritis and Fibromyalgia*

The prevalence of arthritis in the United States has been estimated to range from 15 to 18 percent, or approximately 40 million people. Arthritis is a disease that differentially affects women. In 1997, nearly 30 percent of arthritis sufferers queried in a national survey reported the use of CAM to treat the disease. This represents a significant increase in use in this population since 1990 (18 percent).

NCCAM funds two centers on arthritis. The Arizona Center for Phytomedicine Research in Tucson is concentrating its research efforts on the safety and efficacy of several botanicals purported to have anti-inflammatory actions and to be specific in the treatment of arthritis or other chronic inflammatory diseases. These botanicals include *Curcuma longa* rhizome (powdered turmeric root), *Zingiber officinale* rhizome (powdered ginger root), and the gum resin of *Boswellia serrata* (boswellia). The Center for Alternative Medicine Research of Arthritis at the University of Maryland Medical School is conducting multidisciplinary research on both clinical and basic research aspects of arthritis, including safety, efficacy, and cost-effectiveness studies on acupuncture for osteoarthritis of the knee and electroacupuncture for persistent pain and inflammation. In addition, basic research is being conducted to determine the mechanism of action of an herbal combination reported to have immunomodulatory properties.

The most common type of arthritis is osteoarthritis (OA), a progressive disorder that often results in significant pain and limited range of joint motion. Women aged 60 and older are nearly twice as likely as men (30 vs. 17 percent, respectively) to report a history of OA. NCCAM supports definitive clinical trials on two CAM interventions to treat symptoms associated with OA of the knee: acupuncture and glucosamine with or without chondroitin sulfate. These studies have sufficient statistical power to test for treatment effect differences by gender. In addition, NCCAM is funding a study of the consistency of traditional Chinese medicine practitioners' diagnosis of rheumatoid arthritis (RA), and prescription of herbal

formulas for women. Another study of RA in women is being conducted by intramural NCCAM scientists trying to understand the impact of systemically released inflammatory cytokines on the suppression of the GH/IGF-1 axis and the relationship of altered endocrine-immune function with endocrine, metaboic, and vascular functions thought to be associated with RA-related sarcopenia, osteopenia, and increased cardiovascular risk.

Fibromyalgia is a chronic, debilitating disorder that disproportionately affects women. Research demonstrating the therapeutic effectiveness of any single intervention targeting the multisymptomatic nature of fibromyalgia has remained elusive, and NCCAM-supported investigators have proposed a number of CAM interventions. NCCAM-funded investigators at the Center for Alternative Medicine Research of Arthritis in Baltimore are currently evaluating the effectiveness of mind and body therapies for fibromyalgia. Additional work is under way to evaluate the effectiveness of static magnetic fields, mind and body therapies, Reiki, and individually chosen homeopathic treatments for the mental, emotional, and somatic symptoms of fibromyalgia under double-blind conditions.

### *Other Bone and Skeletal Diseases*

The 1-year prevalence of back pain is at least 22 percent, with an estimated lifetime prevalence as high as 84 percent. Work-related cases result in over 1 million lost workdays per year. Direct and indirect costs for this condition are estimated at $50 billion a year in the United States. In spite of the magnitude of this problem, both the etiology and treatment of back pain remain controversial. Given these facts, it is not surprising that back pain is one of the most common reasons cited for the use of CAM therapies. Though gender-specific data are not readily available, nearly one half of back pain sufferers report the use of CAM within the previous year. Chiropractic and massage are listed as the most widely used CAM therapies for this condition. NCCAM is supporting studies on the effect of chiropractic massage and acupuncture on both acute and chronic low back pain, meditation and tai chi for chronic low back pain, and chiropractic for neck pain.

Osteoporosis is a well recognized problem of aging women, resulting in increased disability, chronic pain, and even death among women with spine or hip fractures. Over 50 percent of women who fracture a hip do not regain the level of functioning experienced prior to fracture. Several NCCAM studies on menopausal women (see above) include bone density as an outcome measure in several studies of botanicals and phytoestrogens. An NCCAM botanical center for age-related disease is conducting a project on isoflavones and osteoporosis. NCCAM also supports research on the effect of therapeutic touch on markers of bone formation and resorption in women who have suffered a recent fracture of the wrist.

In addition to the program areas outlined above, NCCAM supports several individual research projects related to other skeletal issues in women. Currently funded as part of the Oregon Center for Complementary and Alternative Medicine Center in Portland is a pilot  Phase II trial to evaluate traditional Chinese medicine and Naturopathic Medicine in comparison with usual care for women with temporomandibular disorders. If either of these alternative interventions is shown to merit a Phase III trial, the investigators plan to design and implement such a clinical trial.

### *Breast and Other Cancers*

A diagnosis of cancer raises many issues for women, including hope for successful medical intervention to control or cure the disease and the management of toxicity and other side effects of therapeutic intervention. These and other factors may be driving patients' search for alternatives and complements to conventional cancer treatment. A substantial proportion of cancer patients report using CAM therapies in addition to conventional cancer treatment. Studies of terminal cancer patients from different countries found significant use of CAM: 60 percent in Canada reported CAM use; 64 percent in Hong Kong and Taiwan;

61 percent in Austria; 58 percent in Germany; and 42 percent in Norway. In several surveys, similar proportions of male and female cancer patients used CAM, but use was greater among younger patients. A variety of CAM modalities are used by cancer patients, with herbs and herbal teas (Essiac, echinacea, traditional Chinese medicines) being the most frequently reported. Other common CAM modalities included vitamins and minerals (beta carotene, melatonin, enzymes, hydrazine, coenzyme-Q10), mind-body approaches (imagery and visualization, faith healing, meditation), and biologics (cartilage and mushrooms).

Although CAM is used at various stages along the disease continuum, many cancer patients report using CAM therapies 4 to 6 months after the initial diagnosis, a time when ongoing treatment outcomes may be uncertain. Concurrent use of CAM and conventional therapies also raise questions about interactive effects. Some NCCAM clinical research projects are looking at the effects of complementary approaches used in the context of conventional treatment, while others compare alternative therapies with conventional treatments. For example, one study is looking at chemotherapy plus radiation therapy, with or without shark cartilage, in the treatment of patients with non-small cell lung cancer that cannot be removed surgically. Another is studying the use of enzyme therapy with nutritional support for the treatment of inoperable pancreatic cancer. Among patients with melanoma, mistletoe, herbs, metabolic therapies, and mental and spiritual approaches were used at the later stage, whereas homeopathy was used at the earlier stage of disease.

NCCAM cofunds with NCI five comprehensive cancer centers at the Johns Hopkins University, the University of New Jersey, the University of Colorado, and the University of California–San Francisco. It also funds the Johns Hopkins Center for Cancer Complementary Medicine, as well as a broad range of research projects at other institutions, on CAM therapies for cancer treatment, including shark cartilage, the Gonzalez regimen, and self transcendence. Some research is clinically focused, such as a study of acupuncture to treat shortness of breath in cancer patients. Others are focused on basic research questions, such as the effects of herbs on transcription and cell proliferation.

NCCAM also funds over 15 projects that involve women with breast cancer. A study within the Johns Hopkins Center for Cancer Complementary Medicine in Baltimore will test the impact of personal and group prayer intervention on neuroendocrine and immune response in African American women with breast cancer. CAM therapy will begin 1 to 2 months following surgery and radiation. Work elsewhere is focused on interactive effects between soybean phytochemicals and tamoxifen on breast cancer, and whether plant estrogens are beneficial or harmful for breast cancer patients. Another study is looking at the effect of massage therapy on breast cancer-related lymphedema.

Healing touch is a biofield therapy that seeks to manipulate hypothesized energy fields around the body. Healing touch is used as a complementary treatment for cancer patients to reduce side effects of conventional treatments and to maintain immune competency. NCCAM is supporting an exploratory study to compare the effects of healing touch to conventional care on cellular immune function, and short-term side effects of treatment among women receiving chemotherapy and radiation for advanced cervical cancer.

### *Cardiovascular Disease*

Cardiovascular disease (CVD) is the leading cause of mortality for both men and women in the United States. More than 500,000 Americans die of heart attacks each year. Approximately 10 percent of women between the ages of 45 and 64 have heart disease; this figure is doubled in women aged 65 and older. Common conventional medical treatments for CVD can be invasive and costly. As the U.S. population turns more frequently to complementary and alternative medicine, it is not surprising that alternative treatments for CVD are popular. NCCAM supports a diverse portfolio in this area.

The University of Michigan CAM Research Center for Cardiovascular Diseases in Ann Arbor is studying the effectiveness of Reiki to control pain in patients with cardiovascular risk factors and chronic diabetic neuropathy; the use of the botanical, hawthorn, to treat congestive heart failure; and the effect of spirituality and Qi gong on cardiac surgical rehabilitation. The Center for CAM, Minority Aging, and Cardiovascular Disease in Fairfield, Iowa is studying Ayurvedic medicine, a form of traditional Indian medicine that incorporates herbal formulations and meditation to treat cardiovascular disease in older African Americans. The work at this center includes basic research on the mechanisms of meditation on atherosclerotic cardiovascular disease, a phase II clinical trial of transcendental meditation on carotid atherosclerosis in older black women, and a study on the mechanisms and clinical effects of traditional herbal antioxidant versus conventional vitamin supplementation on carotid atherosclerosis and other cardiovascular disease risk factors. NCCAM supports a clinical trial to assess chelation therapy which is used for a variety of cardiovascular symptoms and diseases. NCCAM also supports studies looking at the effects of acupuncture and biofeedback on hypertensive patients. If initial pilot phase data are promising, an acupuncture and hypertension study will move into a Phase III trial with adequate sample to perform appropriate gender analysis. Further work is ongoing regarding the effects of a ginkgo biloba extract on vascular function, the consumption of flaxseed meal on lipid metabolism and oxidative stress, and the use of Ayurvedic herbals on lipids and atherosclerosis.

### Initiatives

Urinary tract infections (UTIs) are a serious and common health problem. Only respiratory infections occur more frequently. Each year UTIs account for more than 9.6 million doctor visits. UTIs are more common in women than men. One woman in five develops a UTI in her lifetime. Among women with a history of UTIs, 20 percent report a second infection, and 30 percent report three or more infections. Most UTIs are caused by a bacteria found in the gastrointestinal tract, *Escherichia coli*. UTIs are generally treated with antibiotics, but these drugs can be expensive, have side effects, and can lead to resistant strains. Cranberry juice is widely used to prevent or treat UTIs. Existing data suggest that cranberry constituents impair adhesion of pathogenic coliforms to uroepithelial cells, a necessary stage in disease pathogenesis, but the data are inadequate to assess the efficacy of cranberry to prevent or treat UTIs, and standardized cranberry products are not available. Thus, in 2002, NCCAM sought a contractor to develop standardized products for cranberry, a necessary antecedent step for subsequent clinical trials.

## NATIONAL CENTER FOR RESEARCH RESOURCES

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

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

The *Clinical Research Division* provides clinical research infrastructure for medical scientists who conduct patient-oriented research. This research may be supported by the NIH or by funds provided though other federal, state, and local agencies, and the private sector. The division administers programs to increase the opportunities for clinicians to be involved in patient-oriented research; to procure and distribute a wide variety of human tissues and organs for medical research; to provide vectors for clinical trials of gene therapies; and to support meetings and workshops dedicated to understanding or treating human diseases. The division also participates in federal set-aside programs designed to support innovative clinical research, with commercial potential, conducted by small business ventures.

The *Comparative Medicine Division* provides high quality, disease-free models and specialized animal research facilities for biomedical investigators. This is accomplished by: supporting the development of a wide range of research models, including nonhuman primates, rodents, aquatic species, and invertebrates; providing access for biomedical researchers to an array of important biological materials such as viruses, bacteria, fungi, cell lines, and genetic material; supporting the identification and development of new and improved animal models for the study of human diseases; supporting training for veterinarians; and supporting the improvement of the health and well being of laboratory animals. The division supports research activities at eight National Primate Research Centers.

The *Research Infrastructure Division* expands the Nation's ability to conduct biomedical and behavioral research by developing research infrastructure of all kinds. This includes support for renovation of biomedical and clinical research laboratories and animal facilities, recruitment of new faculty, performance of pilot projects, and acquisition of research equipment. Support from this division is provided to predominantly minority-serving institutions that award doctorates in the health or health-related sciences, and institutions in states that have historically had limited NIH support. This support enables junior college, baccalaureate, and master's degree-granting institutions to significantly enhance their capacity to conduct biomedical and behavioral research by developing and strengthening formal, collaborative agreements with research-intensive, doctoral degree-granting institutions. The goal of these funding programs is to encourage scientists to work with educators and community organizations to improve science education and the public's understanding of health-related science, to increase the interest of young people in science careers, and to make biomedical research participation accessible to all Americans.

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

## Research Report

### *NCRR Activities Specifically Designated to Focus on Research on Women's Health*

The NCRR Division of Research Infrastructure supports a Center of Biomedical Research Excellence in Women's Health at the University of Kentucky. This center is funded for 5 years through an Institutional Development Award as part of its Centers of Biomedical Research Excellence Program. The center contains research core activities in imaging, modern genetic and cell biology techniques, the breeding of genetically modified mice as models, and bioinformatics. The theme of this program is the role of female reproductive hormones and selective estrogen receptor modulators in manifestations of health and disease in women. There are four interdisciplinary and interactive scientific projects that include: a study of the mechanisms by which estrogen regulates ovarian function; the effects of estrogen on brain and pituitary function; the role of estrogen in modulating HIV-induced neurodegeneration; and the action of estrogen on cognition and mood. The program involves ten junior faculty members, and 13 mid-level or senior faculty members from six different departments. There are also plans to recruit new faculty members, and funds for two to four pilot projects annually to enlist existing faculty members to participate in the program. Thus, more than 40 investigators may eventually be involved in research related to women's health over the 5-year course of this program.

### *Accomplishments*

#### Estrogen May Protect Against HIV Brain Damage

Many people with human immunodeficiency virus (HIV) infection that has advanced to severe symptoms of acquired immune deficiency syndrome (AIDS) suffer from dementia. Researchers at the University of Kentucky have made some important discoveries regarding a protective effect of estrogen against brain cell damage from HIV infection. Estrogen is a class of female hormones; 17-beta estradiol is the chemical name of one particular form of estrogen that is produced in the ovaries. With funding from NCRR, these researchers have collected evidence that 17-beta estradiol protects laboratory cultures of brain cells against damage caused by HIV. The only cells in the brain that are susceptible to HIV infection are the microglial cells; these cells function as a kind of connective tissue, and are also part of the immune system of the brain. If the microglial cells are stimulated to act incorrectly, this can lead to brain inflammation and tissue damage. AIDS dementia has been shown to involve an activation of microglial cells. Although the mechanism of microglial activation is not fully understood, it appears that HIV releases a protein called "Tat" that plays a major role in activating these cells. In the laboratory, pre-treatment of microglial cells with biologically normal concentrations of 17-beta estradiol suppressed their activation by Tat. This research thus raises the possibility that maintaining normal estrogen levels in the blood of HIV-infected women may protect them against AIDS dementia.

#### Female Animals Show Superior Ability to Function Under Stress

Researchers at Hunter College, City University of New York, with funding from the Research Centers at Minority Institutions Program of the NCRR, are using an animal model to determine gender-specific differences in response to stress. Male and female rats were restrained for up to 21 days as a means of generating stress. The researchers are particularly interested in the roles of estrogen, a class of female hormomes, and of corticosterone, a class of hormones produced by the adrenal cortex region of the brain that regulate not only sexual function, but also salt and water balance, metabolism, and immune system function. Researchers reported that male rats were impaired on spatial and non-spatial learning and memory tasks following 21 days of chronic stress. In contrast, performance of females was enhanced (spatial task) or not affected (non-spatial) following the same stress. Proposed

experiments will further describe sex differences in the stress response and may indicate how neurochemical and behavioral differences depend on an interaction between specific regions of the brain, the adrenal glands, and the male and female sex organs.

**Increasing Fertility in Women with Polycystic Ovary Syndrome**

Women with polycystic ovary syndrome (PCOS) tend to be overweight and have difficulty in becoming pregnant due to infrequent menstrual cycles. The cause of the condition is not known, but a tendency for the disease to cluster within families suggests that there are genes that, when inherited from a parent, increase the risk for the disorder. Women with PCOS are less sensitive to the actions of the hormone, insulin. Studies funded through several NCRR General Clinical Research Centers now show that treatments that improve the body's response to insulin (losing weight or taking certain drugs) also increase the regularity of the menstrual cycle in women with PCOS; this return to normality should make it easier for affected women to become pregnant. Other studies are directed towards identification of gene(s) which when inherited increase the chance for developing the disorder. While prevention of PCOS must be the long-term aim, at least some of the problems associated with the disorder cannot be reversed.

**Improved Detection of Ovarian Cancer**

Advanced ovarian cancer is responsible for approximately 14,000 deaths annually in the United States. A major reason for this high mortality rate is our inability to find cancerous cells that remain after initial treatments. A number of different non-invasive diagnostic techniques (ultrasound, computerized tomography, magnetic resonance imaging) have been tested for the ability to find these remaining cells, but they are all inferior to having a surgeon look at the area following treatment. Sadly, even these second-look exploratory surgeries have a very high false-negative rate. With support from a number of different parts of NIH and NCRR, a research group at the University of California–Irvine has been developing techniques to use lasers to find and treat ovarian cancer. This group recently reported success in an animal model. They washed the cancerous tissue with a chemical that emits a red light when excited with a fluorescent lamp. They discovered that this red marker made finding very small groups of cancerous cells relatively easy. The results were sufficiently successful to suggest that human trials should be initiated.

**Maternal Behavior is Heritable in Nonhuman Primates**

Variations in human maternal behavior result from a complex interplay of environmental factors, and may also have a genetic component. The possible genetic influence on differences in human maternal behaviors is difficult to determine because of the highly outbred nature of human populations. In contrast, the genetics of maternal behavior can be studied in baboons. Researchers at the Southwest National Primate Research Center in San Antonio, Texas, with funding from NCRR, have analyzed maternal behavior in a large, pedigreed baboon colony, for which a genetic map is also available. They have characterized differences in maternal behavior and have demonstrated for the first time in a nonhuman primate that specific maternal behavior phenotypes are heritable. They have identified specific regions of the baboon genome that appear to be linked to these behaviors. Because the baboon genome is very closely related to that of humans, these experiments may also help identify human genes that influence maternal behavior.

**Effects of Long-term Estrogen Replacement Therapy on Osteoarthritis in a Monkey Model**

Recent epidemiological studies suggest that the incidence and progression of osteoarthritis is lower in women who have taken estrogen replacement therapy than in untreated women. However, these studies are limited by potentially confounding factors such as differences in general health and weight in the population of

women studied and by differences in dosages and products used for estrogen therapy. Researchers at the University of Minnesota, with funding from NCRR, have analyzed the effects of estrogen replacement therapy by examining the cell structure of the bones in a group of cynomolgous monkeys that have naturally occurring osteoarthritis. They found that estrogen replacement therapy significantly reduces the severity of osteoarthritis in this animal model. This result will have to be considered in light of recent findings regarding deleterious effects of long-term estrogen replacement therapy.

**Nonhuman Primate Oocyte Cryopreservation and *in vitro* Maturation**

Studies of the parameters affecting cryopreservation of nonhuman primate oocytes (unfertilized eggs) may lead to better methods for oocyte preservation and *in vitro* fertilization in humans. In the human, fewer than 1 percent of cryopreserved oocytes result in live births after fertilization. In a collaborative project, scientists from the California, Tulane, and Wisconsin National Primate Research Centers, with funding from NCRR, are investigating factors that affect the maturation and survival of cryopreserved oocytes from rhesus monkeys. They have dramatically improved methods for collecting immature oocytes from the monkeys and for *in vitro* fertilization. They have also examined the effects of freeze-thaw conditions on the distribution of chromosomes and the protein structures needed for chromosome division within the oocyte. These results will be used to further develop methods for cryopreservation of nonhuman primate oocytes that may also be applicable to human oocytes.

**A Monkey Model for Preterm Delivery**

Preterm delivery in humans is a serious health concern, given the low survival rate and high health care costs associated with infants born at very early gestational ages. Development of biomarkers for likely preterm birth would be very useful to clinicians. Scientists at the Southwest Foundation for Biomedical Research in San Antonio, Texas, with funding from NCRR, have found that female marmosets subjected to moderate daily food restriction (75 percent of their normal daily intake of calories) reliably show preterm delivery of infants. The moderately calorie-restricted marmoset may thus become a valuable model for studying many aspects of preterm delivery.

## Initiatives

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 2001 or 2002. However, through its support of unique resources, NCRR contributes a significant portion of its budget to women's health and behavior research. The demand for NCRR-supported resources is determined by scientific and funding shifts. Therefore, future increases in women's health and behavior research supported by other components of NIH will result in corresponding NCRR increases.

### *Research on Health Disparities among Special Populations of Women*

The NCRR Research Centers in Minority Institutions Program provides support for research in health disparities with a focus on minority women. At the University of Puerto Rico, Medical Sciences Campus, a Health Disparities Research Program is developing intervention models for women with breast cancer, performing studies on menopause and health in Hispanic women in Puerto Rico, and creating a Women's HIV Empowerment Program. At Ponce School of Medicine, genetic studies on endometriosis in Puerto Rican women are being conducted.

At Charles R. Drew University of Medicine and Science in Los Angeles, California, NCRR provides resources to support a Biometry and Survey Research Core to address the need for methodologically sound, culturally and linguistically appropriate strategies in health disparities research. This core has

developed a battery of surveys that will be useful in generating data to address disparities in health for African Americans and Hispanics in the areas of diabetes, menopause, and hormone replacement. This core also supports research focusing on stress reduction and atherosclerotic cardiovascular disease morbidity and mortality in African American women.

### *Gender Analysis or Sex and Gender Studies During 2001 and 2002*

Through its unique role in providing technologies, equipment, building renovations, training opportunities, and infrastructure in its broadest sense in support of multidisciplinary biomedical research, NCRR has provided funding for many studies that have analyzed sex and gender differences. Some highlights of this research appear above.

## National Center on Minority Health and Health Disparities

The National Center on Minority Health and Health Disparities (NCMHD) was authorized by Public Law 106-525, the *Minority Health and Health Disparities Research and Education Act of 2000,* and established in January 2001. The mission of the center is to promote minority health and lead, coordinate, support, and assess the NIH effort to reduce and ultimately eliminate health disparities. In this capacity, the NCMHD will: conduct and support basic, clinical, social, and behavioral research; promote research infrastructure and training; foster emerging programs; disseminate information; and reach out to minority and other health disparity communities.

The Congress has authorized the NCMHD to develop a Strategic Research Plan and Budget that will guide all of the NIH's health disparities activities, in collaboration with the NIH Office of the Director and the other institute and center (IC) directors at NIH. The NCMHD has also been given the authority to fund three core programs to enhance the research capacity of institutions engaged in biomedical and behavioral research to the field of health disparities, as well as to attract more individuals from minority and underserved populations to this area of research. These programs, which have been successfully launched with substantial assistance from the other NIH ICs, lay the foundation for NCMHD efforts to eliminate the health disparities in this country:

- *Centers of **EX**cellence in **P**artnership for **C**ommunity **O**utreach, **R**esearch on Health Disparities, and **T**raining (Project EXPORT) Program* supports the conduct of research, research training, and community outreach activities in the field of health disparities at Centers of Excellence.

- *Research Endowment Program* is designed to build minority health and other health disparities research capacity at Health Resources and Services Administration (HRSA) Section 736 Centers of Excellence.

- *Loan Repayment Programs* aim to increase the participation of health professionals in health disparities research and to increase the participation of individuals from disadvantaged backgrounds in clinical research.

The center also administers the *Research Infrastructure in Minority Institutions (RIMI) Program* to provide support for institutions that enroll a significant number of students from minority health disparity populations to develop and enhance their capacity and competitiveness to conduct biomedical or behavioral research.

NCMHD programs provide an opportunity for the center to focus its efforts to eliminate health disparities by funding the expansion of the infrastructure of institutions that are committed to health disparities research and support the education and training of racial and ethnic minorities, as well as the medically underserved.

## Accomplishments

### *Follow-up Study for Causes of Illness in Black Women*

In this study, cofunded by NCMHD and NCI, investigators propose to continue the largest followup study of the health of African American women yet undertaken, the Black Women's Health Study (BWHS). The aim is to determine the effects on breast cancer incidence (and eventually other cancers) of potential risk factors including physical activity, obesity, alcohol, diet, oral contraceptives, and postmenopausal female hormones. In addition, factors specific to African American women, including experiences and perceptions of racism and use of hair-straightening products (which is very common), will be assessed. Because prevention programs require an understanding of the determinants of risk factors, they will also assess correlates of important risk factors.

### *Center for Collaborative Research on Genomic Analyses of Diseases that Disproportionately Affect African Americans (Including Database Management Core)*

The center's investigators, cofunded by NCMHD and the National Human Genome Research Institute, propose to conduct a comprehensive epidemiology/genetic study to determine environmental and familial/genetic risk factors for prostate and breast cancer in Barbados. The desired outcome of this work will be that it will lead to a better understanding of the genetic basis for these diseases and its disproportionate impact on people of African descent. The study will include a population-based, case-control study that will enroll all incident prostate and breast cancer cases in the country and age-sex matched population controls over a 4-year period (approximately 800 cases and 1,600 controls). In addition, it will include a separate and smaller family-based study to identify families with hereditary forms of prostate and breast cancer, which will assist in evaluating the genetic factors involved.

### *Sleep during the Perimenopause in a Multiethnic Cohort*

Four applications are part of an Interactive Research Project Grant (IRPG), cofunded by NCMHD and the National Institute on Aging, to characterize the relationship between menopausal characteristics and sleep. In a sample of 430 women, drawn from participants in the ongoing Study of Women's Health Across the Nation (SWAN), there will be 200 Caucasian, 150 African Americans, and 80 Chinese Americans. Although sleep disruptions, insomnia, and the incidence of sleep-disordered breathing increase in mid-life women, little is known about the relationship between menopause and sleep.

The few data that now exist suggest that the sleep-menopause relationship is not one merely of age, but that a variety of relevant psychobiological factors contribute. This IRPG will recruit a sample of pre- and perimenopausal women from the SWAN cohort, conduct ambulatory polysomnography at their homes, and collect sleep diary data and current and past data on menopausal characteristics (bleeding patterns, vasomotor symptoms, hormone levels, and related psychosocial and biological data) from the 5 years of SWAN core data. The specific aims are to: 1) characterize sleep problems in a large multiethnic sample of mid-life women; 2) characterize relationships between menopausal characteristics and sleep problems; 3) evaluate the influence of relevant psychobiological and psychosocial factors on sleep problems during the early menopausal transition; and 4) establish baseline data on menopausal-related sleep problems for future longitudinal study.

### *Alcohol Research Development Collaboration: Meharry Medical College and University of Wisconsin*

In 2001, NIAAA collaborated with NCMHD on a developmental project that would eventually examine behavioral and pharmacological therapies for alcoholism in African American and low SES populations. During the first year, staff from research-intensive

institutions worked with faculty at Meharry Medical College to assess their potential for building the capacity to conduct alcohol treatment research. The long-term aim of this project is to conduct research in a system that currently provides alcohol treatment (clinical) services, to develop alcohol research infrastructure at Meharry, to increase the number of alcohol investigators at Meharry, and to serve minority and underserved clinical populations.

### *Outcome of Systemic Lupus Erythematosus in Minorities*

This project, cofunded by NCMHD and the National Institute of Arthritis and Musculoskeletal and skin Diseases, is successfully achieving its objectives of identifying the relative importance of biological, behavioral, and social variables affecting outcomes of lupus in the three major U.S. ethnic/racial groups. The investigators continue the annual followup of active LUMINA/PROFILE cohort patients as per protocol (197 from Alabama and 180 from Texas). So far, six manuscripts have been published – three have been accepted for publication and two are under consideration.

### *Epidemiology of Systemic Lupus and Cardiovacular Disease*

Systemic lupus erythematosus (SLE) is the prototypic systemic inflammatory autoimmune disease that affects predominantly young premenopausal women. African American women are afflicted 3 to 4 times more frequently than Caucasian women, and the risk of myocardial infarction in women with SLE is up to 50 times higher than expected in women aged 35 to 44 years. The investigator, cofunded by NCMHD and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, proposes to: 1) compare the prevalence and extent of subclinical vascular disease in 200 SLE patients and matched controls; 2) determine whether the risk factors associated with subclinical vascular disease in patients with SLE are different from controls; and 3) determine the risk factors associated with progression of carotid atherosclerosis over a 3-year period in women with SLE.

### *Mapping of Vitiligo Susceptibility Genes*

This project, cofunded by NCMHD and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, continues an international collaboration to locate the genes making people susceptible to vitiligo. The majority of the affected families and individuals are African American or British subjects of African descent. Sufficient data has been collected to start genetic analysis. A peer review publication will localize a gene or genes for multiple autoimmune disease susceptibility in these families, with a second gene, not yet with sufficient power to be absolutely certain, which confers vitiligo susceptibility also localized but to a different distinct chromosomal location. The continued collection of samples and their analysis will allow confirmation of the vitiligo susceptibility locus, and the narrowing of the region and/or identification of a single susceptibility gene. With this information will come a better understanding of the disease and potential new interventions or preventative strategies.

### *Ectopic Germinal Reaction in Systemic Lupus*

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-organ involvement and widespread immunologic abnormalities, the most relevant of which are hypergammaglobulinemia, immune complex formation, and complement system activation. Highly specific auto antigen-driven responses, particularly those directed at protein and nucleic acid components of intracytoplasmic and intranuclear particles, are characteristic of SLE patients. At the peak of disease activity and antibody secretion, however, SLE patients are known to display peripheral blood lymphopenia. This project, cofunded by NCMHD and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, endeavors to understand the phenotypes and functional characteristics

of recirculating B cells in the blood of SLE patients. They have been very successful in their endeavors to date.

### *Patient-oriented Research: Systemic Lupus Erythematosus*

There are two research goals of these studies, cofunded by NCMHD and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The first is a cross-sectional study to estimate the differences in bone mineral density between black and white women with lupus, and to determine the association of lupus risk factors with low bone mineral density in women with lupus. The second is a longitudinal study to follow the subjects entered in a cross-sectional study over a 2-year period to estimate differences in rate of bone loss and to determine the association of lupus risk factors with increased rates of bone loss in women with lupus.

### *Infant Mortality Initiative, Washington, DC*

New data show that the District's infant mortality rate has fallen an unprecedented 20.7 percent from 15 per 1,000 live births in 1999 to 11.9 in 2000. Part of this significant decrease is attributed to many intensified and innovative efforts targeting the District's high risk, minority populations. This includes the ongoing DC Initiative, cofunded by NCMHD and the National Institute of Child Health and Human Development.

### *Specialized Reproductive Science Research Centers at Minority Institutions*

The Morehouse University was recently funded by NCMHD and the National Institute of Child Health and Human Development as the first program in the Specialized Reproductive Science Research Centers at Minority Institutions. Its new and innovative work in the area will allow faculty to address reproductive science, a largely unexplored area of research at minority institutions, while training a diverse cadre of investigators in the field.

### *Long-term Follow-up of Post-obese Black and White Women*

This is a competing renewal from a well-established investigator who proposes combining the cohorts from two on-going treatment studies of obese African American and caucasian women for long-term follow-up. The investigators, cofunded by NCMHD and the National Institute of Diabetes and Digestive and Kidney Diseases, will attempt to determine factors contributing to long-term weight control, focusing on free-living energy expenditure. The strengths of this application include the availability of well-characterized populations of women who have undergone weight loss, and an experienced and productive investigative team. Information from this study may provide important information about the causes of obesity and weight regain in African American women, a group disproportionately affected by obesity and its medical consequences.

### *Uterine Leiomyoma Growth Study*

Uterine leiomyomas, commonly called fibroids, are a major health concern for all women of reproductive age and particularly for African American women. These benign smooth muscle tumors are the most common type of tumor found in the reproductive tract, occurring in about 75 percent of African American women and about 50 percent of Caucasian women. The study, cofunded by NCMHD and the National Institute of Environmental Health Sciences, investigates the growth dynamics of uterine leiomyomas in a clinically relevant population of women. They test the hypothesis that uterine leiomyomas are heterogeneous in terms of their growth characteristics and in their clinical symptoms or outcomes, and that differences in leiomyoma growth dynamics can be discriminated by molecular markers and cellular phenotypes. Data analysis is underway to document the heterogeneity of leiomyoma growth, location, and molecular characteristics. As the study is completed, the investigators hope that the data may be used to establish a clinical severity scale and establish diagnostic markers currently

not available for uterine leiomyomas. They hope to advance the understanding of uterine fibroid leiomyoma growth in order to establish better treatment intervention and prevention modalities.

### *Vulnerability and Resiliency in African American Parents*

This research will follow 897 families living in Iowa and Georgia contributing to our understanding of mental health among African American women during a critical developmental period in the lives of their children, adolescence. The model incorporates the influence of neighborhood characteristics on the level of distress and rates of diagnosable mental disorder. The study, cofunded by NCMHD and the National Institute of Mental Health, includes an innovative examination of coping with stressors, such as race-related negative events among care givers with a variety of family structures and caregiving relationships.

### *Engaging Distressed Mothers of Disturbed Children*

The work of this supplement, cofunded by NCMHD and the National Institute of Mental Health, is to compare and contrast African American and Caucasian mothers in terms of the ways they perceive their mental health problems, the availability of resources, and formal helping systems. Responses to the standardized scales used in the parent project are currently being examined. The goal of this supplement is to interview a total of 60 African American mothers and their adolescent children, ages 11 to 17, to examine in-depth their awareness and perceptions of service system and clinician factors that may constitute barriers to care. Particular attention is being paid to the views mothers and their children have about the risks and benefits of participating in therapy and research, and any differences in cultural or racial factors that influence their decision to seek or engage in treatment. The specific aims have not changed and are: 1) to identify barriers to treatment for 60 low-income African American mothers and their adolescent children by conducting an ethnographic exploration of their perceptions of their needs, problems, strengths, and the characteristics of their families, networks, and contacts with the helping system; and 2) to use the information gathered in the qualitative studies of Aim 1 to create a treatment engagement intervention for African American mothers.

### *Pathways to Mental Health Services among Rural Native Women*

This supplement, cofunded by NCMHD and the National Institute of Mental Health, is to address the contextual and individual factors influencing mental illness and its care among rural Native American women. The parent grant proposes two separate but related studies that will provide descriptive and analytic information on the utilization of mental health services by the type of disorder and treatment system, and will identify other influences (e.g., sociocultural factors) on help-seeking behavior as suggested by the Network-Episode Model Theory. The research will test models on the pathways to care that consider social, community, and system variables as determinants of access to treatment, and provide narratives to contextualize the results. One data set to be used for secondary analysis will be drawn from the largest psychiatric, epidemiologic risk and protective factors study conducted among Native Americans (the SUPERPFP study N=3200). The second data set will be drawn from a population of rural Native American women in a primary care setting (N=234). Specifically, the funding will provide additional resources to better understand mental health disorders of rural Native American women.

### *Targeted Delivery of Estrogen in Menopause*

In postmenopausal women, coronary artery disease (CAD) is the leading cause of death. Estrogen replacement therapy appears to offer considerable protection against CAD in postmenopausal women. However, there is great concern about risk for breast and endometrial cancer after long-term estrogen

use in these women. The activation of estrogen receptors and subsequent genomic effects in terms of cell growth appears to play a significant role in estrogen-related carcinogenesis. We hypothesize that desired cardioprotective benefits of estrogens (without carcinogenic effects) can be achieved either through: 1) macro phages targeted for preferential delivery of hydrophobic estrogen acetylated LDL (ac-LDL) complexes to atherosclerotic tissues, or 2) by conjugating these estrogens into lipid microspheres or by coating lipoprotein/estrogen complexes with functionalized (Fc) dextran, both of which have been used for preferential uptake by endothelial cells. Phase I will determine: 1) whether IV-administered hydrophobic estrogens will associate with LDL; 2) tissue distribution and the feasibility of macrophage-targeted (MT) and endothelium-targeted (ET) liposomal preparation of hydrophobic estrogen derivatives for differential delivery to macrophages or endothelium; and 3) whether ET and MT are functionally active. Phase II will deal with their *in vivo* effects on atherogenic indices and suitable lipoprotein-like carriers and enhancers for use as transdermal patch. This trial is cofunded by NCMHD and the National Heart, Lung, and Blood Institute.

## *ECR-LRP*

### Mammogram Screening Practices amongst Minority Women

The purpose of this research, cofunded by NCMHD with its Loan Repayment Program, is to examine the relationship between factors that influence mammography screening practices in minority African American women in an effort to improve breast cancer screening. The specific aims are: 1) to describe and examine the relationship of individual sociodemographic, pregenetic, access, institutional patient-provider factors and individual health beliefs and health behaviors to the rate of mammography usage in African American women; 2) to assess whether lack of trust in the provider is a strong predictor of decreased mammography rate in African American women at risk for breast cancer by SES; 3) to examine whether the predictors for breast cancer screening practices differ by SES in African American and white women; and 4) to measure the variability of the pregenetic, institutional patient-provider factors, health behaviors, and health beliefs between and within different SES groups of African American and white women.

### Preference of Women Evaluating the Risks of Tamoxifen Study (POWER)

This study, cofunded by NCMHD and its Loan Repayment Program, will use data gathered from a larger ongoing trial: 1) to evaluate women's acceptance for the outcomes of tamoxifen prophylaxis of breast cancer; 2) to identify demographic and cultural factors associated with strength of preference for tamoxifen prophylaxis, and to identify the profile of subjects most and least likely to prefer tamoxifen prophylaxis; and 3) to evaluate the perceptions of breast cancer risk and breast cancer prevention and early detection among African American and Latina women.

### Exercise Training in Obesity-prone Black and White Women

This study, cofunded by NCMHD and its NCMHD Loan Repayment Program, is designed to investigate the effectiveness of three intervention strategies (diet alone, diet plus aerobic exercise, and diet plus resistance exercise) as ways to improve free-living physical activity and, consequently, to reduce the probabilities of weight regain in African and European American women. The investigator tested the independent association of ten different candidate genes for obesity-related phenotypes in these females, trying to understand the genetic mechanisms influencing possible racial differences in muscle strength, activity energy expenditure, free-living physical activity, and lower total daily energy expenditure.

**_In utero_ Stem Cell Therapy: Corrections of Ornithine Delta Aminotransferase Deficiency**

The goal of this research, cofunded by NCMHD and its NCMHD Loan Repayment Program, is to examine the feasibility of *in utero* hepatocyte transplantation/stem cell therapy for a murine model of ornithinine delta aminotransferase deficiency. The specific aims of the project are: 1) to characterize the development, time course, and distribution of ornithine delta aminotransferase (OAT) production in mice; 2) to transplant wild-type fetal hepatocytes *in utero* and determine the degree of engraftment; 3) to demonstrate expression of OAT in homozygous knockout pups following *in utero* hepatocyte transplantation and determine its effect on neonatal mortality and retinal degeneration; and 4) to transplant embryonic stem cells into the developing liver of fetal murine pups and determine their fate.

**Alabama Tobacco Free Families Project/ Alabama Practice Base Research Network**

The goal of this project, cofunded by NCMHD and its Loan Repayment Program, is to reduce the smoking prevalence rate among a representative sample of pregnant females whose maternity care is supported by Medicaid. Partnerships have been implemented on the state and local level, along with a statewide media campaign, targeting females of childbearing age and encouraging them to be tobacco free prior to and during pregnancy.

**Development of Community-Provider Partnerships in Enhancing Access to Behavioral Healthcare**

Through this grant, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), the research team are beginning to develop and evaluate strategies to enhance access to behavioral health services among adults and families residing in public and assisted housing who have unrecognized and/or inadequately treated behavioral health disorders. This initiative grew out of concern for the significant number of individuals who find themselves in the above mentioned situation and who face ethnocultural and socioeconomic barriers to treatment. The investigator's role in this grant is to assure the cultural competence of project staff and the cultural relevance and sensitivity of the interventions and measures utilized with people of Hispanic origin. This includes training staff and supervising translations and administration of measures.

**Impacting Breast Health Outcomes using Stylists as Health Mentors**

The investigator aims are: 1) to select and train community-based professional stylists (as messengers) in specific knowledge, attitudes, and practices that will enable their delivery of breast cancer control messages to their customers; 2) to examine, via a randomized controlled trial, the impact of stylist-delivered, breast cancer-control messages on the breast health behaviors (mammography screening, CBE, and BSE) of beauty salon customers; and 3) to develop a portable stylist training-communications package (port-a-paks with training video) to enable the on-going training of stylists, and conduct, via a controlled trial, an outcome evaluation of breast health behaviors of salon customers comparing method of stylist training (video versus live training). This trial is cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP).

**Mechanisms for Racial Disparity in Preterm Birth**

This research is a 5-year population-based prospective cohort study to evaluate the relative contributions to preterm birth of lower genital tract infection, maternal stress, and a genetic predisposition to an enhanced immune response among African American and white American women residing in King County, Washington. This study is cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP).

**Prevalence and Risk Factors for the Acquisition of Genital Herpes in Women**

Worldwide, genital herpes, most frequently caused by herpes simplex virus type 2 (HSV-2), is one of the most prevalent sexually transmitted diseases and it is a significant public health concern. Racial differences in the prevalence of HSV-2 infection may be the consequence of a number of variables, including differences in the prevalence of low socioeconomic status or in disparate access to health education and health care. It is of concern that the promotion of safe sex practices in many countries has not slowed the promulgation of genital herpes. It is, therefore, crucial to identify new factors associated with HSV-2 that might represent opportunities to intervene with either primary or secondary prevention programs. The researcher, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), investigated the risk factors associated with HSV-2 infection in a cohort of 18- to 30-year-old women recruited from three Pittsburgh, Pennsylvania area health clinics.

**Greater Denver Latino Cancer Prevention and Mammography Screening for Underserved Women in Metro Denver and Partnership to Increase Hispanic Cancer Research in Colorado**

The investigator's role entails facilitating discussions between network scientific and community partners for collaboration in pilot project proposals ideas development; setting up timelines and technical assistance for community-based organizations that are interested in pursuing a pilot project; assisting in the identification of potential minority junior investigators, senior mentors/investigators, and/or interested community-based organizations for collaborative proposals. This work is cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP).

**Impact of Culturally Tailored Counseling on Psychobehavioral Outcomes and *BRCA* Decision Making among Women with Cancer**

The investigator's research responsibilities are on a new, federally funded study of culturally tailored genetic counseling for *BRCAI* and *BRCA2* with African American women. This study, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), is designed to investigate whether culturally tailored counseling might be more effective than standard and, if so, to determine if psychosocial variables render the counseling more effective for a subset of African American women.

**Obesity and Related Health Issues in Hispanic Women**

In collaboration with the mentor, this investigator will identify specific treatment needs for Hispanic populations and develop a clinically based research study (e.g., testing the efficacy of a cognitive-behaviorally based therapy in Spanish that considers and incorporates culturally relevant issues). This represents a programmatic interest dating back to the investigator's dissertation project that examined the dissemination of behavioral treatment for alcohol abuse to primary care physicians in Mexico. This also represents a natural extension of the investigator's current training at Yale with an increased focus on developing clinical research skills. The goal is to have these research projects, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), culminate in several publications in peer-reviewed journals and serve as pilot data for a grant application.

**Epidemiology of Female Pelvic Floor Disorders: Impact of Age, Parity, and Mode of Delivery**

The primary aims of the investigator's current research project, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), are to: 1) validate and implement a Spanish and English version of a multifaceted questionnaire for large population screening that includes information related to urinary incontinence (stress and urge), anal incontinence, and prolapse symptomatology; 2) establish the prevalence of individual PFD across a full age spectrum of a multiethnic population; and 3) determine whether the effects of pregnancy, vaginal delivery, or aging act as independent risk factors for the development of PFD. The first phase of the study will consist of the validation of a questionnaire to evaluate PFD. This phase will begin with a test-retest of 100 asymptomatic and 100 symptomatic patients.

**Chicago Great Lakes Program – Health Effects Associated with Consumption of Resources**

The mission of the project is to characterize health effects associated with consumption of resources, such as fish, provided by the Great Lakes basin region. The research program, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), is supported by local health departments and academic institutions along the Great Lakes basin. The University of Illinois project was developed to study the polychlorinated biphenyl (PCB) and pesticide exposures associated with Great Lakes fish consumption in pregnant African American women. The effects on development in children born to exposed African American women were to be determined through a followup cohort study.

**The Effectiveness of HIV/STD-related Practices for Pregnant Women with the Ultimate Goal of Improving the Health of Women at Risk for Reproductive Complications**

The mission of CWHP is to study the effectiveness of HIV/STD related practices for pregnant women with the ultimate goal of improving the health of women most at risk for reproductive complications and reducing existing racial and economic disparities in birth outcomes. This study is cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP).

**Reaching Vietnamese American Women to Prevent Cervical Cancer – Vietnamese Community Health Promotion Project**

The goal of our REACHing Vietnamese-American Women Project is to reduce cervical cancer incidence rates by promoting pap smear screening among Vietnamese American women. To accomplish this, a partnership has been established with a community coalition to develop and implement a community action plan that will ensure access to affordable, culturally competent, and linguistically appropriate pap smear screening services. This action plan, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), REACHes Vietnamese American women through six integrated components: a mass media campaign; lay healthworker outreach groups; a Vietnamese-staffed cervical cancer screening clinic; a pap registry; continuing medical education for Vietnamese American physicians; and facilitation of community mobilization to obtain state funding for cervical cancer screening for low-income women.

**Racial Differences in Post-treatment Cancer Surveillance in Medicare Population of Breast Cancer Survivors**

While breast cancer incidence rates in African Americans are lower than in Caucasians, breast cancer mortality rates in African Americans are higher – in fact, they are the highest of all racial groups. The reasons for this disparity are unclear; possible explanations include the relative underuse of mammography leading to a higher proportion of late-stage cancer diagnoses, racial differences in the use of primary treatments for breast cancer, and racial differences in post-treatment care. This last hypothesis will be the focus of the investigator's research, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP).

**Understanding the Socioeconomic, Psychological, and Behavioral Impact of Cancer on American Indian Families: Piloting a Qualitative Case Study Methodology**

This will be a case study to explore the family unit as a social group experiencing cancer in their lives over a 6-month period of time. Data collection procedures will include in-depth interviews and observations. Participants will be one American Indian patient's family of ten to 20 members. Using a thematic matrix approach, transcripts will be analyzed. Conclusions will be drawn and supported with direct quotes and observational descriptions. Graphs, charts, and networks will be used as supportive and explanatory documentation. Consultants will be used to validate interpretations and assist with analysis. The culminating narratives will be a representation of the Native oral tradition and benefit the participants by giving voice to their experience. It is expected that the findings from such studies, cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP), may also help to understand American Indian's suffering from other chronic illnesses, such as diabetes.

**Women Veterans and Breast Screening**

This is a 5-year prospective study cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP). The study compares a targeted and tailored intervention to promote mammography that utilizes the trans-theoretical model. The investigator's responsibilities on this project are to conduct the validation study to verify mammography dates with the participants' physicians, and to conduct the evaluation process to determine the suitability of the intervention materials.

**Center for Drug Use and HIV Research**

The center's theme, "Understanding Social-Level Influences," addresses the fact that disparities in the risk of HIV cannot be understood by examining individual-level factors alone, but require attention to higher-level influences such as racial and gender hierarchies, network characteristics, economic stratification, formal policies, etc. The center is cofunded by NCMHD and the Loan Repayment Program for Health Disparities Research (HDR-LRP).

## Initiatives

In fiscal year 2002, NCMHD launched the Project EXPORT program. Due to the program's infancy, the projects listed below may not specifically pertain to health disparities among women but, instead, health disparities among minority and other health disparity populations. As such, women would be included in these research studies. As the program expands in the coming years, we hope that research initiatives, specifically on women's health, will emerge.

***Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Centers of Excellence – Resource-related Research Grants)***

These R24 grant applications will focus on the development of resources in infrastructure at various institutions as a prelude to initiating full-scale health disparities research, community outreach, and training. (RFA: MD-O3-001)

- **Center for Research and Outreach in Hispanic Mental Health**

  The center will provide significant support to the current research infrastructure in the Carlos Albizu University by facilitating the performance of high-quality research in health disparities with special focus on the development of effective and novel approaches to the diagnosis, prevention, and treatment of the mental health disorders affecting Hispanics. The long-term goal of the center is to contribute to reduce Hispanic and other minorities' health disparities with an emphasis on, but not limited to, reducing the disparity in the burden of mental health disorders.

- **Shaw University Project EXPORT R24 Program on Disparity**

  The goal of the Shaw University Project EXPORT R24 (SUPER) Program is to establish infrastructure support to Shaw University junior-level faculty to conduct health services research on racial disparities among various minority populations by providing training, resources, and mentorship opportunities through collaborative linkages with senior researchers at Shaw and at other universities.

- **Hampton University Health Disparities Project**

  This program will integrate research, training, and outreach to establish a scientific base for eliminating health disparities and improving the health and well being of ethnic minority populations. The program will: 1) promote research to reduce health disparities through a pilot feasibility funding mechanism; 2) foster the generation and testing of culturally specific, health-related theories and interventions from a multidisciplinary perspective; 3) establish a means for enhancing community involvement as research is conducted and disseminated; and 4) expand the number of minority researchers involved in minority health issues.

***Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project Export – Establishing Exploratory Centers)***

These P20 grant applications will focus on health disparities research, community outreach, and training. (RFA MD-03-002)

- **Creation of a Hispanic Health Research Center in Lower Rio Grande Valley**

  The purpose of this grant is to create a Hispanic Health Research Center within the existing academic institutions of a predominantly Hispanic community, designed to address the disease burdens and the paucity of research capacity in this low socio-economic, undereducated, and medically underserved Hispanic population. The activities of the Hispanic Health Research Center will encompass research on health disparities in Hispanics, provide a source of data on Hispanic health, develop and evaluate intervention strategies for Hispanic cultures, evolve research collaborations with other Hispanic communities, and build research capacity in South Texas Lower Rio Grande Valley. Nine cores will be developed, of which three are research cores with projects addressing specific aspects of the major killers of the Hispanic population of South Texas – diabetes, cardiovascular disease, and cancer.

- **Partnerships for Diabetes-related Disparties in Hawaii**

  MedStar Research Institute and the University of Hawaii have partnered to address health disparities among Native Hawaiians (NHs) and Pacific Peoples (including Pacific Islanders and Filipinos) in Hawaii. It is well known that a high rate of obesity and diabetes exist among the NHs – the indigenous people of Hawaii compared

to the U.S. population. In accordance with these trends, rates of cardiovascular disease among NHs have been on the rise while rates in the general U.S. population have been decreasing. This partnership will also form the groundwork for future opportunities to examine common correlates of health disparities among native populations in the United States that share similar inequities in health status.

- **The Drew/UCLA Project EXPORT Center**

  The center will address health disparities in the largest and one of the most diverse counties in the United States. The center will emphasize diabetes mellitus and mental health and illness in Latinos and African Americans in its initial years, but eventually will address disparities in other conditions.

- **Reducing Health Disparities in Alabama's Black Belt**

  Tuskegee University and the University of Alabama at Tuscaloosa will expand, strengthen, and better integrate and focus their infrastructure and programs in public health and bioethics, biomedicine, bioscience, and behavioral and social science research in ways that will maximize their impact on ameliorating the five disparity disease areas – diabetes, cardiovascular, cancer, HIV/AIDS, and infant mortality.

***Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT – Establishing Comprehensive Centers)***

These P60 applications will focus on health disparities research, community outreach, and training. (RFA MD-03-003)

- **San Diego Export: A University Community Partnership**

  The goals of the San Diego EXPORT Center are to strengthen the infrastructure for minority health and health disparities research and training at the University of California, San Diego School of Medicine (UCSD) and San Diego State University (SDSU). This will be achieved by promoting HIV and cardiovascular disease research; expanding the Community Outreach Partnership Center; promoting the participation of health disparity groups in biomedical and behavioral research, prevention, intervention, and dissemination activities; and developing and implementing a minority health disparities curriculum for UCSD School of Medicine medical students and SDSU graduate students in public health and epidemiology.

- **San Diego EXPORT: A University-Community Partnership**

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- **Columbia Center for the Health of Urban Minorities**

  Although disparities are multifactorial in etiology, there is little evidence of biological underpinnings of racial and ethnic health disparities and extensive evidence of disparities in receipt of quality health care. Accordingly, the research focus of the Columbia Center for the Health of Urban Minorities will be access to care. One research core will focus on primary (financial) barriers to care, and other cores will focus on non-financial barriers in four specific areas: ardiovascular disease, mental health, diabetes and injury, and disability prevention.

- **Overcoming Barriers to Effective Care for Minorities**

  The Mount Sinai School of Medicine at NYU's Center will be developed around the theme of improving health and reducing disparities by enhancing self-management skills among patients in East and Central Harlem. The center's research core will enhance two already-funded intervention trials to examine the effectiveness of a peer-led patient support group intervention (one in patients with uncontrolled hypertension and a second in those with stroke); an intervention will be added to a third already-funded trial that will match women with early-stage breast cancer and specific needs for support to existing community services. A vigorous community outreach core that will aim to embed successful programs in the community to maximize the likelihood that they will remain after the research studies are concluded will supplement these research strategies. The center will strengthen existing linkages and build new ones with community leaders and organizations to maintain a mutual exchange of information between the community, researchers, and educators.

- **EXPORT**

  This EXPORT Center at the University of Arizona will focus on health disparities among American Indians and Hispanics in three areas: diabetes, substance abuse, and women's cancer prevention. The goals are to conduct, coordinate, and foster health-disparities research focused on the unique needs and challenges of the Mexican American and American Indian communities of Arizona; develop health disparities research capacity through training programs and infrastructure development, guided and focused by the community and grounded in sound science; and translate research findings into useable information and activities that address the needs of multiethnic communities.

- **NCMHD Working Groups on Women's Health**

  Currently, there are no NCMHD working groups specifically designated to focus on research on women's health.

## National Eye Institute

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

The major causes of blindness (glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer than men do on average, more women than men are affected by these age-related eye diseases in the United States.

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

### Accomplishments

#### *Optic Neuritis*

Optic neuritis is an acute debilitating inflammation of the optic nerve that affects more that 25,000 Americans each year,

primarily women between the ages of 18 and 45. People with this disease usually have rapid vision loss and ocular pain. The NEI-supported Optic Neuritis Treatment Trial (ONTT) compared oral corticosteroid, intravenous steroid followed by oral corticosteroid, and placebo for the treatment of new cases of optic neuritis. Results from the ONTT showed that oral corticosteroid, the most common treatment of the disease, when used alone is ineffective in treating the disease and actually increases a person's risk for future attacks; whereas intravenously administered corticosteroids promoted more rapid recovery and did not increase the rate of recurrence. Based on data collected from 2 years of followup of patients enrolled in the ONTT, researchers found that treating first-time optic neuritis patients with a combination of intravenous and oral corticosteroids lowers their risk of developing multiple sclerosis. The results from this research offered the first scientific evidence that intravenous corticosteroids help to delay the progression of multiple sclerosis. This study also demonstrated that the presence of multiple enhancing 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. At present, the Longitudinal Optic Neuritis Study (LONS), which follow patients originally enrolled, is underway.

### *Dry Eye*

Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition. Dry eye can result from insufficient secretion of fluid by the lacrimal glands; or from defects in the surface of the eye, mucin, or mucous production, or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, e.g., in Sjögren's syndrome, but also occurs in association with aging, nerve dysfunction, radiation therapy, and with antidepressant and anti-psychotic drug therapy.

Lacrimal insufficiencies affect roughly two million Americans, particularly postmenopausal women. NEI-supported researchers are investigating the hypothesis that lacrimal insufficiency is triggered by loss of hormonal support for the lacrimal gland's secretory capacity. Much of the dry eye disease that afflicts women after menopause, during oral contraceptive use, pregnancy, lactation, and the late luteal phase of the menstrual cycle appears to be attributable to lacrimal gland atrophy following decreases in available androgen levels. In addition, new findings suggest that the pathogenesis of dry eye may have an autoimmune component; thus, tying it to Sjögren's syndrome.

### *Corneal Endothelial Dystrophy*

Corneal endothelial dystrophy is a slowly progressing disease of the endothelium that usually affects both eyes and is more common in women than men. Although physicians can often see early signs of the disease in people in their 30s or 40s, the disease rarely affects vision until a person reaches their 50s and 60s.

The corneal endothelium is a layer of cells lining the inner surface of the cornea. The endothelial cells are responsible for pumping fluid out of the cornea. The cornea is normally clear despite being bathed in tear on the outer surface and in aqueous humor on the inner surface. This clarity is maintained by the endothelial cell layer. If endothelial cells are diseased or absent, permanent corneal edema, loss of corneal transparency, and eventual blindness may occur.

NEI-supported scientists are attempting to determine why endothelial function deteriorates following cell loss, age, or trauma. Delineating the optimal conditions for the tissue culture of corneal endothelium will help evaluate the problems involved in transplanting these cultured cells and assuring their survival. With further refinement of endothelial culture techniques, it will be possible to determine whether cell-cycle stimulatory and inhibitory factors arise from other cells and whether the endothelium can be induced to repair itself. Parallel gene therapy studies are being pursued in animals with the aim of developing vectors to therapeutically deliver factors to the eyes of patients with the disease.

### *Keratoconus*

Keratoconus arises when the middle of the cornea thins and gradually bulges outward, forming a rounded cone shape. This abnormal curvature changes the cornea's refractive power, producing moderate to severe distortion (astigmatism) and blurriness (near- and farsightedness) of vision. These changes may also disrupt the normal, light-conducting arrangement of corneal protein, causing swelling and a sight-impairing scarring of the tissue. Keratoconous has become better understood though investigations into the genetic predisposition of the disease, detection of early forms of the disorder through computerized topographic analysis, and advances in understanding the enzymology that underlies corneal thinning. Microarray technology is proving to be highly valuable in developing profiles of diseased tissue and comparing them to those of normal tissue.

The Collaborative Longitudinal Evaluation of Keratoconus Study is a NEI-supported, multicenter, observational study designed to characterize the progression of keratoconus over a broad spectrum of disease severity. Information on participants' vision, quality of life, corneal shape, and corneal scarring is being collected to characterize the disease across its course and to identify risk factors and protective factors that determine the severity and progression of the disease. Investigators are continuing to conduct patient followup examinations.

### *Age-related Macular Degeneration*

Age-related macular degeneration (AMD) is not only the leading cause of blindness in patients over the age of 65, but is now the most common cause of blindness in the United States. The incidence of AMD continues to rise in the population as the result of the increasing percentage of elderly persons, with women at 50 percent greater risk than men.

The macular is a specialized region near the center of the retina responsible for the high-resolution vision that permits activities such as reading. Degeneration of this region is believed to be the result of a complex set of interactions involving genes/gene products and environmental factors. A high priority has been placed on identifying predisposing genes and their products and then determining what environmental factors impact these gene products to produce or protect against the disease. The Age-related Eye Disease Study is a multicenter clinical trial and epidemiological study, now in its 11th year, designed to assess the clinical course, prognosis, and risk factors of AMD and to evaluate the effects of antioxidants and zinc in slowing the progression of the disease. A second multicentered clinical trial, The Complications of Age-related Macular Degeneration Prevention Trial, will assess the safety and efficacy of laser treatment in preventing vision loss in patients in whom the disease is manifested bilaterally. Another study, Late Macular Degeneration in Older Women, aims to determine the incidence, progression, and association with specific risk factors, such as diabetes and cataract surgery, of age-related macular degeneration in women over 80.

## Initiatives

NEI and the National Advisory Eye Council (NAEC) have established in *Vision Research – A National Plan: 1999-2003*, goals, objectives, and research priorities for improving visual health and preventing blindness, including diseases that have a higher incidence and prevalence for women than for men. These include studies on:

- *optic neuritis* – Research priorities are to develop an animal model of this disease to better understand the pathogenesis of the disorder, to develop immunomodulating therapies to limit optic nerve damage from inflammation, and to understand the relationship between optic neuritis and multiple sclerosis;

- *dry eye* – The overall objective is to determine the role of sex hormones on lacrimal gland function. A body of experimental evidence supports the notion that androgen sex hormones and prolactin modulate lacrimal gland function, thus providing an explanation for the observed gender bias of this condition and suggesting hormone modulation as a possible treatment.

- *corneal endothelial dystrophy* – Research priorities are aimed at understanding the biologic and functional structures of endothelial cells.

- *keratoconous* – 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.

The Women's Health Initiative Observational Study affords NEI the opportunity to pursue epidemiological studies in women-only cohorts. This will allow gender-specific analyses of risk factors in major blinding and debilitating diseases. The following study is ongoing:

- *The Carotenoids and Age-related Eye Disease in the Women's Health Initiative* will follow a cohort of women enrolled in three of the Women's Health Initiative Observational Study sites to assess the role of dietary xanthophyll carotinoids in preventing the development of age-related macular degeneration and cataract.

## National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) supports a wide range of basic, clinical, and epidemiological research on diseases of the heart, blood vessels, lungs, and blood; uses of blood and management of blood resources; and sleep disorders. NHLBI also has administrative responsibility for the NIH Women's Health Initiative.

Highlights of FY 2001 and 2002 activities include the following:

- Building upon years of research to identify modifiable risk factors associated with development of heart disease in women – hypertension, high blood cholesterol, smoking, overweight, physical inactivity, diabetes – NHLBI has launched *The Heart Truth*, a campaign to make women aware of their vulnerability to heart disease and of ways in which they can reduce their risk.

- NHLBI is placing much emphasis on addressing heart disease risk factors that begin to develop during adolescence. It currently supports the *Girls Health Enrichment Multisite Studies* (*GEMS*) to prevent excessive weight gain in black girls as they go through puberty and the *Trial of Activity for Adolescent Girls* (*TAAG*) to prevent the decline of physical activity that typically occurs in girls during adolescence.

- Data from the *Women's Ischemia Syndrome Evaluation* (*WISE*) study, which investigated issues related to the presentation of chest pain and diagnosis of coronary heart disease (CHD) in women, are being used to develop specific messages for women about heart attack symptoms as part of the *Act in Time to Heart Attack Signs* campaign. The campaign, which targets patients and the general public as well as physicians, encourages recognition of heart attack symptoms and calling 911 as soon as symptoms begin.

Additionally, results from the WISE study are helping shape future directions of research on CHD in women.

- Recent findings from the NIH *Women's Health Initiative* and the NHLBI *Women's Angiographic Vitamin and Estrogen* (*WAVE*) trial have produced persuasive evidence that, contrary to long-held expectations, use of postmenopausal hormone therapy is not useful in primary or secondary prevention of heart disease, and may, in fact, be harmful.

## Accomplishments

### *Women's Heart Health Education Initiative*

In September 2002, NHLBI unveiled a new campaign of public and professional education called "The Heart Truth." Its goal is to increase awareness that heart disease is the leading cause of death among U.S. women and to motivate women to take heart health seriously, talk with their doctors about it, and take steps to reduce risk. The Heart Truth includes consumer television, radio, and print public service announcements that use graphic visuals and testimonials to deliver the message that every woman should focus at least as much attention on her inner self as she does on her outward appearance, because "heart disease doesn't care what you wear." Additionally, educational materials are available to assist community leaders in spreading the word about heart disease to women at the local level. An initiative to alert health care providers about the effort and encourage them to speak with their women patients is also under way. The campaign is the culmination of the NHLBI Women's Heart Health Education Initiative that was launched in March 2001 at a strategy development workshop attended by almost 80 experts on women's health. Their charge was to develop the framework for a national action plan to reduce the toll of heart disease on American women. The Heart Truth is sponsored by NHLBI in partnership with the Office on Women's Health of the U.S. Department of Health and Human Services, the American Heart Association, WomenHeart: The National Coalition for Women with Heart Disease, and other organizations committed to the health and well being of women.

### *C-Reactive Protein and Cardiovascular Disease Risk*

High blood pressure, high blood cholesterol, smoking, obesity, and diabetes are well-established risk factors for cardiovascular disease (CVD), and now an additional predictor of CVD may be on the horizon. Researchers investigated the prognostic value of C-reactive protein, a marker of inflammation, using data from nearly 28,000 healthy American women who were followed for an average of 8 years. They found that C-reactive protein levels, especially when considered in combination with low-density lipoprotein cholesterol levels, were strongly predictive of subsequent CVD events. If additional studies confirm this observation, physicians may have a powerful new approach to screen people for CVD risk and to motivate high-risk patients to take steps to improve their prognosis.

### *Retinal Arteriolar Narrowing and Coronary Heart Disease Risk in Women*

Women, more than men, exhibit symptoms of ischemic heart disease without having significant coronary artery obstruction, and it is hypothesized that microvascular dysfunction plays an important role in the development of myocardial ischemia and CHD in women. To investigate this hypothesis, researchers examined the association between retinal arteriolar narrowing, a marker of microvascular damage from hypertension and inflamation, and development of CHD in more than 9,600 men and women aged 51 to 72 years who participated in the Atherosclerosis Risk in Communities Study. They found that retinal arteriolar narrowing was related to increased risk of CHD in women, but not in men, thus indicating that microvascular disease may play a greater role in the risk of CHD in women than men. If these findings are confirmed, further investigation of the clinical implications of this

sex-based difference will be needed to determine the most effective prevention and treatment strategies of CHD in women.

### *Evaluation of Chest Pain in Women*

Building on the major findings of the Women's Ischemia Syndrome Evaluation (WISE) study, NHLBI sponsored an October 2-4, 2002 workshop focused on the diagnosis and pathophysiology of ischemic heart disease in women. The workshop presented a unique opportunity to chart a new course for applied research in CHD in women and to develop an updated educational message promoting the early recognition of CHD in women. Experts in CHD detection, research translation, and health communications reviewed findings from the WISE study and other women-focused CHD studies to develop a better understanding of the ways in which signs and symptoms of cardiac ischemia differ between men and women. Additionally, lessons in CVD protection, learned from hormone therapy trials, and the need for clinical practice to re-emphasize the importance of heart-healthy lifestyles were discussed. Recommendations from the workshop focused on key research findings that should be translated into clinical practice and strategies for educating health care professionals on the gender-specific differences in the presentation and diagnosis of ischemia. Workshop participants also outlined key elements of science-based education programs for the public that will focus on CHD symptoms specific to women.

### *Sex-based Differences in the Effect of Heart Failure Medicine*

Differences between men and women in the prognosis and treatment of heart failure are complex and not well understood. To explore variations in response to digoxin, a commonly used therapy, researchers conducted a subgroup analysis of data from the Digitalis Investigation Group trial. Overall, the trial had found that treatment with digoxin did not reduce mortality among patients with heart failure and left ventricular dysfunction. The subgroup analysis upheld this finding for men, but revealed that women receiving digoxin actually had a greater death rate than women receiving a placebo. Moreover, while hospitalizations for worsening heart failure were reduced by about one-third in men on digoxin, the magnitude of benefit in women was much smaller. These findings suggest that the use of digoxin therapy for women with heart failure should be reexamined and that sex-specific treatment guidelines may need to be considered.

## Update on NIH Women's Health Initiative

The Women's Health Initiative (WHI) is a 15-year study of strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in postmenopausal women. Launched by NIH in 1991, WHI has been administered by NHLBI since FY 1998. More than 160,000 women from across the United States, who were between 50 and 79 years of age at the time of their recruitment, are enrolled in its clinical trials and observational study; almost 30,000 of these volunteers are minorities. The clinical trial component consists of three prevention studies examining the effects of postmenopausal hormone therapy on CHD, osteoporosis, and breast cancer risk; the effects of a low-fat diet in preventing breast and colorectal cancers and CHD; and the role of calcium and vitamin D supplementation in preventing fractures. The observational study component is identifying predictors of disease. In addition, a community prevention component, described below, focused on health promotion strategies.

### *Postmenopausal Hormone Therapy Trial*

The hormone trial consists of an estrogen-plus-progestin component for women who have a uterus, and an estrogen-alone component for women who have undergone a hysterectomy. In spring of 2000 and again in 2001, the independent WHI Data and Safety Monitoring Board (DSMB), which oversees the safety of all study participants, recommended that NHLBI inform all hormone trial participants about some initial

findings that were not foreseen at the outset of the study. Specifically, women who were taking hormones had somewhat more CVD events (heart attacks, strokes, and blood clots in the legs and lungs) than women taking a placebo. Since the actual number of women experiencing any one of these events was small, the increases did not exceed the statistical boundary for stopping the trial. Participants received letters outlining the facts and were invited to attend a full briefing at their clinical center. Very few women dropped out as a result of this information.

Then, in light of data reviewed at its regularly scheduled meeting on May 31, 2002, the DSMB recommended that the estrogen-plus-progestin trial be stopped. Compared with women taking a placebo, study participants taking estrogen plus progestin experienced higher rates of invasive breast cancer, and their elevated risks of heart attack, stroke, and blood clots that had been noted earlier were still present. Although the women taking the hormones had a lower incidence of colon cancer and fewer hip fractures, the overall balance of risks and benefits was unfavorable. In response to the DSMB recommendation, NHLBI and WHI investigators developed informational materials for WHI participants, and on July 9, 2002, the estrogen-plus-progestin trial was halted. Its participants were sent letters informing them of the results and asking them to stop taking study medications. They were offered further counseling by their clinical centers, and they will continue clinic visits so that their health outcomes can be followed. WHI participants in other study components were sent a letter summarizing the estrogen-plus-progestin trial findings and encouraging them to continue participation in the study.

### *Community Prevention Study*

The Community Prevention Study was a collaborative effort between NIH and the Centers for Disease Control and Prevention (CDC). It comprised 11 separate studies conducted at seven of the CDC's university-based Prevention Research Centers. The activities, which began in October 1995 and continued for 5 years, touched the lives of over 18,000 women.

This component of WHI focused on community-based prevention strategies to enhance adoption of healthful behaviors, with a particular emphasis on women of diverse races, ethnic groups, and socioeconomic strata. Its goals were to develop and carefully evaluate model programs suitable for dissemination and establishment in a wide range of communities across the United States. Areas of interest included CVD peer support in African American women; environmental factors and physical activity in women; osteoporosis prevention, education, and outreach; diabetes care in minority women; methods to enhance physical activity in women; and determination of attitudes of women regarding surgical menopause and postmenopausal hormone therapy.

### *Women's Angiographic Vitamin and Estrogen Trial*

Previous findings from the Heart and Estrogen/Progestin Replacement Study (HERS), supported by industry, raised doubts as to the effectiveness of postmenopausal hormone therapy for secondary prevention of CVD events. Recent results from the NHLBI-sponsored WAVE trial reinforced those findings and indicated that antioxidant vitamins, too, are ineffective in reducing future CVD events. In the WAVE trial, more than 400 postmenopausal women with CHD were randomly assigned to receive hormone therapy or a placebo and high doses of vitamins C and E or a placebo. Angiograms were performed when women entered the study and approximately 3 years later to evaluate the progression of blockages in the blood vessels of the heart. Researchers analyzed the results using a ranking system that incorporated both clinical events, such as heart attack and death, and angiographic change, a predictor of future CHD events. They found, much to their surprise, that the women who took both hormones and vitamins had the highest death rate while

the women who took placebos had the lowest death rate. Furthermore, participants taking hormones and vitamins experienced as much or more progression of their CHD as participants taking placebos. These findings add to the growing body of evidence that postmenopausal hormone therapy is not helpful in preventing or treating heart disease and also provide new evidence of the absence of benefit from high-dose antioxidant vitamins.

### *Bone Loss after Discontinuing Postmenopausal Hormone Therapy*

Given the new recommendation to limit long-term use of postmenopausal hormone therapy, many women and their health care providers are concerned about bone loss following discontinuation of the therapy. Results from a followup of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial found that bone is not lost at an accelerated rate after hormone use is discontinued, but rather that the rate of loss appears to revert to that of women who have not used hormones. The study also found that the gains in bone mineral density, associated with postmenopausal hormone therapy use, are realized during the first 3 years of treatment.

### *Postmenopausal Hormone Therapy Fact Sheet*

Choosing whether or not to use postmenopausal hormone therapy can be one of the most important health decisions women face as they age. To help women weigh their personal risks and benefits of taking hormones, the NHLBI developed a 20-page fact sheet. In easy-to-understand language, it explains research findings, issues related to long- and short-term hormone use, risk factors for heart disease, and alternatives to hormone therapy. The fact sheet also provides information on risk factors for stroke, osteoporosis, and cancers of the breast, uterus, ovaries, and colon/rectum; tips for talking with health care providers; and resources to contact to learn more about hormone therapy-related topics.

### *Fish Consumption and Risk of Heart Disease and Stroke*

Previous studies have suggested that ingestion of fish oil (which contains omega-3 fatty acids) may reduce the incidence of sudden cardiac death, and researchers have found evidence that a diet rich in fish also decreases the likelihood of experiencing a stroke. Recent data from the Nurses Health Study provide additional evidence of the benefits of eating fish. One analysis found that higher consumption of fish containing omega-3 fatty acids was associated with a lower risk of CHD events and, especially, CHD death. The other study revealed that women who ate fish two to four times per week had half the incidence of thrombotic stroke (stroke caused by blood clots) and the same risk of hemorrhagic stroke (stroke caused by bleeding in the brain) as women with similar CVD risk factors who ate fish less than once a month. These results suggest that increased consumption of fish could be a cost-effective, population-wide approach to preventing CHD deaths and reducing the risk of heart disease and stroke. Findings from these and other studies have already led the American Heart Association to recommend that individuals include at least two fish meals per week in their diets.

## Interventions to Improve Fitness

Although physical inactivity is an important risk factor for many prevalent diseases and conditions, including CHD, hypertension, diabetes, and obesity, the majority of U.S. adults fail to complete the recommended 30 minutes of sustained physical activity on 5 or more days per week. The Activity Counseling Trial (ACT) tested the effects of two physical activity counseling programs conducted in primary medical care settings for sedentary patients and compared them with the currently recommended intervention of physician advice and educational materials. One program consisted of counseling sessions at the time of physician visits plus interactive mail, such as monthly newsletters and mailed feedback. The second program comprised the same components

plus regular telephone counseling and behavioral classes. The cardiorespiratory fitness of the women in both counseling programs significantly increased over a 2-year period. Although the two programs varied in intensity (an average of 22 contacts totaling 3 hours versus an average of 44 contacts totaling 9 hours over 2 years), they were equally effective. In contrast, no improvement in fitness levels was observed after 24 months for the women who received physician advice only. All three interventions in men were associated with a significant increase in fitness 6 months after the study began, but the improvements were not sustained, and all groups of men reverted to the initial fitness level by the end of the study. Since the ACT counseling interventions were successful in improving the cardiorespiratory fitness of women, but not of men, these types of interventions appear to be best suited for inactive women interested in increasing their physical activity.

### *Physical Inactivity and Weight Gain among Adolescent Girls*

Obesity in children and adolescents has been increasing, particularly over the past 20 years, and low levels of physical activity may be a reason for this trend. To understand changing patterns of physical activity during adolescence, researchers tracked the exercise habits of girls starting when they were 9 or 10 years old and ending 10 years later. They found that by the time the girls were 16 or 17 years old, 56 percent of black girls and 31 percent of white girls reported no habitual leisure-time physical activity. For girls of either race, a higher body mass index (a measure of body weight adjusted for height) at the beginning of the study was associated with a steeper decline in activity levels, with the heaviest girls experiencing the greatest declines. Additional factors that predicted lessening amounts of physical activity included pregnancy, smoking, and lower levels of parental education.

These findings suggest that intervention programs to increase physical activity in girls should start by 12 to 13 years of age, when the precipitous drop in physical activity occurs. NHLBI is developing and testing such a program in its Trial of Activity for Adolescent Girls (TAAG), which is using a coordinated school- and community-based multicomponent intervention in middle-school girls. The intervention will provide skills building, supportive environments, and opportunities for participation in physical activity during and outside of the school day. It will be implemented for 2 years during the 7th and 8th grades. The two primary outcome measures will be cardiorespiratory fitness and self-reported levels of participation in moderate and vigorous physical activity in and outside of school.

A second NHLBI initiative, the Girls Health Enrichment Multi-Site Studies (GEMS), is developing and testing promising interventions to reduce weight gain in black pre-pubertal girls. During the first phase of the program, several interventions addressing diet, physical activity, and psychosocial and familial influences were developed. The efficacy of those interventions will be evaluated during the second phase, which is currently under way. Examples of activities offered in one intervention include an after-school dance program and a family-based program to reduce use of television, videotapes, and video games. Future research plans include adapting the most efficacious interventions for use with other populations of black girls, as well as members of other racial and ethnic groups.

### *Exercise for Heart Health*

New research has shed light on how frequently women should exercise in order to reduce their risk for CHD, what the duration and intensity of each exercise session should be, and whether exercise benefits women who are at higher-than-normal risk for CHD. Researchers found that participating in even mild-to-moderate levels of physical activity decreased a woman's risk of CHD. Walking at least 1 hour per week at a pace of 2 miles per hour was beneficial compared with no regular walking. Moreover, time spent walking was more predictive of lower CHD risk than walking pace. These

results apply not only to women with average risk of CHD, but also to those who are at high risk because they smoke, are overweight, or have high blood cholesterol levels. Although women should engage in physical activity at least 30 minutes per day on most days of the week (according to federal guidelines), this study shows that even a modest amount of exercise is beneficial.

### *Desire for Thinness and Smoking Initiation*

Cigarette smoking has long been known to be a preventable risk factor for CVD and respiratory disease, yet despite substantial public health efforts, many adolescents smoke. A better understanding of the environmental, social, and psychological risk factors associated with smoking is needed to help design more effective approaches to reducing teenage smoking. A 10-year cohort study of more than 2,300 girls found that concerns about body weight and a drive to be thin increased the risk that a girl would become a daily smoker by the age of 18 or 19 years. A drive for thinness among black girls had not been previously reported. The study found that other factors early in life also increased the risk of later smoking, including experiencing stress, having a parent with no formal education beyond high school, being from a one-parent household, drinking alcohol, and performing or behaving poorly in school. The degree to which each factor increased the risk varied between black and white girls. By helping to identify key factors involved in a girl's decision to smoke, the study may lead to more effective smoking prevention strategies, including healthy ways for teenage girls to control their weight and cope with stress.

### *Angiogenesis in Primary Pulmonary Hypertension*

Primary pulmonary hypertension (PPH) is a rare and debilitating lung disease of unknown cause that disproportionately affects women of childbearing age. It is characterized by progressive elevation of pulmonary artery pressure that ultimately leads to right-heart failure and death. The lungs of patients with PPH contain unique structures called plexiform lesions. They involve cells that pile up and cluster within the blood vessels, completely obstructing them. Using microarray technology to analyze DNA patterns, investigators discovered a distinctive pattern of gene expression and cell growth behavior that characterized PPH lung tissue. Plexiform lesions isolated from lungs of PPH patients produce vascular endothelial growth factor at high amounts, which causes abnormal growth of blood vessels by a process called angiogenesis. They also produce high amounts of membrane protein that is found in endothelial and smooth muscle cells and is important in cell signaling and transport. The concept that abnormal proliferation and disorderly growth of endothelial cells within plexiform lesions occurs in PPH due to altered gene expression opens the way for new studies to investigate the causes of PPH and to identify new treatment strategies. Testing of anti-angiogenesis or anti-cancer agents may lead to more effective treatments or even a cure for PPH.

### *Inhaled Steroids and Bone Loss in Women with Asthma*

Premenopausal women who use inhaled corticosteroids to treat persistent asthma may experience accelerated bone loss in the hip compared with those who do not use inhaled steroids, according to results of an NHLBI-supported study of 109 women aged 18 to 45 years. Researchers found that the effect of the inhaled steroids was directly related to the dose – that is, the bone density loss increased with the number of puffs per day – and persisted throughout the 3-year study. Although the yearly losses were small, the long-term cumulative effect could ultimately put some women at high risk of hip fracture. Because poor asthma control can lead to complications and diminished quality of life, use of inhaled steroids is still recommended since it provides the best daily control of persistent asthma. However, women are encouraged to work with their doctors to develop a comprehensive treatment plan that includes the lowest dose of inhaled steroids needed to control their asthma symptoms, as well as measures, such as adequate calcium intake, to ensure good bone health.

## Sarcoidosis

Sarcoidosis is a systemic disease involving multiple organ systems. Its cause is unknown, but appears to involve a combination of genetic predisposition and environmental exposure that instigates invasion of normal tissue by inflammatory cells called granuloma. Although it occurs in both sexes and all races, sarcoidosis is most prevalent among young black women and women of Irish, Scandinavian, German, or Puerto Rican heritage. Investigators in A Case Control Etiologic Study of Sarcoidosis (ACCESS), which included a large group of patients and their relatives, found that parents and siblings of sarcoidosis patients were nearly six times more likely to develop sarcoidosis than the general population. Data also indicated that white patients were more likely to have relatives with sarcoidosis than black patients. ACCESS researchers also found that age, gender, and race influenced organ involvement: sarcoidosis that involved an organ other than the lung was more likely to occur in black patients, younger patients, and female patients.

While this research helps to provide a clearer picture of how sarcoidosis affects different types of patients and different organs, much remains to be learned. To encourage scientific and clinical advances, NHLBI sponsored a working group on Future Directions in Sarcoidosis Research in August 2002. Investigators with expertise in pulmonary diseases (especially sarcoidosis), genetics, identification of infectious agents, immunology, molecular biology, and inflammatory bowel disease participated. They reviewed current knowledge about the disease, identified gaps in research, pinpointed obstacles to progress, and explored other areas of research that may be applicable to sarcoidosis. Also in attendance were representatives from patient support groups and other organizations concerned about sarcoidosis. Working group recommendations included identifying genetic factors involved in sarcoidosis and providing better guidance to primary care physicians to improve the management of patients with the disease.

## Lymphedema

Lymphedema can compromise quality of life severely, as it diminishes the physical, psychological, and social functioning of its victims. Unfortunately, currently available interventions provide little relief, and little in the way of new therapies is on the horizon. To stimulate investigator-initiated research on the pathogenesis of primary and secondary lymphedema and to develop more specific and effective therapies, NHLBI and three other NIH components issued a program announcement in December 2000. In addition, the Trans-NIH Coordinating Committee on the Lymphatic System has been formed to review research needs and expand collaboration on lymphatic research among NIH components and with outside groups, including public interest organizations. This concerted effort will help construct a strategic research agenda that is expected to lead ultimately to development of improved therapeutic interventions for women suffering from lymphedema.

## Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare lung disease that primarily affects young women; it causes shortness of breath, chest pain, cough and, ultimately, death from respiratory failure. Lung transplantation is the only therapy currently available for LAM patients with end-stage lung disease. However, the recurrence of LAM in transplanted lung has been documented in several LAM patients, and researchers have found that the cells forming the LAM lesions in grafted lungs originated from the patients, not from their donors. Thus, it appears that LAM cells, though benign in appearance, can migrate or metastasize into a transplanted lung. New studies also indicate that tuberin, the product of the TSC2 gene that normally suppresses tumor formation, has a role in cell adhesion and migration. The findings may have broad significance, beyond LAM, for understanding how human cells migrate and metastasize.

NHLBI scientists reported that women with LAM have a high prevalence of meningioma, a type of brain tumor. The meningiomas were detected in an ongoing study of the natural history of LAM being conducted by the NHLBI intramural program. In an effort to determine whether patients with LAM also showed signs of tuberous sclerosis, a rare genetic neurological disorder associated with LAM, scientists performed magnetic resonance imaging (MRI) and computed tomography (CT) brain scans on 250 women with LAM. Unexpectedly, the MRI scans revealed that eight patients had meningiomas – a rate that far exceeds the 1 in 20,000 expected in the general population. According to the investigators, it is not clear whether the meningiomas are caused by LAM itself, by hormonal treatments for the disease, or by a combination of the two. Based on these findings, study investigators recommend that LAM patients be screened for meningiomas, and that patients with meningiomas have yearly MRIs to evaluate tumor growth. Surgery is the preferred treatment for these tumors, which grow slowly and rarely spread to other parts of the body.

In FY 2002, recruitment for the LAM registry project was completed with a total of 225 LAM patients enrolled. The registry is jointly funded by NHLBI and the NIH Office of Research on Women's Health. Its goal is to identify a cohort that can be used to characterize the clinical features and natural progression of LAM, assess the efficacy of lung transplantation, provide lung tissue for future research, and participate in future therapeutic trials.

## Exposure to Domestic Violence and Asthma Development

Since December 2000, NHLBI has supported an investigator-initiated project titled "Chronic Life Stress and Incident Asthma in Adult Women." This large-scale observational study is using the Nurses Health Study II cohort (N=64,000) to explore the hypothesis that women exposed to high-level chronic stress in the form of intimate domestic violence are at greater risk of developing asthma than women without such exposure. A substudy is examining the association between exposure to violence and various measures of neuroendocrine and immune function.

## Cardiac Function of Children Born to Women with HIV Infection

Results from a 5-year pediatric AIDS study supported by NHLBI and the National Center for Research Resources demonstrated that infants born to HIV-infected mothers had significantly worse cardiac function than infants whose mothers were not infected. Cardiac abnormalities were noted irrespective of an infant's HIV status, although the hearts of HIV-positive infants tended to be larger and less efficient. Researchers hypothesize that the intrauterine environment may play an important role in the development of heart abnormalities, perhaps through factors such as maternal nutrition and the inflammatory process triggered by HIV. These findings demonstrate the importance of being alert to the possibility of cardiac complications when caring for children born to HIV-infected mothers and the need for careful followup of such children. In addition, they reinforce the U.S. Public Health Service recommendations to screen pregnant women for HIV, and to take steps to reduce transmission from mother to infant.

## Initiatives

*Program Announcement*

- **Pathogenesis and Treatment of Lymphedema**

  NHLBI issued this program announcement with the National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Cancer Institute to stimulate research to identify the developmental, molecular, and cellular defects that contribute to lymphedema and lead

to effective therapeutic interventions to treat both primary and secondary lymphedema. Lymphedema may appear at birth or arise from surgery, radiation, or the presence of a tumor in the area of lymph nodes. Knowledge gained from this research will help to enhance the lives of women suffering from lymphedema by improving early diagnosis and the choice and timing of treatment. (PA-01-035; FY 2001)

*Workshops and Working Groups*

- **Obesity and Asthma**
  **July 15-16, 2002**
  Bethesda, Maryland

- **Future Directions in Sarcoidosis Research**
  **August 23, 2002**
  Bethesda, Maryland

## National Human Genome Research Institute

The National Human Genome Research Institute (NHGRI) leads the National Institutes of Health's contribution to the International Human Genome Project (HGP), which has as its primary goal the sequencing of the human genome. As this project nears successful completion, the NHGRI's mission has expanded to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease. NHGRI continues to develop research tools that will accelerate scientists' understanding of the molecular basis of disease and ultimately lead to improved diagnostic, prevention, and treatment strategies.

NHGRI also supports research to study the ethical, legal, and social implications of genomic research. NHGRI has designated five major goals which include: 1) examine issues surrounding the completion of the human DNA sequence and the study of human genetic variation; 2) examine issues raised by the clinical integration of new genetic technologies and information into health care and public health activities; 3) examine issues raised by the integration of knowledge about genomics and gene-environment interactions into non-clinical settings; 4) explore ways in which genetic knowledge interacts with a variety of philosophical, theological, and ethical perspectives; and 5) explore how socioeconomic factors, gender, and concepts of race and ethnicity influence the use and interpretation of genetic information, the utilization of genetic services, and the development of policy.

Through its extramural and intramural research programs, NHGRI contributes to identification of genes involved in human disease and to the study of the functions of these genes and their products. HGP provides data, material resources, and technology that will improve the ability of scientists to conduct biological research rapidly, efficiently, and cost effectively. This infrastructure has already dramatically accelerated the study of human inherited disease. In the laboratories of the Division of Intramural Research, with the tools produced by HGP, scientists are developing and using the most advanced techniques to study the fundamental mechanisms of inherited and acquired genetic disorders.

### Accomplishments

#### *Structural and Functional Analysis of Mammalian Chromosomes: Mapping and Sequencing*

A central activity of the ongoing Human Genome Project is the mapping and sequencing of mammalian genomes. The major aims of the Physical Mapping Section are to construct integrated and annotated physical maps of mammalian chromosomes, to facilitate the sequencing of the corresponding DNA, and to utilize the resulting information for studying important biological problems. This project initially focused on the ~170-megabase human chromosome 7, which as a result found a tumor suppressor gene relevant to multiple forms of cancer, including breast and ovarian cancer. There are several ongoing projects aiming to study regions of chromosome 7

associated with human genetic disease. These efforts have resulted in the identification of the Pendred syndrome gene, a gene responsible for cerebral cavernous malformations, and a long sought-after tumor suppressor gene. These findings have opened up numerous new avenues of biological study relating to the structure and function of the genes and their encoded proteins, including the development of mouse models for these genetics disorders.

### *Microdissection Technology and Molecular Probe Development*

This study focuses on development and implementation of genomic technologies for the study of cancer and other complex diseases. Older technologies are largely inadequate to deal with complex changes in the structure of the genome and alterations of gene expression occurring during oncogenesis. Improvements in technology for placing molecular probes onto the cytogenetic, genetic, and physical maps now enable the large-scale characterization of the structure and function of the disturbed cancer genome with the following approaches: 1) high-resolution positional reagents and visualization methods encompass microdissection technology, as well as high-resolution fluorescence and multicolor *in situ* hybridization (FISH). These methods are being applied to the analysis of previously intractable problems in cancer cytogenetics; 2) the use of cDNA microarrays has been developed to allow simultaneous evaluation of cellular mRNA levels for thousands of genes, enabling sensitive comparisons of gene transcript levels between cells from various pathological stages; and 3) evaluation of results obtained with the above technologies can be examined with the new approach of tissue microarrays, allowing the simultaneous examination of copy number change and gene expression in thousands of tumor specimens. Automated devices with bioinformatic support enable the unprecedented acquisition of vast amounts of data linked to biological and clinical endpoints.

### *Biochip Technology Development*

One of the many outcomes of the Human Genome Program has been the need to develop high-throughput technologies for analyzing many genes and proteins at once. High-throughput biology research has now become routine with the development of cDNA microarray technologies that enable analyses of expression of thousands of genes at once. As useful as this is, the cDNA microarray data often only provide hypotheses to be tested in future studies or candidate target genes whose involvement in a biological or clinical process should be further investigated. Often the number of these genes to be tested is in the range of hundreds or thousands. The Translational Genomics Section is developing novel tools, technologies, and bioinformatic solutions for validating functional genomics data of cancer. The following four approaches are utilized: 1) results from different kinds of biochips are integrated to define the most important gene targets first. For example, researchers are utilizing data to prioritize genes that may be targets of a genetic rearrangement in cancer; 2) new high-throughput functional validation are being developed, such as the use of cell arrays to test the function of hundreds of genes at once on the cell phenotype; 3) pharmacogenomic profiling of cancer cell lines is performed to identify genes, pathways, and molecular mechanisms that are important for therapy response; and 4) researchers are developing bioinformatic tools to visualize gene expression data and integrate such data with results from other biochip technologies.

### *Functional Genomics of Cancer*

One of the major problems in cancer biology is to define the aberrant pattern of gene expression in tumor cells and to relate this pattern to specific genomic alterations which occur during tumorigenesis. To address this issue, a novel technology, cDNA microarray hybridization, is being applied to analyze the consequences of chromosome anomalies at the level of gene expression. Using a robotic device, it is possible to print thousands of DNA clones representing thousands of genes on a single

microscope slide. Fluorescent probes, prepared from any cell or tissue source of interest, are then hybridized to these arrays providing a large-scale view of gene expression. The ultimate goal of this project is genome-wide expression analysis. In this fashion, it is proving possible to profile individual diseases, and to determine the consequences of a given genetic alteration on gene expression. This technology is now being applied in model systems carrying alterations in tumor-specific genes affected by translocation, amplification, or inactivation, and in models which have distinct biological properties, such as metastasis or responsiveness to hormones. Information obtained from model systems is then integrated with gene expression profiles derived from the statistical analysis of expression data from tissue specimens. Recent efforts have applied this technology to pediatric cancers, adult sarcomas, melanoma, and breast cancers. Researchers at NHGRI have been able to establish the potential of microarrays for the accurate diagnosis of pediatric cancers and for distinguishing estrogen receptor-positive breast cancers from receptor-negative tumors. Using data from laboratory models, researchers have uncovered patterns of gene expression related to important clinical properties, such as estrogen sensitivity in breast cancer and metastasis in melanoma and osteosarcoma.

### *Molecular Cytogenetics of Gene Amplification*

Using DNA probes generated by chromosome microdissection, cDNA microarray analysis, and CGH findings, scientists at NHGRI have identified a series of chromosomal regions involved in human breast, ovarian, and prostate cancer. In order to isolate candidate target genes from these regions, scientists have developed technologies based on chromosome microdissection and integrated genome mapping, including DNA microarray analysis. These technologies are being utilized to isolate candidate genes from amplified regions in breast and ovarian cancer and sarcomas. The methodology previously described illustrates the importance of developing rapid techniques for the identification of genes amplified in a series of key human tumors. In addition to recognizing known sites of gene amplification, scientists have identified several previously unidentified genes amplified in breast, prostate, and ovarian cancers. The current focus is on breast cancer where candidate genes can function as coactivators of the estrogen receptor. Their mechanism of action will be studied with model systems based on gene transfer, gene inactivation, and biochemical techniques. In addition, scientists are developing a comprehensive database of amplified chromosomal regions in soft tissue and bone sarcomas using microarray-based CGH. This is a powerful approach for the identification of genes playing a causal role in disease genesis or progression and may provide novel prognostic markers, as well as therapeutic targets.

### *Linkage Analysis of Breast Cancer*

Researchers at NHGRI are working in a collaborative linkage study of breast cancer families that are not segregating mutations at either the *BRCA1* or *BRCA2*. Collaborators in Finland, Iceland, and Sweden are working together with NHGRI to add more families to the data set. Genotyping of several candidate regions and a genome-wide scan was performed on these samples. Linkage analysis is ongoing and a research paper was published in *Proceeding of the National Academy of Sciences* in early FY 00, suggesting the possibility of an additional locus (*BRCA3*) about 20 cM from the *BRCA2* locus. In FY 2001, additional mutation detection, genotyping, and analysis was performed to show that the positive linkage evidence at 13q21-22 is not likely to be due to contamination of samples by undetected *BRCA2* families. These results were presented at the International Union Against Cancer meeting in Beijing, China and at the 2001 meeting of the American Society of Human Genetics, and a paper is under review. Families that did not appear linked to *BRCA1*, *BRCA2* or this novel *BRCA3* locus were genotyped for a genome scan panel of marker loci. Several regions show some evidence for

linkage and the regions with the strongest evidence for linkage will be followed up with fine mapping studies. Results of these analyses were presented at the International Genetic Epidemiology Society meeting and at the 2001 meeting of the American Society of Human Genetics, and a manuscript is in preparation. Additional genotyping and analyses are expected in the future, and new families may be added to the dataset.

### *Regulation of a Critical Cell Cycle Checkpoint by the Breast Cancer Gene* BRCA1

Studies in the mid 1990s identified mutations in the *BRCA1* gene that are the major cause of hereditary breast and ovarian cancer, and also play a role in causing other cancers. Women inheriting these mutations have a significant lifetime risk of developing breast cancer and/or ovarian cancer. This discovery has led to a great deal of work aimed at better understanding the function of the *BRCA1* gene. Recent studies by researchers at NHGRI have helped establish that the *BRCA1* gene likely plays a role in the development of proteins that govern cell proliferation. When DNA, the genetic material of a cell, suffers damage, the cell normally stops reproducing and activates a complex of proteins that can find and repair the damaged sections of DNA. This "pause and repair" step prevents the replication of damaged cells. Unless the cell carries out this repair step, the damaged DNA can be propagated to daughter cells. If the DNA mistakes are located in critical places, this can lead to cell growth that causes cancer. Studies indicate that mutations in *BRCA1*, which normally acts as a quality control, can disrupt the ability of cells to recognize DNA damage and halt division. Such studies narrow where in the DNA damage pathway *BRCA1* functions. Research on *BRCA1* will also lead to greater understanding of the basic mechanisms of many cancers and of cell proliferation.

### *Genetics of Colon Cancer*

Hereditary non-polyposis colon cancer (HNPCC) is characterized by an autosomal dominant inheritance pattern of colorectal, uterine, urological, and upper gastrointestinal malignancies. Mutations in the DNA mismatch repair genes MLH1 and MSH2 have been identified in many families with HNPCC, but a significant fraction of families remain unexplained. Furthermore, in an effort to enhance the rapid detection of mutations in known mismatch repair genes, a novel high-density oligonucleotide array (HNPCC DNA Chip) was designed. Analyses are ongoing in patients with known mutations, as well as those with previously unidentifiable DNA mismatch repair gene mutations. Finally, researchers have identified a new member of the DNA mismatch repair gene family, MLH3, and have knocked out its mouse homolog (Mlh3) using homologous recombination technology. Both male and female Mlh3-/- are infertile. The Mlh3 protein immunolocalizes on meiotic chromosomes from mid-pachynema to diplonema, and to meiotic chiasmata during early diplonema. Surprisingly, Mlh3 is required for Mlh1 binding to meiotic chromosomes during later pachynema and diplonema. Many Mlh3-deficient male germ cells reach metaphase I, a phenotype distinct from that observed in the other MMR mouse null allele models, before succumbing to programmed cell death. In females, Mlh3-deficient ocytes exhibit meiotic aneuploidy before becoming inviable. These data provide evidence that Mlh3, Pms2, and Pms1, while structurally similar, interact with Mlh1 to create a combinatorial code specifying distinct functions for different DNA mismatch repair complexes in mammalian meiosis.

### *Outcomes of Education and Counseling for HNPCC Testing*

This study proposes to identify factors influencing decisionmaking regarding genetic testing for HNPCC and the psychological and behavioral outcomes of the testing process. Those with a cancer meeting selection criteria, or in a family with a known HNPCC mutation, complete a baseline questionnaire assessing knowledge, expectations, mood, attitudes, perceived cancer risk, cancer worries, family relationships, spirituality, and coping and health beliefs are assessed. Participants are then provided with educational and counseling

sessions focused on HNPCC; the availability of genetic testing; its risks, limitations, and potential benefits; and cancer screening recommendations for families with HNPCC. Participants are presented with a choice of whether or not to undergo genetic testing. Those choosing genetic testing undergo a separate informed consent specifically focused on the process of genetic testing and the potential risks, benefits, and limitations of genetic testing. Psychological and behavioral outcomes are reassessed through telephone questionnaire at 6 and 12 months following risk notification or the decision not to undergo testing. For those receiving genetic test results, notification occurs in person along with discussion of available surveillance options. Follow-up counseling and support are provided for all individuals participating in the study. First-degree adult relatives of individuals with identified HNPCC germline mutations are also offered participation in the study. In the process of offering testing to this population, researchers have collected a growing number who do not have mutations identified, however, clearly have inherited forms of colon cancer. This finding is leading to the development of a protocol which explores the impact of inconclusive results on family communication and cancer screening practices.

### *The Genetics of Folate and Vitamin B12 Metabolism Related to Neural Tube Defects*

A group of NHGRI researchers is focused on defining changes in the genes that underlie inherited susceptibilities to common birth defects, such as spina bifida (a form of neural tube defect). It is known that inadequate folate in the diet can increase a women's risk of having a child with neural tube defects. Inherited variation in the genes involved in folate metabolism may also lead to an increase in risk. Folate genes are also involved in the methylation of DNA and brain function. NHGRI researchers are searching for variants in genes related to folate, methionine, and homocysteine metabolism. Individuals affected with neural tube defects, such as spina bifida, are being tested for these variants to identify genes associated with disease risk. In the past year, more than 15 genes have been tested for variants that might perturb folate metabolism and, therefore, be associated with an increased risk of having a child with a neural tube defect. These researchers have found that variants in one of these genes, TC2, appear to affect the levels of vitamin B12 in the maternal circulation during pregnancy. This finding may be related to birth defects and also may help to explain why some elderly individuals become anemic and suffer neurological symptoms from vitamin B12 deficiency. They have also found that mothers carrying a specific variant in a second gene, MTHFD1, have a 50 percent increased risk of bearing a child with a neural tube defect. This previously undescribed variant may be responsible for up to 25 percent of all neural tube defects in the United States. Approximately one in five individuals in the population carry one of these risk factors. These genes have been recreated in the laboratory and are currently being used as an experimental system to determine exactly how these variants alter the function of these proteins. Detailed knowledge of the function of these two genes will add to the understanding of neural tube defects and potentially help guide public health policy in the area of nutritional supplementation.

## Initiatives

In FY 2001 and 2002, the Ethical, Legal, and Social Implications (ELSI) Research Program funded a number of grants focused on issues of particular concern to women.

- **BRCA1** ***Testing in a Large African American Kindred***

  This project proposes to address a critical gap in the literature regarding cancer susceptibility testing by examining utilization of genetic counseling and testing, and behavioral and psychosocial responses to the receipt of genetic information among a large, extended African American kindred linked to a specific *BRCA1* mutation. A prospective study of approximately 150 members and their spouses/partners will be

performed over a 4-year period. Genetic education and counseling will be provided when testing is offered and at the results session. Data will be collected through detailed questionnaires, before and after testing, on a wide range of behavioral and psychosocial measures. The specific aims are to: 1) identify predictors of the decision to choose or decline genetic counseling and testing services; 2) examine the attitudes towards *BRCA1* testing among spouses/partners of adult female and male kindred members and determine how they influence *BRCA1* testing decisions; 3) evaluate the effects of genetic counseling and testing for *BRCA1* mutations on psychological and social well being of kindred members and their spouses/partners; 4) identify how genetic counseling and testing, and knowledge of *BRCA1* mutation carrier status influences utilization of health services and health behaviors among adult women and men; and 5) describe facilitators and barriers to genetic counseling and testing and utilization of screening and preventive measures for *BRCA1* mutation-linked cancers.

- ***Computer Education for Breast Cancer Genetic Testing***

  The long-term goal of this project is to improve patient understanding about breast cancer risk and genetic testing. This project will conduct a clinical trial to evaluate the effectiveness of a CD-ROM, called "Counseling by Computer: Breast Cancer Risk and Genetic Testing," aimed at educating women about breast cancer risk, and options and implications of genetic testing. This project will take 36 months to complete and involves two specific aims: 1) to evaluate the effectiveness of the CD-ROM at educating women about breast cancer risk, and the options and implications of genetic testing through a randomized, pretest-posttest control-group, crossover trial of 210 patients at three study sites. (In preparation for this trial, 40 women [at least one-fourth of whom are minorities] will be recruited from a general internal medical clinical and breast cancer support group to evaluate the usability and effectiveness of the CD-ROM. This feedback will be used to refine the CD-ROM and study instruments); and 2) to evaluate the impact of a prior computer-based educational session on subsequent interactions between patients and genetic counselors. Comparisons will be made between those educated by a genetic counselor alone, and those educated by a computer prior to their session with a genetic counselor, by measuring: the amount of time spent with a genetic counselor; the quality and quantity of questions directed to the genetic counselor; patient's and genetic counselor's satisfaction; and perceived effectiveness of the counseling session.

- ***Attitudes about Hereditary Breast Cancer***

  This project will examine the knowledge, attitudes, and beliefs of women from diverse backgrounds concerning the etiology of familial breast cancer. Twenty-five women with suspected hereditary breast cancer from diverse ethnic/racial, socioeconomic, and geographic backgrounds will participate in qualitative interviews designed to assess knowledge, beliefs, and attitudes regarding the etiology of familial breast cancer. Based on themes from these interviews, a larger survey exploring these issues will be designed. Approximately 400 women will complete this survey of their knowledge and attitudes concerning hereditary breast cancer etiology. The influence of sporadic versus suspected hereditary breast cancer, ethnicity/race, socioeconomic status, and urbanicity will be assessed using a multivariant ANOVA. Finally, the results of both the qualitative interviews and the larger-scale survey will be used to design and evaluate educational strategies for women at risk for hereditary breast cancer and their clinicians.

- ***Process and Outcomes of* BRCA1/2 *Clinical Testing***

  Intensive evaluation of women undergoing testing for *BRCA1/2* germline mutations has been conducted, and has demonstrated that women participating in genetic testing through highly structured and supportive programs, conducted largely at academic institutions, have generally done well through the process and in the long term. In the United States, the vast majority of *BRCA1/2* testing is now performed by a single commercial clinical laboratory (Myraid Genetics Laboratory [MGL]), with the test available to women directly through their physicians. A substantial portion of testing is now accomplished through this mechanism, but the extent to which clinical testing as it is now performed approximates the intensive support provided in the structured research programs is unknown. The outcomes of women tested clinically outside of academic centers have not yet been studied. This project will explore areas in which data have been lacking, using the unique resource of the unselected population of women tested through MGL. The project involves surveys of women who have provided specimens to MGL for *BRCA1/2* analysis, their providers, and control physicians. The information learned from this project may help to create a standard for the optimal conduct of *BRCA1/2* testing, and potentially for other predisposition testing as well.

## National Institute of Allergy and Infectious Diseases

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

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

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

STDs are critical global and national health priorities because of the devastating impact on women and infants, and the interrelationships with HIV/AIDS. STDs and HIV are linked by biological interactions and infections occurring in the same populations. Infection with certain STDs can increase the risk of HIV acquisition and transmission, as well as alter the course of disease progression. Recent studies indicate

that the more prevalent non-ulcerative STDs (chlamydial infection, gonorrhea, bacterial vaginosis, and trichomoniasis), as well as the ulcerative diseases (genital herpes, syphilis, and chancroid), increase the risk of HIV transmission by at least two- to fivefold. In addition, STDs can cause long-term health problems, particularly in women and infants. Some of the sequelae of STDs include:

- Pelvic inflammatory disease
- Infertility
- Fetal wastage
- Low birth weight
- Congenital/perinatal infection
- Chronic conditions, such as neurosyphilis, tubal, or ectopic pregnancy
- Cervical cancer
- Increased risk of HIV infection
- Perinatal or congenital infections in infants born to infected mothers

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

## Accomplishments

### *Infectious Diseases*

#### Acquired Immunodeficiency Syndrome (HIV/AIDS)

The number of HIV-infected women in the United States is steadily growing. The epidemic among women began expanding in the mid-1980s, and its effects are being felt as more HIV-infected women develop AIDS. Women develop different HIV-related complications than men, such as recurrent yeast infections, pelvic inflammatory disease, genital ulcer disease, severe herpes infections, human papillomavirus infections, cervical tumors, and vulvar and vaginal carcinomas.

NIAID fosters research on: 1) the natural history of HIV/AIDS disease in women; 2) the mechanisms of HIV/AIDS infection in women; 3) the virologic, immunologic, and hormonal factors that play a role in HIV/AIDS acquisition and disease progression in women; 4) the impact of new drugs on HIV/AIDS disease; and 5) the role of substance abuse, sexual behavior, and psychosocial factors.

NIAID is studying the unique features of HIV/AIDS in women through two cohort studies: the Women's Interagency HIV Study (WIHS) and the Women and Infants Transmission Study (WITS). The WIHS is a multicenter, prospective cohort study established in August 1993 to study the natural history of HIV infection in women. It conducts investigations of biological and psychosocial aspects of HIV infection in women. Launched 8 years ago, the WITS studies the pathogenesis of disease progression in women and children, many who are on therapy, and evaluates the factors related to perinatal HIV transmission and disease progression in women and children.

Clinical protocols are either underway or planned to address woman-specific treatment research questions. These studies have been conducted through three NIAID-supported clinical research mechanisms: the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Each of these networks is committed to ensuring the inclusion of HIV-infected women in trials; conducting research on HIV-associated conditions that specifically affect non-pregnant and pregnant women; and identifying real and potential barriers to the recruitment and retention of women into clinical trials.

Within the Adult ACTG, there is a Women's Health Committee formed to optimize the design, conduct, and analysis of clinical trials, and to maximize the recruitment and retention of women into

clinical trials. This committee strives for a goal of at least 20 percent female enrollment in antiretroviral-naïve trials, and at least 15 percent in recovery and opportunistic infection trials to learn more about whether there are gender differences in treatment and response.

The FY 2001 figures for women in therapeutic clinical trial networks are as follows:

- *Adult ACTG*: 17 percent (20 percent when including women-specific studies)
- *Pediatric ACTG*: 51 percent
- *CPCRA*: 20 percent

Currently, a total of 2,607 HIV-infected and -uninfected women are enrolled in the WIHS. Of those, 56 percent are African American, while more than 25 percent are Hispanic. WITS enrolled a total of 158 women in FY 2002 (10/01/01 to 09/30/02), 50 percent of whom were African American, while 36.7 percent were Hispanic.

NIAID scientists continue to study HIV epidemiology and transmission in collaborative studies of high-risk groups in Uganda, Congo, Zambia, Zimbabwe, South Africa, India, China, and the United States. Many important findings have resulted from this ongoing research. For example, scientists examined the association between HIV viral load and fertility among women in Uganda and found that the median viral load in HIV-infected pregnant women was significantly lower than in HIV-infected women who could not become pregnant. Statistically significant reductions in pregnancy were observed in women with viral loads greater than 100,000 copies/ml, suggesting a strong negative effect on women's health and fertility.

Scientists have also developed a model to determine the effect of antiretroviral therapy or vaccines in the reduction of HIV incidence in developing countries. Using DHHS treatment guidelines in the model, antiretroviral therapy alone will have a negligible effect on the spread of the epidemic, although it will provide beneficial effects in many other ways for the individual and the population. In contrast, a preventive vaccine, or a therapeutic vaccine that reduces viral load, will dramatically reduce HIV transmission and HIV incidence.

NIAID established two global research networks for HIV vaccine and prevention research. The HIV Vaccine Trials Network (HVTN) develops and tests preventive HIV vaccines, and the HIV Prevention Trials Network (HPTN) explores alternative measures, besides AIDS vaccines, that may be able to block or reduce infection with HIV. The HVTN and HPTN strengthen NIAID's capability to discover new and better measures to protect people, especially women and children, from HIV infection. Other accomplishments include:

**Therapeutic Research**

- Awards were made to renew funding for the *Pediatric AIDS Clinical Trials Group* in March 2002. The 5-year awards will support 18 university-based clinical trial sites, a statistical and data management center, and a coordinating and operations center. The network will have a greater focus on both adolescent and international pediatric research.
- The *Women's Health Committee of the Adult AIDS Clinical Trials Group* was initially formed to optimize the design, conduct, and analysis of clinical trials, and to maximize the recruitment and retention of women into clinical trials. The committee recently updated its research agenda for all three areas of the Adult ACTG research scope: HIV disease, complications of HIV infection, and immunologic impact of HIV infection. The committee also elicited proposals from AACTG sites to increase enrollment of women into clinical trials. The group will fund at least four of these proposals for implementation at the sites and, if successful, will broaden implementation of these strategies group wide.
- The *Women's Health Committee of the AACTG*, in conjunction with the *Pediatric AIDS Clinical Trials Group*, has developed a scientific agenda to promote research

in the area of gender and sex-specific research in HIV/AIDS. Several research protocols are now open or in development in the following areas:

- *Pharmacokinetics of contraceptives* (Depo Provera) in the setting of highly active antiretroviral therapy (HAART) (A5093).
- *Pharmacokinetics of an estrogen patch* for HIV-infected women on lopinavir/ritonavir (5188).
- *Antiretroviral therapy in pregnancy (P1022):* Comparison of a protease inhibitor regimen and a protease inhibitor-sparring regimen in pregnancy.
- *Gender differences in HAART responses evaluated in large naïve treatment trials (A5095):* Comparison of three protease inhibitor-sparing regimens for the initial treatment of HIV infection; A5142: Comparison of LPV/r + EFV vs. LPV/r + D4T (or ZDV) and 3TC vs. EFV plus D4T (or ZDV) and 3TC for initial therapy of HIV-1 infection.
- *Prospective cohort study of mother-infant pairs (PACTG 1025):* Assessment of the effectiveness and safety of antiretroviral therapy, and mode of delivery prescribed for prevention of vertical transmission of HIV and/or for women's health.
- *Toxicities and complications (A5029):* Assessment of prevalence and persistence of human papillomavirus (HPV) DNA in HIV-infected women who are protease-inhibitor-naive and have initiated HAART; HIV viral kinetics (A5077): Virologic studies in compartmental samples from HIV-infected subjects changing or initiating potent ARV therapy; A5166s and A5160s: Viral dynamics sub-studies of A5095 and A5142.
- *Changes in immunologic responses (A5137s):* Female Genital Secretions sub-study; A5150: Observational study of virologic and immunologic changes in HIV-infected women during the partum and postpartum period.
- *Metabolic complications of HAART (A5084):* Evaluation of metabolic complications associated with ARV medications in HIV-1-infected pregnant women, such as hepatic steatosis and chronic HIV infection.

Scientific advances in women's health include a recent study conducted in the Women's Interagency HIV Study that found HAART improved cervical cytologic pathology associated with oncogenic HPV among HIV-infected women. WIHS analyzed the effect of HAART on cervical Papanicolaou (Pap) smear results in women with HIV and an oncogenic HPV infection. Further studies will be needed to confirm the benefits of HAART regimens on HPV-induced cervical changes. This analysis, however, should inform treatment interventions and care of women with HPV infection – one of the most common sex-specific consequences of HIV disease and the causative pathogen of precursor changes of cervical cancer in women.

- Highly active antiretroviral therapy has also resulted in significant declines in AIDS and death in the *Women's Interagency HIV Study*. WIHS compared the rates of AIDS and/or death prior to October 1994–April 1996, and after April, 1996–March 1999, the time HAART became available in the United States. Despite the lack of universal use, there were substantial drops in AIDS and death from the pre-HAART to the post-HAART periods.
- NIAID-funded researchers also estimated the usefulness of isotretinoin for preventing the progression of low-grade squamous intraepithelial lesions (SIL) of the cervix to high-grade lesions or invasive cervical cancer. In summary, isotretinoin was not associated with longer time to progres-

sion of low-grade SIL. This appears to be a chronic condition in HIV-infected women, with a low risk of progression and significant rate of resolution. This study strengthens results from observational studies that management of SIL in HIV-infected women probably does not need to differ significantly from that of the general population, i.e., observation without excisional therapy may be appropriate for HIV-positive women with low-grade SIL.

- The effect of fluconazole use on the susceptibility of Candida isolates recovered from HIV-infected women was evaluated in a randomized, double-blind, placebo-controlled trial. Women with CD4 + cell counts less than or equal to 300 cells/mm received either fluconazole (200 mg/week) or placebo as prophylaxis. The antifungal susceptibility of specimens was evaluated. There was significant azole cross-resistance among the non-albicans Candida species isolates. Although the rate of azole resistance did not significantly increase after fluconazole prophylaxis, there was a trend toward more *in vitro* azole resistance in *C. glabrata* isolates from patients assigned fluconazole. The study concluded that use of azoles for prophylaxis in an individual patient needs to be balanced against the risk of promoting colonization with resistant opportunistic strains.

**Prevention**

The HIV Prevention Trials Network (HPTN) is a worldwide collaborative clinical trials network designed to evaluate the safety and efficacy of non-vaccine prevention interventions, alone or in combination, using HIV incidence as the primary endpoint. HPTN research encompasses a number of important areas of women's health including drugs and/or vaccines that are practical and easy to use to prevent mother-to-infant HIV transmission; microbicides, substances designed for vaginal or rectal use, to prevent sexual transmission of the virus; interventions to reduce behavior that exposes people to HIV; programs to check the spread of HIV through reducing intravenous drug abuse; measures to control other sexually transmitted diseases (STDs) and thereby decrease the risk of co-infection with HIV; antiretroviral therapy that may protect high-risk uninfected adults before they are exposed to HIV; and emergency therapy to treat victims of sexual assault.

Prevention research is also supported through individual, investigator-initiated grants. One grant that was recently awarded supports Phase III trials using acyclovir to prevent HIV infection in women and men who have sex with men with/or at high risk for herpes simplex type-2 (HSV-2). HSV-2 is the primary cause of genital ulcers and one of the most prevalent sexually transmitted diseases worldwide. More than 20 studies have found HSV-2 infection to be a risk factor for HIV acquisition.

**Perinatal Transmission**

Studies for the prevention of perinatal transmission are conducted through the Pediatric AIDS Clinical Trials Group and the HIV Prevention Trials Network.

In the Pediatric AIDS Clinical Trials Group, a number of early, Phase I studies are closed and in various stages of data analysis. These include:

- *PACTG 386:* a Phase I trial of the safety, pharmacokinetics, and tolerance of fortovase (saquinavir SGC), coadministered with low-dose zidovudine (ZDV) and lamivudine (3TC), in HIV-infected pregnant women during gestation and postpartum, and in their infants' post-maternal dosing.

- *PACTG 358:* a Phase I trial of the pharmacokinetics, safety, and tolerance of indinavir, when given in combination with 3TC and ZDV, to HIV-infected pregnant women. The study will also assess the pharmacokinetics of indinavir in cord blood and neonatal samples following maternal dosing, and the safety and tolerance of prior maternal dosing in the newborn.

- *PACTG 354:* a Phase I study of the safety, tolerance, and pharmacokinetics of ritonavir, when given in combination with 3TC and ZDV, to HIV-infected pregnant women. The study will assess the pharmacokinetics of ritonavir in cord blood and neonatal samples following maternal dosing, and the safety and tolerance of prior maternal dosing in the newborn. It will also determine an initial dosage regimen of ritonavir for infants up to 4 weeks of age.

- *PACTG 353:* a Phase I study to assess the pharmacokinetics of nelfinavir, when given in combination with ZDV and 3TC, and to assess the safety and tolerance of the triple-combination therapy in HIV-infected women during pregnancy and postpartum, and in HIV-exposed infants.

- *PACTG 316:* a followup of an earlier study conducted in Uganda that reported a marked reduction in mother-to-child transmission of HIV with a single dose of nevirapine to mother and infant regimen. In order to determine if this same simple regimen could further reduce the rates of HIV transmission in the United States, Europe, Brazil, and the Bahamas, PACTG 316 included 1,270 women who received their country's standard of care for their health status. Most of these women received combination antiretroviral therapy during pregnancy, and about a third of the women had elective cesarean delivery. The study was stopped early, at the recommendation of NIAID's Data and Safety Monitoring Board (DSMB), because the overall mother-to-infant transmission rate was 1.5 percent, a much lower rate than originally anticipated and one which made it impossible to assess an additional beneficial effect of nevirapine with the planned study design. The nevirapine 2-dose regimen was well tolerated by both mothers and infants; no differences were seen in toxicity assessments between the placebo and nevirapine arms. This study demonstrates the dramatic reductions in mother-to-child transmission of HIV that can be achieved when HIV-infected women receive current obstetrical and antiretroviral standard of care as recommended by the Public Health Service perinatal treatment guidelines.

- NIAID-funded researchers recently examined the emergence and fading of nevirapine (NVP) resistance (NVP[R]) mutations in HIV-1-infected Ugandan women and infants who received single dose NVP to prevent HIV-1 mother-to-child (vertical) transmission. NVP(R) was examined in women and infants who received a single dose of NVP in the HIVNET 012 clinical trial. In summary, NVP(R) was detected more frequently in infants than women following NVP prophylaxis, and different patterns of NVP(R) mutations were detected in women versus infants. NVP(R) was detected infrequently in infants with late HIV-1 infection. NVP-resistant HIV-1 faded from detection in both women and infants over time.

- In the HIV Prevention Trials Network (HPTN) a Phase III trial of antibiotics to reduce chorioamnionitis-associated perinatal transmission of HIV (HIVNET/HPTN 024) was initiated in Malawi, Tanzania, and Zambia.

- Enrollment is underway for two investigator-initiated studies supported by cooperative agreement awards. These studies – one in Ethiopia and one in India – are designed to evaluate a 6-week regimen of nevirapine administered to HIV-uninfected infants born to HIV-infected breastfeeding mothers. A third similar trial is expected to begin enrollment in 2003 in Uganda, and will include an additional arm that examines the benefit of administering HIV-immune globulin (HIVIg) to the infant.

- A small retrospective study had previously raised concerns that HIV-infected pregnant women, who received combination antiretrovirals for their health and to reduce the risk of HIV transmission to their infants, had an increased risk of premature delivery. As a result, researchers compiled data from seven clinical studies of HIV-infected pregnant women (including the Women and Infants Transmission Study and Pediatric AIDS Clinical Trials Group protocols) to better assess the risk of adverse outcomes of pregnancy. Overall, combination antiretroviral therapy was not associated with a risk of an adverse outcome, such as premature delivery or low birth weights. The use of potent combination antiretroviral regimens is recommended by Guidelines issued by the Public Health Service for most HIV-infected pregnant women, and is associated with a dramatic decrease in the rate of mother-to-child HIV infections. This study provides information on the safety of these regimens that is likely to be reassuring to HIV-infected pregnant women and their health care providers.

**Vaccines**

Vaccines can provide a safe, effective, and efficient means to prevent illness, disability, and death from infectious diseases. Research leading to new and improved vaccines is a high NIAID priority. In addition to improving the health of the public, vaccines have been shown to greatly reduce both direct and indirect health care costs. Recent accomplishments include the establishment of two new comprehensive research networks, one focused on HIV vaccines and one on prevention research.

## *Other Sexually Transmitted Diseases*

The number of cases of sexually transmitted diseases (STDs) continues to increase dramatically worldwide, yielding serious economic, social, and health consequences. According to the Centers for Disease Control and Prevention (CDC), more than 65 million people live with an incurable STD in the United States, with an additional 15 million people acquiring one or more STDs each year, some of which have lifelong consequences. STDs are critical global and national health priorities because of their devastating impact on women and infants, and their interrelationships with HIV/AIDS. STDs can lead to infertility, tubal pregnancy, cervical cancer, low birth weight, congenital/perinatal infections, increased risk of HIV infection, and other chronic conditions such as neurosyphilis.

NIAID supports a broad STD research portfolio (*http://www.niaid.nih.gov/dmid/stds/*) addressing these diseases through investigator-initiated research grants and a variety of research programs, including the: 1) STD Cooperative Research Centers (CRCs), which bridge basic biomedical, clinical, behavioral, and epidemiological research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research; and 2) STD Clinical Trials Unit, which conducts clinical trials to test safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STDs. The following highlight accomplishments in these areas:

**Prevention and Risk Factors**

- Several promising vaccine candidates for the prevention of gonorrhea have been identified.

- Protegrins, a novel class of microbicides that are active both *in vivo* and *in vitro*, have a broad antimicrobial spectrum that includes *Neisseria gonorrhoeae*, *Haemophilis ducreyii*, *Chlamydia trachomatis*, *Candida albicans*, and HIV-1.

- Clinical studies on a lactobacillus suppository to prevent bacterial vaginosis were initiated in August 2000.

- Two studies on adolescents and social/sexual networks were started in FY 2000. The emphasis is on adolescent development and the acquisition of infection, including risk factors, immunologic correlates of viral STD pathogens, and the diffusion of infection through networks of sexual partners.

- A clinical trial to assess if an investigational vaccine is safe and effective in preventing genital herpes symptoms in young women, not infected with herpes simplex virus (HSV), was initiated in 2002.

- NIAID researchers continued to study a mouse model of chlamydia genital tract infection to define what constitutes protective immunity against chlamydia. Their aim is to use this information to develop a chlamydia vaccine. Earlier approaches using various pieces of the organism have not been successful, so NIAID scientists are now developing candidate vaccines using live, weakened chlamydia strains.

- NIAID scientists also made important discoveries that may result in improved therapies for chlamydial infection. They demonstrated that novel chlamydial genes encoding a toxin and an enzyme appear to help the organism evade host defenses and persist within the genital tract epithelium, with important consequences for disease transmission and chronic infection. These findings suggest new targets for the design of strategies aimed at diagnosing and controlling chlamydial STD.

- NIAID completed participation in a multicenter study to evaluate an antiviral drug called valacyclovir for preventing the transmission of herpes simplex virus (HSV) in heterosexual couples in which only one member was infected with HSV. Approximately 1,500 couples took part in the study at outpatient centers in the United States, Canada, and Europe. The study found that the risk of acquiring a clinical genital herpes infection among susceptible persons taking the drug was 77 percent lower than among those receiving a placebo. This finding and additional study data have encouraged the maker of valacyclovir to pursue FDA approval.

**Treatment**

- A study is underway to evaluate the efficacy of azithromycin as antibiotic therapy for early syphilis, compared to the current recommended treatment: benzathine penicillin G. The current treatment is administered as an intramuscular injection, whereas azithromycin would be much easier to administer and would be offered as an alternative for patients who are allergic to penicillin.

- NIAID investigators are conducting a randomized, multicenter, double-blind, placebo-controlled Phase III study to evaluate the effect of valacyclovir in preventing the transmission of HSV in 1,500 heterosexual couples in which only one member has type-2 HSV.

- Research is progressing on the development of natural and synthetic porphyrins and metalloporphyrins. These compounds possess potent and broad-spectrum antibacterial activity. A number of porphyrin compounds have been found to have potent virucidal activity against HSV-2 alone, and against both HSV-1 and HSV-2.

**Diagnostics and Screening**

- The institute continues to provide support for the development and evaluation of STD diagnostics through the Small Business Innovation Research (SBIR) mechanism.

- NIAID studies using non-invasive screening with molecular assays for *Chlamydia trachomatis* genital tract infections have documented extremely high rates of infection (31 percent) in sexually active female adolescents. These studies have shown the median time to

repeat infection was 7 months, resulting in a new recommendation to the PHS for routine screening of all sexually active adolescent females every 6 months for this common infection.

**Animal Models**

- Research is progressing on the development of a human vaginal graft model in immunocompromised mice.
- Research is progressing on the development of a mouse animal model of gonococcal infection.

**Genomics**

- In FY 2000, NIAID genomic sequences of *Neisseria gonorrhea*, *Haemophilis ducreyi*, *Chlamydia trachomatis*, and *Treponema palladium* were completed. The genome sequence of *Lactobacillus crispatus* (normal vaginal flora) and *Ureaplasma urealyticum* were also initiated. These genome sequences have provided new insights into the pathogenesis of these diseases, and pave the way for new diagnostic, drug, vaccine, and microbicide development opportunities.
- In FY 1999, NIAID established a relational database (STD GEN) for pathogens that cause sexually transmitted diseases (*http://www.stdgen.lanl.gov*) at the Los Alamos National Labs to serve as an international resource for the compilation, analysis, and dissemination of genetic sequence and associated data for STD pathogens. In FY 2000, several new features were added, and the genomic sequence of type-1 HSV was incorporated.

More information on advances related to STDs may be found in the Topical Microbicide and Vaccine sections.

## *Topical Microbicides*

HIV/AIDS and other STDs are spread predominantly through sexual transmission. Therefore, the development of chemical and physical barriers that can be used intravaginally or intrarectally to inactivate HIV and other STDs is critically important for controlling infection. Across the globe, women face the greatest risk of acquiring HIV and STDs due to substantial mucosal exposure to seminal fluids, the prevalence of non-consensual sex, sex without condom use, and hidden, high-risk behaviors of their partners. Despite the overwhelming risks presented to them, women have the fewest available means for protection against HIV and other STDs. An inexpensive, reliable, female-controlled method for preventing STDs is urgently needed so that women can protect themselves. Ideally, chemical barriers, known as *topical microbicides*, should be undetectable, non-irritating, safe, and inexpensive. In addition, microbicides should be available in both contraceptive and non-contraceptive formulations since women presently may put themselves at risk for acquiring HIV and other STDs in order to conceive a child.

The NIAID research effort for the development of topical microbicides includes basic research, preclinical product development, and clinical evaluation. A number of animal models currently exist for testing microbicides, including nude mice for HPV infection, macaques for simian immunodeficiency virus (SIV), simian/human immunodeficiency virus (a modification of SIV that contains key elements of HIV), and guinea pigs and mice for genital herpes.

Research continues to evaluate and confirm the use of animal models for studying topical microbicides. NIAID-funded researchers have established a reproducible non-human primate model for studying safety and effectiveness of a topical microbicide for the prevention of chlamydial infection. This research found that the anatomy and vaginal flora of pig-tail macaque monkeys and humans are remarkably similar. Several significant research advances include:

- *A study of the safety and tolerability of Carraguard™, a novel vaginal microbicide, in sexually active, uninfected women*. Carraguard, a 3-percent carageenan gel derived from seaweed, is a promising candidate microbicide that has been

shown to inhibit HIV entry during preclinical and Phase I clinical trials. In this expanded Phase II safety trial, a total of 400 women in two sites in South Africa were randomized to receive either Carraguard™ or placebo (methyl cellulose) following informed consent. Women were asked to insert gel at least 3 times per week and prior to each act of sexual intercourse for up to 1 year. Pelvic examinations, interviews, and safe-sex counseling were performed monthly. Preliminary data indicated that both Carraguard™ and the placebo gel were safe. In both groups, more than 90 percent of women reported no symptoms that were attributable to gel use. Upon pelvic examination, approximately 90 percent in both groups had no visible vaginal or cervical abnormalities. Data collection has been completed and full analysis of results is underway. Should preliminary data be confirmed upon full analysis, a Phase III effectiveness evaluation of Carraguard™, currently in planning stages, will be considered.

- *The safety and acceptability of BufferGel® and PRO 2000/5 Gel in HIV-infected men*. BufferGel acts to protect against the sexual transmission of HIV by maintaining the normally acidic pH of the vagina, a nonpermissible environment for HIV, in the presence of ejaculate. PRO 2000/5 Gel acts by inhibiting viral entry. Phase I studies of both products among women and uninfected men have demonstrated favorable safety profiles. HPTN conducted this study to evaluate the potential of the two products for penile toxicity among HIV-infected men, since it is likely that they will be exposed to these products in Phase III trials. While analysis of the full data set is not yet complete, preliminary data have indicated that BufferGel® and PRO2000/5 Gel are relatively safe in HIV-infected men. One of these products may enter a Phase III efficacy and effectiveness trial in FY 2004, conducted by HPTN.

- *A mouse model for screening potential microbicides to block vaginal transmission of cell-associated HIV-1*. Newly acquired HIV-1 infections are largely the result of heterosexual transmission. Since HIV-1 cell-free virus and HIV-infected cells are present in semen and cervical mucosa of infected individuals, both may be involved in transmission of HIV-1 through the anorectal and cervicovaginal mucosal routes. Therefore, prevention studies must consider blocking transmission of both cell-free and cell-associated viruses. Antibodies that target HIV-1 virions have been shown to prevent vaginal transmission of cell-free virus in macaques. However, vaginal transmission of cell-associated virus has not been reliably demonstrated using SIV in nonhuman primate models. Therefore, a model for studying vaginal transmission of cell-associated HIV-1 is critically needed. A team of NIH-funded investigators has used a mouse model in which severe combined immunodeficient (SCID) mice were reconstituted with human peripheral blood leucocytes (HuPBLs) to demonstrate reproducible vaginal transmission of cell-associated HIV-1, but not of cell-free virus. The HuPBL-SCID model of vaginal transmission should be useful for investigating the mechanisms of transmission of cell-associated HIV-1, and for screening potential microbicides to block vaginal transmission.

**Studies of Topical Microbicides**

- **Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel**

  A clinical trial at three domestic sites within the HPTN to determine the safety and acceptability of PMPA gel for vaginal use among sexually abstinent and active HIV-uninfected and -infected women. The trial will also determine the acceptability of PMPA gel among their male sexual partners (when relevant). (HPTN 050)

- **Phase I Safety and Acceptability Study of the Vaginal Microbicide 6 Percent Cellulose Sulfate Gel among HIV-infected Women**

  A clinical trial, at four domestic sites within the HPTN, to assess the safety and acceptability of 6 percent cellulose sulfate (CS) gel for vaginal use versus a control gel among HIV-infected women. The trial will also assess the acceptability of CS gel among the HIV-infected male sexual partners of female participants. (HPTN 049)

- **A Double-blind, Randomized Trial of Oral Metronidazole with *L. crispatus* CTV 05 or Placebo Intravaginal Capsules for the Treatment of Bacterial Vaginosis**

  A clinical trial completed during 2002. Although the initial analysis was not encouraging, a reanalysis predicts that a new product formulation, combined with a different treatment regiment, may improve results.

- A multisite clinical study to determine the concordance of trichomoniasis between male and female partners being conducted by the DMID Sexually Transmitted Disease Clinical Trials Unit. This will include a microbicide acceptability questionnaire. Data from this study will provide STD prevalence that will be relevant for future domestic microbicide efficacy trials.

A number of programmatic accomplishments have also been made to help further topical microbicide research:

- **Integrated Preclinical/Clinical Program for HIV Topical Microbicides** (PA-01-075)

  Awards were made to three multidisciplinary, multi-project programs submitted in response to a Program Announcement, cosponsored with NICHD, the purpose of which is to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The overall goal is to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations, and to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies in order to segue these studies into large safety and efficacy clinical trials within the HPTN or through the R01 mechanism. The awards were made to:

  - Dr. Richard Bax, Principal Investigator, Biosyn, Inc., *Integrated Cyanovirin Preclinical/Clinical Microbicide Program*
  - Dr. Michael Lederman, Principal Investigator, Case Western Reserve University, *Topical Agents to Prevent Mucosal HIV Transmission*
  - Dr. Sharon Hillier, Magee-Women's Health Corporation, *Development of Non-nucleoside Reverse Transcriptase Inhibitors as Combination Microbicides*
  - Dr. Betsy Herold, Principal Investigator, Mount Sinai School of Medicine, *Multi-targeted Microbicide Combinations to Block HIV*

- A panel of outside experts was convened in August 2002 to review a draft of the NIAID Topical Microbicide Strategic Plan. Panel members provided recommendations regarding the following major areas of microbicide research and development addressed in the plan:

  - The overall strategy for prioritizing the most promising candidate microbicides
  - The role of animal models for evaluating safety and efficacy
  - The transition to and conduct of efficacy trials

  The draft document is undergoing revision to reflect panel recommendations and will be available in printed form and on the NIAID website in FY 2003.

- **Innovation Grants in AIDS Research**

  A Program Announcement was released to stimulate new, scientifically challenging, and untested ideas into AIDS research with a particular focus on microbicide research. In brief, applications were encouraged in several areas of new approaches for microbicides, including viral and cellular processes involved in the transmission, local propagation, and spread of HIV; processes for cervicovaginal and rectal transmission of HIV; improved methods of formulation and delivery; and preclinical systems to test microbicide safety and efficacy. The applications have been received and will soon undergo review. Those of highest scientific merit will be funded in FY 2004. (PA-02-046)

- **Specialized *In Vitro* Virological Evaluations of Strategies to Combat HIV/AIDS**

  Awarded to Southern Research Institute for continued *in vitro* screening of potential topical microbicides. Microbicide candidates found to be active in the primary screens are evaluated for potential toxicity against two strains of lactobacillus that colonize the healthy human vagina and represent a potential nonspecific protective barrier against sexually transmitted infections. In the past year, 29 unique compounds from outside sponsors, and 346 unique compounds for the National Cancer Institute repository, were tested. The colorless, or lightly colored, compounds with a therapeutic index greater than 50 are undergoing additional evaluation to assess their potential for development as topical microbicides. (N01-AI-05415)

- The STD Prevention Primate Unit (DMID contract N01AI95388) for preclinical evaluation of topical microbicides and vaccines at the University of Washington evaluated six candidate microbicides for safety (effects on surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques this past year. Results from DMID-supported testing are being coordinated.

*Workshop*

- **Topical Microbicides Program Project Reverse Site Visit (formerly known as the Pre-clinical Topical Microbicides Workshop) January 9-10, 2002**

  The primary goal of this Washington, DC site visit was to assess the progress of research conducted by the Topical Microbicide Program Projects toward the pre-clinical development and evaluation of candidate products for preventing sexual transmission of bacteria, protozoa, and viruses, including HIV. Scientists from all projects of the six DMID-supported Topical Microbicide Program Projects, principal investigators of six newly funded Microbicide Preclinical Development Program projects (DAIDS and NICHD), representatives of government staff with responsibility for research programs, and several external reviewers attended the site visit. The overall consensus of the reviewers was communicated to the Principal Investigators.

NIAID scientists have continued to make important discoveries that promote the development of an effective, easy to use, female-controlled method to protect from sexual transmission of HIV. Based on their fundamental insights into how HIV gains entry into target cells, NIAID scientists designed a novel agent to neutralize HIV infection, which they plan to develop as a topical microbicide for preventing sexual transmission of HIV. Research is ongoing to make the inhibitor effective against a wide array of HIV strains. Progress has also been made in engineering lactobacillus, a bacterium normally found in the vagina, to produce this inhibitor. Researchers believe that colonizing the vaginal tract with the engineered lactobacillus may provide a method for durable protection against sexual transmission of HIV that is economically feasible and controlled by women.

### *Tuberculosis*

Tuberculosis (TB) is an ancient bacterial infection caused by *Mycobacterium tuberculosis*. The bacteria are spread from person-to-person by airborne droplets expelled from the lungs when a person with active TB disease coughs, sneezes, or speaks. Infection typically takes root in the lung air sacs. In healthy people, TB infection is barricaded behind a "wall" of cells that limits the spread of TB within the host. This contained infection is referred to as latent or persistent TB and may be present throughout an individual's lifetime. If the body's immune system becomes weakened from HIV infection, malnutrition, aging, or other factors, the bacteria may become "reactivated" and begin to spread within the lungs or to other tissues resulting in active and infectious TB.

TB is the leading infectious killer of women of reproductive age worldwide, causing more deaths in women than all causes of maternal mortality combined (WHO report on the Tuberculosis Epidemic 1996). Across the world, more than 900 million women between ages 15 and 44 are infected with TB; 2.5 million get sick; and 1 million die from TB each year (*WHO Press Release*, 1998). DMID supports a robust portfolio of basic and applied TB research projects (*http://www.niaid.nih.gov/dmid/tuberculosis/*). Recent accomplishments are as follows:

- Two projects are devoted to the sequencing of the entire genome of a potent clinical isolate of *Mycobacterium tuberculosis,* and the sequencing of *M. smegmatis*, which serves as an important model system in TB research. The *M. tuberculosis* genome sequencing is complete and annotation of the genome is almost complete. The sequence information is available in public databases (*http://www.tigr.org*).

- Under the SBIR Program, four grants to develop new TB diagnostic tools and one grant for TB drug target identification were awarded in FY 2000 and are ongoing.

- Through its new Challenge Grants Program established in FY2000, NIAID is providing matching funds to companies that are committing their own dollars and resources toward developing new drugs and vaccines against TB, malaria, influenza, and dengue virus. This program, established through the support of the U.S. Congress, has awarded $19 million to eight companies. Three challenge grants focus on TB:

  - to test variants of ethambutol (one of the drugs in the standard combination regime used to treat TB) for the next generation of drug therapy.

  - to create and test variants of thiolactomycin, which could lead to promising new therapeutics against TB, malaria, trypanosomiasis, and *Staphylococcus* infections.

  - to conduct preclinical and clinical testing of a new antituberculosis candidate vaccine.

- The TB Research Unit is a multidisciplinary, international team dedicated to identifying and validating surrogate markers of human tuberculosis disease progression and correlates of the human protective immune response to *M. tuberculosis* infection. Overseen by Case Western Reserve University, the unit has made progress in developing surrogate markers of disease and human protective immunity, and in conducting clinical trials of potential new TB therapeutic, preventive, and diagnostic strategies. See website for additional information at *http://www.tbresearchunit.org*.

### *Immunology and Immune-mediated Diseases*

#### Autoimmune Diseases

In autoimmune diseases, immune cells mistakenly identify the body's own tissues

as foreign and mount an inappropriate immunological attack. Physicians and scientists have identified more than 80 distinct autoimmune diseases that affect an estimated 5 to 8 percent of the U.S. population, and disproportionately afflict women. These diseases are a significant cause of chronic morbidity, costing billions of dollars annually in health care expenses and lost productivity. NIAID has placed a high priority on research in autoimmunity and autoimmune diseases, and supports a broad portfolio of basic, pre-clinical, and clinical research aimed at understanding the pathogenesis of these chronic diseases, investigating new ways to modify the immune response, and applying this knowledge to the identification and evaluation of promising approaches to treat and prevent these diseases. Research on the immune system in the last two decades has resulted in a wealth of new information and extraordinary growth in understanding the immune system. These accomplishments now provide promising opportunities for major advances in the diagnosis, treatment, and prevention of autoimmune diseases.

NIAID scientists uncovered unique molecular events involving a molecule called the adenosine receptor that triggers the body to stop inflammation. Though inflammation is one of the body's protective mechanisms against injury or infection, too much inflammation causes the tissue damage seen in rheumatoid arthritis, multiple sclerosis, and other diseases. This finding suggests opportunities for the design of new anti-inflammatory drugs that target extracellular adenosine and its cellular receptor.

NIAID scientists have made progress in studies to characterize the factors that precipitate autoimmune symptoms in a mouse model of myasthenia gravis. This work may shed light on the feasibility of antigen-specific therapy directed at inducing the death program of activated T lymphocytes that cause autoimmune diseases. NIAID scientists also furthered their work aimed at learning how to induce tolerance to the proteins that trigger autoimmune diseases by administering small amounts of the proteins orally over time. This concept has shown promising results in animal studies.

## *Scientific Advances*

### Disease Burden

Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys the insulin-producing islet cells of the pancreas. An estimated 500,000 to 1,000,000 Americans have type 1 diabetes, which is characterized by elevations in blood sugar that, over time, lead to severe and life-threatening complications, including: heart disease; blindness, kidney failure, and peripheral neuropathy. Treatment requires insulin administration through either multiple daily insulin injections or use of an insulin pump. While insulin is essential for survival, even the most medically compliant patients are rarely able to maintain "tight" or physiologic control of their blood sugar. As a result, existing treatments can delay and diminish, but not prevent, many of the complications of diabetes. Even with careful attention to control of blood sugar, type 1 diabetes results in a drastic reduction in quality of life and shortens life span by up to 15 years.

### Advances

An important study conducted by the Autoimmunity Centers of Excellence demonstrated that the loss of insulin production in patients with new-onset type 1 diabetes can be diminished for 1 year after treatment with a recombinant anti-T cell monoclonal antibody. Further trials will be needed to determine the longer-term benefits of this experimental therapy. Nonetheless, these preliminary results indicate that novel immune therapies can interrupt the destructive immune processes in autoimmune diseases and have potentially long-lasting effects. A larger Phase II trial is in development in the Immune Tolerance Network.

If successful, this treatment could dramatically improve the quality of life for those afflicted with type 1 diabetes.

**Risk**

NIAID joined NIAMS, NCI, and ORWH, in supporting an IOM study to evaluate the status of research related to the safety of silicone gel breast implants. One aspect of the study evaluated research regarding the immune response to silicone. According to the report, postoperative infections and complications pose the major health risk associated with silicone gel breast implants. This risk is compounded by the fact that followup procedures, such as replacement of leaking implants, are often required. The IOM found no reliable data to support the claim that silicone breast implants increase a woman's risk for developing autoimmunity, and that many of the studies published to date on the impact of silicone gel breast implants are seriously flawed. Results, published June 1999, and can be obtained online at *http://www.nap.edu/books/0309065321/html*.

**Treatment**

- NIAID investigators have conducted a randomized, double-blind, placebo-controlled trail to determine whether fludrocortisone is efficacious for individuals with chronic fatigue syndrome (CFS). Participants completed self-assessment forms on mood, energy, activity, and performance. The primary indicator of efficacy is a 15-point improvement (on a scale of 1-100) in the test being performed. The treatment was well tolerated with no serious adverse reactions. The study data were analyzed and reported at the American College of Cardiology annual scientific meeting in March 2000.

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## *Program Accomplishments*

**Multidisciplinary Research Programs**

More information on the Immune Tolerance Network can be obtained at *http:www.immunetolerance.org.*

- *Autoimmunity Centers of Excellence* (*ACEs*) conduct integrated basic, pre-clinical, and clinical research activities. The basic and pre-clinical components focus on elucidating the mechanisms of autoimmunity, immune tolerance, and/or immune modulation. The clinical component supports studies of promising immunomodulatory therapies for autoimmune diseases. ACEs are presently enrolling participants in two trials: 1) a Phase I trial of anti-CD20 in systemic lupus erythematosus; and 2) a Phase I/II study of the combination of copaxone and albuterol versus copaxone alone for treatment of multiple sclerosis. Several other single and multisite cooperative clinical trials for new immunomodulatory interventions and studies of mechanisms of action are in development, as well as protocols for clinical trials of potential therapies in type 1 diabetes. Collaborations among ACEs investigators will address the immune mechanisms underlying the immunomodulatory activity of

agents evaluated in these trials. Advancing the understanding of the causes and underlying immune mechanisms involved in autoimmunity and autoimmune diseases may lead to the development of new approaches to treat autoimmune diseases. NIAID, NIDDK, NIAMS, and the Juvenile Diabetes Research Foundation cosponsor the ACEs.

- The *Immune Tolerance Network* (*ITN*), cosponsored by NIDDK and the Juvenile Diabetes Research Foundation, was established by NIAID to accelerate the clinical development and application of immune tolerance-inducing strategies to prevent and treat immune-mediated disorders, including type 1 diabetes, asthma, and allergic diseases, and rejection of transplanted solid organs. Multiple trials are either ongoing or in development to evaluate potential treatments for immune-mediated diseases, including type 1 diabetes, multiple sclerosis, and allergic rhinitis, and to induce tolerance induction in pancreas islet transplant recipients.

- ITN has completed enrollment in the multisite *Edmonton Protocol* to evaluate pancreatic islet transplantation in type 1 diabetes. It is anticipated that results of this international trial will establish the baseline success rate and current standards for islet transplantation. In FY 2003, ITN will launch a larger efficacy trial of a tolerance induction regimen for islet transplantation. If successful, tolerance induction would: 1) enable life-long, rejection-free maintenance of transplanted organs and cells; and 2) eliminate ongoing organ injury and loss of function in autoimmune disease without the many adverse effects of broadly immunosuppressive drugs. More information on ITN can be obtained at *www.immunetolerance.org*.

- The *Autoimmune Disease Prevention Centers* conduct basic research on the development of new targets and approaches to prevent these diseases. Promising approaches will be evaluated in pilot clinical studies. In FY 2002, the Prevention Centers supported 12 projects to investigate molecular and cellular mechanisms controlling immune regulation that may lead to the development of novel targets for disease prevention. The Prevention Centers are cosponsored by NIDDK, the National Institute of Child Health and Human Development (NICHD), the ORWH, and the JDRF.

- **Sex-based Differences in the Immune Response Research Program**

  In FY 2002, NIAID, in collaboration with NIAMS, NINDS, ORWH, and the National Multiple Sclerosis Society, established this program and funded 14 new research projects. In addition, NIAID, with the NIH Office of AIDS Research and ORWH, funded a program project to investigate the female genital mucosal immune response. While differences in the immune response of males and females have been documented, including the increased incidence of autoimmune diseases in women, pregnancy-induced changes in immune-mediated diseases, and differences in the rate and severity of infection, the reasons are unclear. Increased understanding of the mechanisms underlying the differences in the immune response in males and females should facilitate more targeted approaches for prevention and treatment of disease

- **Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases**

  NIAID is developing clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat several autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and scleroderma.

Studies of the underlying immune mechanisms of autoimmune diseases will be performed along with the clinical trials. More information about NIH clinical research studies is available at *http://www.clinicaltrials.gov/*.

- As a result of congressional appropriations language (FY 1999), NIH was encouraged to support increased research in autoimmunity and autoimmune diseases. NIAID was designated the lead institute and solicited the collaboration of all institutes with an interest in this area (NIAID, NIDDK, NIEHS, NIAMS, NINDS, NIDCR, NEI, NICHD, NIMH, NCI, NHLBI, NCRR, and ORWH). New initiatives continue to be created and increased support is provided for initiatives in more advanced stages of development. In response to these research initiatives, many meritorious applications were received throughout NIH.

**Animal Models**

- **Non-Human Primate Transplantation Tolerance Cooperative Study Group**

  NIAID, in collaboration with NIDDK (FY 1999), established this study group to evaluate the safety and efficacy of promising tolerance induction treatment strategies in non-human primate models of kidney and islet transplantation. In FY 2002, the number of centers increased to ten, and a monkey breeding facility was expanded. To date, study group scientists have demonstrated long-term graft acceptance in both kidney and islet transplant recipients. The results of these large animal investigations are providing information critical to the design of scientifically sound and ethically acceptable human clinical trials.

**Research Resources**

- **Multiple Autoimmune Disease Genetics Consortium (MADGC)**

  Established by NIAID in FY 1999, MADGC collects medical information, cells, serum, and genetic material (DNA) from families in which two or more individuals are affected by two or more distinct autoimmune diseases. To date, 123 families are being evaluated, with the goal of enrolling 400 families by 2004. Samples from more than 60 families have been characterized and are available to investigators for additional studies. This database and repository of associated materials will promote the discovery of human immune response genes involved in autoimmunity. For more information see *http://www.madgc.org/*.

- **13th International Histocompatibility Working Group (IHWG)**

  NIAID joined several other institutes (FY 2000) and the Juvenile Diabetes Research Foundation in supporting this network of more than 200 laboratories in over 70 countries that collect and share data on genes of the human leukocyte antigen (HLA) complex. These are the genes that encode the surface molecules involved in the immune response. The IHWG studies five diseases for which the HLA associations have been well characterized, including type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy. In addition, IHWG will launch a project to discover single nucleotide polymorphisms (SNPs) in type 1 diabetes-related genes. SNPs are naturally occurring genetic variations that may be used to identify the genes underlying susceptibility to type 1 diabetes.

- **North American Rheumatoid Arthritis Consortium (NARAC)**

  Cofunded by NIAID, NIAMS, and the Arthritis Foundation, NARAC collects medical information and genetic material (DNA) from families nationwide in which two or more siblings (between 18 and 60 years old) have developed rheumatoid

arthritis and have at least one surviving parent. To date, 902 of 1,000 families have been enrolled. Samples from more than half the families have been analyzed, including 600 affected sibling pairs. NARAC samples have been used by investigators to identify genes associated with the development of rheumatoid arthritis and provide insight into the pathogenesis of this disease. This research could lead to the development of new prevention and treatment strategies.

**Genetics**

In FY 2000, NIAID joined several other institutes and the Juvenile Diabetes Research Foundation International to support the *13th International Histocompatibility Working Group* (*IHWG*) in cataloging the HLA gene complex. In the process, the consortium will explore the HLA gene complex's differences among populations worldwide in an effort to improve the ability to predict, diagnose, and treat immune-mediated diseases, including type 1diabetes. NIAID supports an IHWG project to identify single nucleotide polymorphisms in immune response genes. These variations may account for the increased susceptibility of certain individuals or groups to immune-mediated diseases.

**Outreach**

- ***Understanding Autoimmune Diseases***

  NIAID's informational brochure enhances the public understanding of the immunologic basis for these diseases and the promise of immunomodulation for the treatment and prevention of these diseases in the future.

**General**

- ***NIH Autoimmune Diseases Coordinating Committee (ADCC)***

  NIAID chairs the ADCC established in FY 1998 at the request of Congress to increase collaboration among the NIH institutes, other federal agencies, foundations, and voluntary health organizations interested in these diseases. The first report of the ADCC, published in October 2000, provides details on the individual initiatives, sponsors, and on current and planned autoimmune diseases research. The report is located at *http://www.niaid.nih.gov/dait/pdf/adccrev.pdf*.

  In December 2002, the ADCC submitted to Congress its NIH Autoimmune Diseases Research Plan in fulfillment of the requirements under Sections 409E(c) and (d) of Public Law 106-310, the Children's Health Act. The report highlights research opportunities that could lead to improvements in the diagnosis, treatment, and prevention of these devastating illnesses. The report is located at *http://www.niaid.nih.gov/dait/pdf/ADCC_Report.pdf*

## *Multiple Sclerosis*

In multiple sclerosis (MS), activated immune cells attack the myelin nerve fibers. Myelin is a fatty sheath that surrounds nerve fibers and insulates the nerve. Without proper myelin insulation, messages sent between the brain and other parts of the body may be slowed or blocked. Damage to myelin causes the symptoms of MS. NIAID supports several large, multidisciplinary research programs that conduct basic, preclinical, and clinical research on autoimmune diseases, including MS. The NIAID's Immune Tolerance Network (ITN) is planning a clinical trial using CTLA4-Ig for treatment of relapsing MS. The ITN is also developing a clinical trial to evaluate atorvastatin as a potential treatment for MS. Atorvastatin (e.g., Lipitor) is a cholesterol-lowering drug that has been shown in animal models to reduce the symptoms of MS. NIAID's Autoimmunity Centers of Excellence are enrolling patients in a clinical trial of the combination of copaxone and albuterol compared to copaxone alone for treatment of MS.

### *Systemic Lupus Erythematosus*

Systemic lupus erythematosus (SLE), an autoimmune disease, varies greatly in severity, from mild cases requiring minimal intervention, to those in which significant and potentially fatal damage occurs to vital organs (e.g., lungs, heart, kidneys, brain). At least 239,000 Americans are diagnosed with, or are suspected of having, SLE, which disproportionately afflicts African American women (approximately four out of every 1,000 African American women are affected compared to one out of every 1,000 caucasian women). NIAID's Autoimmunity Centers of Excellence are enrolling patients in a Phase I study to evaluate the safety of anti-CD20 antibody as a treatment for SLE. NIAID will continue to support clinical trials on SLE through its research programs, including ITN and ACEs.

### *Other Research*

#### *Chronic Fatigue Syndrome*

Chronic fatigue syndrome (CFS), a condition of unknown cause characterized by chronic debilitating fatigue and frequent subjective constitutional symptoms, has been a subject of NIAID-funded research for almost 20 years. NIAID's long-standing involvement resulted from early theories that CFS might be caused by Epstein-Barr virus (EBV). Additionally, the observation that a number of symptoms of CFS overlap those associated with many infectious diseases led to the suggestion that other infectious organisms might play a role in the etiology or pathogenesis of this disease. To date, no single cause has been found for CFS, nor has any microbiologic, immunologic, or physiologic marker proven to be diagnostic or prognostic. Although a purely infectious or immunologic cause of CFS now seems unlikely, it is conceivable that infection could trigger CFS through unknown pathways. The eventual understanding of the complex symptomatology of CFS will require continued interdisciplinary research efforts.

Prevalence and incidence rates for CFS have been difficult to obtain for several reasons, including lack of an objective diagnostic criteria, differences in case definitions used by investigators in different countries, and potential biases related to case ascertainment. Given these factors, different estimates have been obtained by different investigators. Current NIAID accomplishments are as follows:

- NIAID has supported CFS Cooperative Research Centers to conduct research addressing basic science and clinical and epidemiological aspects of CFS since the early 1990s. These sites support studies examining immunological and cardiovascular issues, and cognitive behavioral stress therapy.

- In FY 2002, NIAID funded a new study that uses a mouse model to look at enterovirus RNA and its relation to fatigue (R01 AI051270; Dr. Patricia Tam, University of Minnesota). Enteroviruses are a sub-group of small viruses from the picornavirus family that typically multiply in the gastrointestinal tract. This application was submitted in response to a NIAID RFA entitled "Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection" (*http://grants2.nih.gov/grants/guide/rfa-files/RFA-AI-01-004.html*).

- NIAID, in partnership with the National Institute for Nursing Research, is currently cosponsoring a large-scale clinical trial of cognitive behavioral therapy and graded exercise in CFS patients (R01AI49720, "Activity Intervention for Chronic Fatigue Syndrome," Principal Investigator: Dr. Jason Leonard, De Paul University, Chicago). It is hoped that this study will provide important new information about response to treatment and possibly individual host factors that may influence response in CFS.

## Initiatives

*Requests for Applications (RFAs)*

- **Innovative Grants in Immune Tolerance**

  NIAID issued this RFA to support exploratory/developmental research projects on the molecular mechanisms and applications of antigen-specific immune tolerance. This initiative is cosponsored by NIDDK and NHLBI with awards planned for FY 2001. (RFA AI-00-006)

- **Microbicide Preclinical Development Program**

  Awards were made to six program projects submitted in response to RFA HD-00-018; three of which were funded by NICHD. The purpose of the RFA is to expand the range of microbicide candidates, with and without contraceptive activity, through support of discovery and preclinical development of novel or underexplored microbicides. (RFA HD-00-018)

- **Cooperative Study Group for Autoimmune Disease Prevention**

  In FY 2000, NIAID issued this RFA to establish a collaborative network of investigators focused on the development of interventions to prevent autoimmune diseases, including type 1 diabetes. NIDDK, NICHD, NIDCR, NIAMS, ORWH, and the Juvenile Diabetes Research Foundation International cosponsored this RFA. Awards are planned for FY 2001. (RFA AI-DAIT-00-016)

- **Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection**

  This RFA was issued to solicit applications on the development of novel or improved technologies to identify and validate the role of pathogens in chronic diseases. (RFA AI-DMID-01-004)

- **Gene Therapy Approaches for Diabetes and Its Complications**

  NIAID, NIDDK, and NHLBI issued this RFA to support the development of novel gene therapy approaches for the treatment of diabetes and its complications. This is supported, in part, from trans-NIH Diabetes Initiative funds. (RFA DK-01-006)

- **Sex-based Differences in the Immune Response**

  In FY 2002, 14 research projects were funded under this research initiative. In addition, NIAID, with the NIH Office of AIDS Research and ORWH, funded a program project to investigate the female genital mucosal immune response. While differences in the immune response of males and females have been documented, including the increased incidence of autoimmune diseases in women, pregnancy-induced changes in immune-mediated diseases, and differences in the rate and severity of infection, the reasons are unclear. Increased understanding of the mechanisms underlying the differences in the immune response in males and females should allow more targeted approaches at prevention and treatment of disease. Cosponsors include NIAMS, NINDS, ORWH, and the National Multiple Sclerosis Society. (RFA AI-01-005)

- **Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG)**

  The NHPCSG was established in FY 1998 to develop novel approaches to tolerance induction and to evaluate the safety and efficacy of tolerogenic regimens in large animal models of kidney and islet transplantation. In FY 2002, the number of centers was increased to ten and a monkey breeding facility was expanded. To date, study group scientists have demonstrated long-term graft acceptance in both kidney and islet transplant recipients. (RFA AI-01-006)

- **Gene Therapy Approaches for +Diabetes and Its Complications**

  In FY 2000, NIDDK, NIAID, and NHLBI issued this RFA to support the development of novel gene therapy approaches for the treatment of diabetes and its complications. Awards are planned for FY 2001. This is supported in part from trans-NIH Diabetes Initiative funds. (RFA DK-01-006)

- **Sex-based Differences in the Immune Response**

  See *http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-01-005.html.* (RFA AO-01-005)

*Requests for Proposals (RFPs)*

- **Primate Models to Evaluate HIV Prevention and Therapeutic Strategies**

  Issued to maintain the Division of AIDS' capability to evaluate microbicides and potential therapies. This resource will be used for: 1) studies of new microbicide or therapeutic approaches where "proof of concept" in a primate model would provide critical information to advance development; 2) studies that cannot be addressed in other animal models of HIV infection for lack of appropriate viral or cellular target; 3) candidates/strategies in an advanced stage of development that require optimization; and 4) confirmatory studies of candidates/strategies that have proven promising in other animal models of HIV infection. Contracts were awarded to the University of Washington and Southern Research Institute for a period of 7 years beginning September 2001. (RFP NIAID-DAIDS-01-17)

- **Simian Vaccine Evaluation Units**

  The primary purpose of this RFP is to provide non-human primates for immunization with candidate SIV or HIV vaccines. (RFP NIAID-DAIDS-01-04)

- **Prevention of Group B Streptococcal Disease**

  See *http://www.niaid.nih.gov/contract/archive/RFP0213.pdf.* (RFP NIAID-DMID-02-13)

*Program Announcements (PAs)*

- **Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP)**

  This PA was released to continue to stimulate iterative preclinical and clinical research for novel therapeutic and microbicide strategies against HIV infection. The overall goal of the IPCP is to establish proof-of-principle of new and pioneering therapeutic or microbicide modalities in a small number of patients, and then segue these studies to large clinical trials under the ACTG or HPTN network. This PA is a re-release of the original IPCP PA released July 1997, but unlike the original PA, groups responding to the PA must have formal interaction with the private sector to expedite the development of promising therapeutics or microbicides. The first set of applications under this PA is expected November 2000. (PA-00-098)

- **HIV Pathogenesis in Women's Interagency HIV Study (WIHS)**

  NIAID, along with six other NIH institutes and the NIH Office of Research on Women's Health, invited applications for highly focused basic research integrated with the WIHS scope and structure. Applications are expected to utilize the WIHS study population, a large cohort of HIV-infected women in the United States, to formulate specific hypotheses concerning HIV/AIDS pathogenesis in women. The WIHS cohort is followed in five large metropolitan areas (New York, Washington, DC, Chicago, Los Angeles, and San Francisco). (PA-97-165)

- **Statistical Methods in HIV/AIDS Research**

  NIAID and the National Institute of Mental Health invited applications for the development of original statistical methods to advance the understanding, treatment, and prevention of human immunodeficiency virus disease/AIDS. (PA-98-054)

- **Integrated Preclinical/Clinical Program for HIV Topical Microbicides**

  Cosponsored with NICHD, this PA is designed to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The overall goal is to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations, and to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies in order to segue these studies into large safety and efficacy clinical trials within the HIV Prevention Trials Network. See *http://grants.nih.gov/grants/guide/pa-files/PA-01-084.html* for more information. (PA-01-75)

- **Pathophysiology and Treatment of Chronic Fatigue Syndrome**

  The trans-NIH CFS Working Group issued a new PA on CFS in order to stimulate research in the area. The PA was released in December 2001 and has already attracted imaginative new CFS applications. This PA may be found at *http://grants2.nih.gov/grants/guide/pa-files/PA-02-034.html*. (PA-02-034)

- **Innovation Grants in AIDS Research**

  This PA was released to stimulate new, scientifically challenging, and untested ideas into AIDS research with a particular focus on microbicide research. In brief, applications were encouraged in several areas of new approaches for microbicides, including viral and cellular processes involved in the transmission, local propagation, and spread of HIV; processes for cervicovaginal and rectal transmission of HIV; improved methods of formulation and delivery; and preclinical systems to test microbicide safety and efficacy. The applications have been received and will undergo review. Those of highest scientific merit will be funded in FY 04. (PA-02-046)

- **Innovative Grants for Research in Human Immunology**

  NIAID, NCI, NICHD, and NIDCR invited applications to test novel approaches for elucidating the biology of the human immune system. (PA-02-073)

*Conferences and Workshops*

- **Topical Microbicide Strategic Plan**

  This blue ribbon panel of outside experts was convened on August 1, 2002, in Bethesda, MD to review a draft of the NIAID Topical Microbicide Strategic Plan. Panel members provided recommendations regarding the following major areas of microbicide research and development addressed in the plan:

  - The overall strategy for prioritizing the most promising candidate microbicides
  - The role of animal models for evaluating safety and efficacy
  - The transition to and conduct of efficacy trials.

  The draft document is undergoing revision to reflect panel recommendations and will be available in printed form and on the NIAID website (*http://www.niaid.nih.gov*) in FY 03.

- **The Role of Animal Models in Advancing the Understanding and Treatment of Autoimmune Diseases January 15-16, 2002**

  NIAID, the NIH Office of Rare Diseases, the NIH Office of Research on Women's Health, and the American Autoimmune Related Diseases Association sponsored

this workshop. A key topic of discussion was the importance of correlating findings in animal models of autoimmune disease with human disease. Animal models are essential tools in understanding the pathogenesis of disease and for testing novel approaches to prevention and treatment. Increased interaction between basic research scientists and clinicians will facilitate the application of findings in animal models to human diseases.

- **International Workshop in Autoantibodies for Prevention of Autoimmune Disease September 12-13, 2002**

  Many rare autoimmune diseases (fewer than 200,000 affecting persons in the United States) are characterized by the development of autoantibodies. Clinicians and basic research scientists discussed the utilization of autoantibodies as predictive markers of disease. While the role of autoantibodies is known in some clinical conditions, such as type 1 diabetes, little is known about the role of autoantibodies in the majority of autoimmune diseases. This meeting addressed methodologies for standardization and validation of assays that would allow their use as predictive diagnostic tools. Development of high-throughput methodologies for these assays was also discussed.

- **The Rectal Microbicide Workshop June 7-8, 2001**

  The workshop was held in Baltimore, Maryland to review the overall state of knowledge in this field, and identify what important research questions must be addressed to make progress in developing and deploying additional methods to reduce the risk of HIV transmission during anal sex. Break-out sessions were focused on several key areas:

  - What is the potential and what are mechanisms for stimulating industry involvement?
  - How can we advance from concept to candidates?
  - What are appropriate aims and endpoints of Phase I/II trials?
  - What are the principal design features for a rectal microbicide efficacy trial?

  In addition to providing an overview of the state of the art in this field, the workshop provided an opportunity to develop the multidisciplinary interactions necessary to advance rectal microbicide development.

- **The Topical Microbicides Pre-Clinical Workshop III January 31-February 1, 2001**

  The primary goal of the workshop, held in Baltimore, Maryland, was to assess the state of current knowledge about preclinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV. The workshop also served to: 1) review the progress of the Topical Microbicide Program Projects; 2) facilitate collaborations among scientists from different disciplines and among academic and private-sector participants; and 3) encourage interactions between FDA regulatory staff and commercial sponsors. Scientists from the public and private sectors, representatives from industry, government staff with responsibility for research programs and regulatory activities, foundation representatives, and members of the topical microbicide advocacy community attended the workshop.

- **The Topical Microbicides Program Project Reverse Site Visit January 9-10, 2002**

  Formerly known as the Preclinical Topical Microbicides Workshop, the primary goal of the Washington, DC site visit was to assess the progress of research conducted by the Topical

Microbicide Program Projects toward the preclinical development and evaluation of candidate products for preventing sexual transmission of bacteria, protozoa, and viruses, including HIV. Scientists from all projects of the six DMID-supported Topical Microbicide Program Projects, principal investigators of six newly funded Microbicide Preclinical Development Program projects (DAIDS and NICHD), representatives of government staff with responsibility for research programs, and several external reviewers attended the site visit. The overall consensus of the reviewers was communicated to the Principal Investigators.

- **NIH Working Group on HPV**

  The institute, in collaboration with NCI, continues to participate in this working group. The purpose of the group is to share information, coordinate research efforts, and explore possible collaborative efforts in the NIH HPV research program.

- **CFS Research Across NIH**

  A trans-NIH working group was established in the NIH OD (coordinated by ORWH) to coordinate and stimulate new research. This group replaces the former NIH CFS Coordinating Committee.

- **Trans-NIH Topical Microbicide Working Group**

  Established in the NIH OD to coordinate and plan for topical microbicide research, the working group meets periodically.

*Publications*

Publications, completed or in process in fiscal years 2001 and 2002, that demonstrate valid analysis for sex/gender and/or race/ethnicity for NIH-defined Phase III clinical trials include: Grimaldi et al., *J Clin Invest* 109:1625 (2002) (Betty Diamond, PI; AI51767). Estrogen alters thresholds for B cell apoptosis and activation. (*Premise*: Estrogen may help sustain B cells [which produce autoantibodies], suggesting a mechanism for increased prevalence of certain autoimmune diseases in women.)

# NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiologic research, research training, and information programs on many of the more debilitating diseases affecting Americans. NIAMS supports research on a number of diseases which disproportionately affect women including: osteoporosis, rheumatoid arthritis, temporomandibular joint disorders (TMJ), systemic lupus erythematosus (lupus), osteoarthritis, and scleroderma. Lupus, osteoarthritis, and scleroderma are diseases in which health disparities have been clearly identified. 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

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

Osteoarthritis is the most common disease of the joints. As the number of older people in our population continues to grow, osteoarthritis can be expected to affect more Americans. To address the need for the identification of new disease targets and the development of tools for understanding how to measure clinically meaningful information, NIAMS has recently launched the Osteoarthritis Initiative (OAI). In cooperation with the National Institute on Aging and several other federal and non-federal components, OAI will provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on biomarkers, x-rays, and outcome measures. In other research in osteoarthritis, NIAMS-supported researchers have examined a genetic link in inherited hand osteoarthritis.

Within the past two decades, there has been a major transformation in the treatments that are available to people with rheumatoid arthritis. Clinical studies in patients with early and established rheumatoid arthritis have broadened understanding of this pathogenesis and have fundamentally changed the therapeutic approach to this disease. Quantum leaps in therapy – including the use of early, aggressive therapy, combination therapy, and the introduction of anti-cytokine agents – have improved patients' quality of life, eased clinical symptoms, retarded the progression of joint destruction, and delayed disability. Not only are new treatment options being examined, but basic research is being conducted to understand disease development. NIAMS-supported researchers are examining several factors, such as enzyme expression, and genetic and non-genetic factors that may predict disease course and outcomes in minority populations.

Lupus is an autoimmune disease that mainly affects women of child-bearing age. Many health risks are associated with lupus disease activity and researchers have recently made advances in understanding the association between lupus and osteoporosis, the nervous system, and cardiovascular disease. Scientists are continuing to unveil information regarding potential genetic and ethnic links to disease manifestation, as well as how different ethnic groups cope with the disease. Additionally, researchers have determined that physicians appear to place more emphasis on laboratory features, while patients place more emphasis on function when evaluating disease activity.

Thanks to recent increases in the NIH budget, NIAMS has been able to expand its basic and clinical grant portfolio in scleroderma. In collaboration with the Office of Research on Women's Health (ORWH), ten new grants were recently awarded that will increase our understanding of the causes of scleroderma and bring us closer to finding treatments. NIAMS has also recently provided support for a Specialized Center of Research in Scleroderma which will investigate the possibility of both genetic and environmental causes of the disease.

Research suggests that TMJ disorders are more prevalent in women than men. These disorders are of interest to NIAMS since they can involve muscle pain, dislocation, and degeneration of the jaw joint. In a joint effort with ORWH, NIAMS has provided support for a Specialized Center of Research which is investigating the sex differences associated with TMJ pain.

## Accomplishments

### *Osteoporosis*

Osteoporosis is a skeletal disorder marked by reduced bone strength that predisposes a person to an increased risk of fractures. Among the bone diseases that afflict Americans, osteoporosis is by far the most prevalent, and is a major health risk for 28 million Americans. It has been estimated that some 10 million women in the United States have osteoporosis, and another 18 million have low bone mass and are at risk for osteoporosis.

The burden of health care costs due to osteoporosis is estimated to be $10 to $15 billion per year.

**Effects of Daily Treatment with Parathyroid Hormone**

Researchers examined bone biopsy specimens from patients with osteoporosis before and after treatment with daily injections of recombinant, human parathyroid hormone (PTH). Treatment for 18 or 36 months with daily injections of PTH were shown to increase the structural integrity of the bone. This effect explains the action of PTH treatment to reduce the incidence of osteoporosis-related fractures.

**Dietary Intake and Bone Mineral Density in the Elderly**

The Framingham Osteoporosis Study recently reported on the relationship between dietary protein intake and the 4-year change in lumbar spine, femoral neck, and radial shaft bone mineral density in this population-based study. Subjects included 391 women and 224 men; the mean age at baseline was 75 years. Results indicated that lower protein intake was significantly associated with greater bone loss at the spine and femur skeletal sites, but not the radial shaft (leg), with subjects having the lowest levels of protein intake showing the highest level of bone loss. Results were consistent after adjustment for important confounding factors, including body weight loss. The two key findings from this study were, first, that protein intake was found to be important in maintaining skeletal health in the elderly population, and second, a higher intake of animal protein did not appear to have any detrimental effects on skeletal integrity. This is an important study concerning the role of diet (particularly protein nutrition) on bone health maintenance of the aging population. The results of this study should encourage an adequate consumption of dietary protein in the elderly population and point to the potential benefits of this dietary change on skeletal health.

**Estrogen and Bone**

It is known that cells have proteins called receptors, which enable the cells to respond to sex hormones, estrogens, and androgens. But it is not clear just which cells are responsible for the effects of estrogen on bone, or even whether estrogen receptors are necessary for estrogen's effects. Two recent reports from NIAMS-supported researchers have provided important clues to the complex relationship between estrogen and bone, and have demonstrated that there is still much to be learned about the action of estrogen and the function of estrogen receptors. In the most surprising development, investigators have extended earlier work showing that estrogen decreases rates of programmed cell death (apoptosis) among bone-forming cells (osteoblasts), thus increasing bone formation and preventing net bone loss. Now they find that either estrogens or androgens can have this anti-apoptotic effect, and that it can be mediated by either estrogen receptors or androgen receptors, regardless of which sex hormone is present. It appears that the effects of sex hormones on bone reflect a previously unrecognized function of the estrogen and androgen receptors, which is distinct from their familiar action on reproductive tissues.

In a second report, investigators have shown that immune cells, called T cells, can contribute to the bone loss that occurs when estrogen levels are low. Whereas estrogen acts directly to prevent the death of osteoblasts, as described above, the moderating effect of estrogen on rates of bone breakdown is indirect. Estrogen levels apparently influence the activity of cells other than the cells (called osteoclasts) that actually resorb bone. T cells produce a protein that stimulates the formation of osteoclasts, and T cells are more numerous when estrogen levels are low. These findings have important implications for public health. Estrogen therapy, while effective, is not appropriate for all women, and cannot be used in men because of its effects on reproductive organs. Thus, there is much interest in developing drugs that

would have estrogen's beneficial effects on the skeleton but would not affect other tissues. The discovery of the novel mechanism by which estrogen prevents osteoblast apoptosis reveals a new target for drug development efforts. Although additional research will be necessary to determine whether this mechanism is also involved in estrogen's effects on other cells, such as T cells, this work opens up new possibilities for controlling bone loss.

**Bone Biology**

Other recent advances emphasize that we still have much to learn about bone biology, and that new knowledge often opens doors to new therapies. A variety of pharmacological agents and biochemical factors, some already familiar in other contexts, has been found to have unexpected effects on bone mass. For example, the actions of the cholesterol-lowering drugs called statins, the hormone leptin (originally identified as important for controlling obesity), and nitric oxide (best known for its effects on the heart and blood vessels) all provide clues to ways that new therapies might improve bone health.

**Osteoporosis Clinical Assessment Tools**

Using data from the Study of Osteoporotic Fractures (in which 7,782 women were studied), a clinical assessment tool was developed that could be used by women and their physicians to assess the risk of fracture. The variables that were used to develop the tool were: age, fracture after 50 years, maternal hip fracture after age 50, weight of less than 125 pounds, smoking status, use of arms to stand up from a chair, and bone mineral density. This assessment tool now needs to be validated in additional studies. In other studies it was shown that imaging, using an MRI scan of bone, in combination with the bone mineral density determination, could enhance the prediction for fracture risk.

**Genetics of Bone Mass**

Studies of the genetics of bone mass are increasingly productive, as new genomic resources become available. Continued effort in this area seems likely to identify still more new targets for development of osteoporosis therapies. For example, in work that drew together the efforts of many scientists, including researchers at one of the NIAMS Core Centers for Musculoskeletal Disorders, a gene that was previously unsuspected of playing any role in bone has emerged as a possible key to restoring bone in cases of osteoporosis. Studying families in which people have unusually dense, strong bones has revealed that an abnormality in a gene called LRP5 is responsible for the extra bone growth. Future work will focus on understanding how LRP5 functions, with the goal of using its action to stimulate new bone growth.

**Osteoporosis and Children**

When most of us hear the term osteoporosis, we think of elderly women whose bones are deteriorating. What we now understand is that osteoporosis may actually start in childhood. This means that we must widen our scope of study to include people of all ages in research on osteoporosis. Research studies on young girls revealed that minor variations in a gene for the bone protein, collagen, can lead to lower bone density. Major mutations (changes) in the collagen gene can lead to very disordered bone as in osteogenesis imperfecta, a disease manifesting in early life with multiple fractures and growth abnormalities. If minor variations in the collagen gene are associated with differences in bone density, these effects should be manifest in childhood. Researchers studied over 100 prepubertal girls, measured the bone mineral density, and also assessed the bone size and the genetic makeup of the collagen gene in each girl. They found that girls with a particular type of collagen gene variant had almost 50 percent lower bone mineral density than girls with a different collagen gene variant. Thus, these minor variations in the gene for collagen protein, while not causing apparent disease, may define a high susceptibility group for osteoporosis later in life. Identifying and understanding genetic susceptibility to osteoporosis early in life may facilitate the targeting

of interventions to those who will most profit from them.

## *Rheumatoid Arthritis*

In rheumatoid arthritis, the immune system, for unknown reasons, attacks a person's own cells inside the joint and results in pain, swelling, stiffness, and loss of function. Scientists estimate that about 2.1 million people, or 1 percent of the U.S. adult population, have rheumatoid arthritis.

### Alternative Therapy for Rheumatoid Arthritis

The roots of Thunder God Vine, a plant whose leaves and flowers are highly toxic, have been used medicinally in China for over 400 years. A root extract of this plant was shown to safely and effectively reduce pain and inflammation in a small group of people with treatment-resistant rheumatoid arthritis, according to a study supported in the Intramural Research Program of NIAMS. This randomized, double-blind, placebo-controlled trial is the first to test the use of an extract of this vine in rheumatoid arthritis patients in the United States. Twenty-one rheumatoid arthritis patients completed a 20-week clinical trial of the ethanol/ethyl acetate extract. Patients were randomly assigned to one of three treatment groups: placebo, low-dose extract, or high-dose extract. After 4 weeks, 80 percent of patients in the high-dose group, and 40 percent in the low-dose group, showed rapid improvement in symptoms compared with no improvement in the placebo group. Side effects were minor for all three treatment groups. Longer-term studies with larger numbers of patients are needed to confirm the safety and benefits of the treatment, but this extract is a promising treatment for rheumatoid arthritis. It is unique, because it slows down the overactive immune system, reduces inflammation by turning off genes that encode inflammatory molecules like tumor necrosis factor, and reduces the activity of B and T cells (immune cells). Researchers believe that this plant extract has the potential to treat other immune diseases such as lupus, and they are planning further studies.

### New Insights into the Development of Arthritis

Both rheumatoid arthritis and osteoarthritis are characterized by inflammation of the joints and destruction of the cartilage in those joints. A particular enzyme (Cyclo-oxygenase-2 or Cox-2) is involved in the production of inflammatory molecules. The expression of this enzyme is increased in the synovial tissue in the joints of rheumatoid arthritis patients and in the affected cartilage in osteoarthritis patients. Consequently, Cox-2 has become a major target for the treatment of inflammatory diseases such as rheumatoid and osteo-arthritis. However, the full physiological role of Cox-2 in the development of these diseases remains unclear. A model for rheumatoid arthritis has been developed by injecting normal mice with collagen, a major component of cartilage. These mice develop an arthritis characterized by the development of antibodies to collagen. Antibody complexes become deposited in the joints resulting in inflammation and swelling of the joints followed by increased numbers of lymphocytes in the joint tissue and cartilage destruction. In addition, normal mice will develop arthritis when injected with antibodies against collagen from arthritic mice. To understand the role of Cox-2 in the pathogenesis of arthritis, researchers injected mice that lack Cox-2 with collagen. These animals did not produce antibodies against collagen and showed no inflammation or cartilage destruction in their joints. In addition, arthritis could not be induced in the Cox-2 deficient mice by the injection of antibodies from normal arthritic mice. In looking at the public health implications of these studies, we know that rheumatoid arthritis and osteoarthritis are common afflictions of the adult population, and that therapeutic agents alleviate discomfort and maintain function for those affected. However, the

pathogenesis of these diseases remains unclear. These recent studies shed new light on the role of Cox-2 in arthritis by showing that Cox-2 is essential for the production of antibodies, as well as inflammatory molecules involved in collagen-induced arthritis. Furthermore, the presence of antibodies against collagen alone does not induce arthritis. Rather, the inflammatory products of Cox-2 are also essential for the induction of arthritis.

**New Research Registry to Examine Rheumatoid Arthritis in African Americans**

Four major medical centers in the southeast United States will soon be gathering data for investigators interested in the genetics of rheumatoid arthritis in African Americans. NIAMS, with support from ORWH and the National Center on Minority Health and Health Disparities, awarded a research contract for the Consortium for the Longitudinal Evaluations of African Americans with Early Rheumatoid Arthritis Registry to the University of Alabama at Birmingham. Other participating centers include Emory University, the Medical University of South Carolina, and the University of North Carolina. The registry will provide clinical and x-ray data and DNA to help scientists analyze genetic and nongenetic factors that might predict disease course and outcomes of rheumatoid arthritis in this population.

### *Temporomandibular Joint Disorders*

TMJ disorders are a heterogeneous group of chronic pain conditions involving the temporomandibular joint and/or surrounding musculature, including the muscles of mastication. While pain is the primary symptom of these disorders, there are indicators that have been used to reflect potential underlying pathology, which may occur with or without pain. Studies suggest that TMJ disorders are more prevalent in the young and in women.

### *Specialized Center of Research on Sex and Gender Factors Affecting Women's Health*

Recently, ORWH has provided support for several new Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health. As part of this initiative, a NIAMS-supported study at the University of Maryland will explore the neural basis of pain associated with TMJ disorders. This research will provide new information regarding the perception of, and response to, painful stimulation and pathological pain.

## Initiatives

*Requests for Proposals (RFPs)*

- **Biomarkers for Rheumatic and Skin Diseases**

  This RFP was issued by NIAMS in February 2001 to solicit proposals that would identify, characterize, and evaluate biochemical/biological markers to assess rheumatic and skin disease risk, onset, progression, and response to treatment. (NIH-NIAMS-BAA-01-05)

- **Innovative Therapies for Rheumatic and Skin Diseases**

  NIAMS issued this RFP in July 2001 to encourage the design, development, and execution of clinical studies to establish the safety and gather enough preliminary evidence of efficacy of new and innovative therapeutic approaches to rheumatic and skin diseases. (NIH-NIAMS-BAA-02-01)

- **Pilot and Feasibility Trials for Osteoporosis**

  The objectives of this initiative were to identify and begin clinical testing of potential bone active agents, and to perform initial dosing trials and select appropriate populations and endpoints for larger-scale testing in appropriately powered clinical intervention trials. This RFP was issued by NIAMS in February 2002. (NIH-NIAMS-BAA-02-05)

*Requests for Applications (RFAs)*

- **Hyperaccelerated Award/Mechanisms for Immunomodulation Trials**

  Issued in October 2000 by NIAID, NIA, NIAMS, NIDDK, and NINDS, this RFA encouraged mechanistic studies in clinical trials of immunomodulatory interventions of immune system-mediated diseases. These include asthma and allergy; graft failure in solid organ, tissue, cell, and stem cell transplantation; and autoimmune diseases. (AI-01-001)

- **Bone Formation and Calcification in Cardiovascular Disease**

  The objective of this initiative, which was issued in January 2001, was to stimulate research that addressed the pathophysiologic and molecular mechanisms of vascular calcification, and the possible links between vascular calcification, bone formation, and cardiovascular disease. Support for this RFA was provided by NHLBI and NIAMS. (HL-01-014)

- **High-risk Arthritis and Musculoskeletal and Skin Disease Research**

  The purpose of this RFA, issued in January 2001 by NIAMS, was to broaden the base of inquiry in fundamental biomedical and biomedical technology research by encouraging research that involves an especially high degree of innovation and novelty and, therefore, requires a preliminary test of feasibility. (AR-01-004)

- **Sex-based Differences in the Immune Response**

  NIAID, NINDS, NIAMS, ORWH, and the National Multiple Sclerosis Society provided support for this RFA, which was released in February 2001, to identify, characterize, and define differences in the immune response between males and females, including responses to exogenous and self-antigens, the innate and adaptive immune response, systemic and mucosal immune response, and regulation of the immune system by hormonal and non-hormonal sex differences. (AI-01-001)

- **High-risk Arthritis and Musculoskeletal and Skin Diseases Research**

  The purpose of this RFA, issued in November 2001 by NIAMS, was to broaden the base of inquiry in fundamental biomedical and biomedical technology research by encouraging research that involves an especially high degree of innovation and novelty and, therefore, requires a preliminary test of feasibility. (AR-01-008)

- **Building Interdisciplinary Research Centers in Women's Health**

  In December 2001, ORWH, NIA, NIAAA, NIAMS, NICHD, NIDCR, NIDDK, NIMH, ODS, and AHRQ supported this RFA which promoted research career development of junior faculty members, to be known as Interdisciplinary Women's Health Research (IWHR) Scholars, who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, clinical, and/or health services research relevant to women's health. (OD-02-001)

- **New Research Strategies for Evaluation and Assessment of Bone Quality**

  NIAMS and NIDCR supported this RFA, issued in December 2001, to encourage research that provided novel means to assess bone quality and elucidate the relationships among disease- and aging-related changes in bone quality, gender-related variations in bone quality, and increased bone fragility and fracture susceptibility. (AR-02-002)

- **Specialized Centers of Research in Rheumatoid Arthritis and Osteoporosis**

  This RFA, issued by NIAMS in December 2001, was designed to foster a coordinated research effort that strongly emphasizes basic disciplines, but also involves significant interaction between basic

research and clinical investigations in one of these two disease areas. (AR-02-005)

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

  ORWH, NIAMS, NICHD, NIDDK, NIDA, NIEHS, NIMH, and FDA supported this RFA, which was released in December 2001 to establish a new program, Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health. These centers provide new opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health. NIAMS is the service center for the administration of this program. (OD-02-002)

- **Multidisciplinary Biobehavioral Rheumatic Diseases Workshop**

  Biopsychosocial perspectives and approaches to research can contribute to our understanding of etiology, course, and outcomes of rheumatic diseases. To increase integration of such approaches into rheumatic diseases research, NIAMS identified a fundamental need to foster interdisciplinary communication and collaboration among behavioral scientists, physicians, and basic scientists with interests in, or relevant to, these diseases and issued this RFA in May 2002 for the development of a workshop to discuss the state of the science. (AR-02-011)

*Program Announcements (PAs)*

- **Biology of the Menopausal Process and Associated Health Conditions during and after Menopause**

  NIA, NIAMS, NICHD, and NIDDK provided support for this PA, released in March 2001, to encourage research that elucidates molecular and cellular mechanisms underlying the menopausal process, and the pathophysiologic connections of that process with various health problems and conditions of peri- and postmenopausal women. (PA-01-067)

- **The Management of Chronic Pain**

  Support for this PA was provided by NINR, NIA, NIAMS, NCCAM, NCI, NICHD, NIDCR, NIDA, and NINDS in July 2001. This PA encouraged research aimed at determining the most effective interventions to remove barriers to effective treatment; the most effective pharmacological and non-pharmacological therapies, including complementary and alternative therapies; the identification of assessment tools for patients unable to verbalize their pain; and the identification of effective pain management strategies for individuals with disabilities and underserved populations. (PA-01-115)

- **Pathophysiology and Treatment of Chronic Fatigue Syndrome**

  Applicants were encouraged to design studies that provided a better understanding of both chronic fatigue syndrome (CFS) pathogenesis and pathophysiology with the goal of developing improved diagnostic and intervention strategies. This PA was issued by ORWH, ODS, OBSSR, NCCAM, NIAAA, NIAID, NIAMS, NICHD, NHLBI, NIEHS, and NINR in December 2001. (PA-02-034)

- **Identifying Functional Links between the Immune System and Brain Function Including Behavior**

  NIMH, NINDS, NIDA, and NIAMS provided support for this PA to study neuroimmune molecules and mechanisms involved in regulating normal and pathological central nervous system function. It was issued in January 2002. (PA-02-045)

- **Women's Health in Sports and Exercise**

  Support for this initiative was provided by NIAMS, NICHD, and ORWH in June 2002. The purpose of this PA was

to improve the basic knowledge of the pathophysiology of sports injuries in women. This research would help to solve the puzzle of why female athletes are more susceptible to certain types of injury. (PA-02-115)

*Conferences and Workxhopx*

- **Menopausal Hormone Therapy**

  In October 2002, NIAMS participated in an NIH scientific workshop entitled "Menopausal Hormone Therapy" to review the results from a critical portion of the Women's Health Initiative (WHI). WHI includes an exceptionally large-scale clinical trial of the effects of hormone therapy and calcium and vitamin D supplementation in postmenopausal women. The Menopausal Hormone Therapy scientific workshop placed these studies in the context of other research on hormone therapy, and helped clinicians and patients understand the implications of the new information for individual decisions about the use of hormone therapy. In addition, the workshop provided information about currently available alternatives to hormone therapy for the treatment of osteoporosis and the symptoms of menopause itself. Finally, workshop participants discussed recent scientific advances that suggest routes to new treatments for postmenopausal osteoporosis. The conference was sponsored by ORWH.

- **NIAMS Fibromyalgia Program Assessment**

  The purpose of the Fibromyalgia Program Assessment was to provide NIAMS staff with information and expert recommendations regarding the NIH-funded fibromyalgia research portfolio. The assessment was intended to provide an update on the current state of funded fibromyalgia research, identify common difficulties in conducting this research and suggest problem-solving strategies, and identify gaps in the current portfolio and opportunities and potential new directions for future research. Further, the process was designed to enhance communication and promote collaboration among investigators – invigorating research efforts aimed at understanding, treating, and preventing this disorder.

## *Health Disparities*

The NIAMS Strategic Health Plan for Reducing Health Disparities targets three diseases that disproportionately affect minority women: lupus, scleroderma, and osteoarthritis.

- **Systemic Lupus Erythematosus**

  Lupus is an autoimmune disease that mainly affects women of childbearing age. Common symptoms of lupus include painful or swollen joints, unexplained fever, skin rashes, kidney problems, and extreme fatigue. Women are nine times more likely than men to have the disease. It is also three times more common in African American women than in Caucasian women, and is more common in women of Hispanic, Asian, and Native American descent. African American women tend to develop the disease at a younger age and to develop more serious complications than Caucasian women.

- **Lupus and Associated Health Risks**

  Because survival rates of people with lupus have improved over the last two decades, investigators are now paying increasing attention to the complications leading to mortality later in life, as well as progressive morbidity. Increasing numbers of young women with lupus are experiencing fractures, strokes, and heart attacks, complications that are typically associated with aging women without lupus. In recent studies, investigators have demonstrated an association between decreased bone mineral density and both an increased carotid plaque index and the presence of coronary artery calcification in a cohort of young women with lupus. These findings indicate that women

with lupus are at increased risk for both clinical osteoporosis and cardiovascular complications at a much younger age, and suggest that more aggressive control of the risk factors for atherosclerosis and osteoporosis are needed to prevent these conditions in women with lupus.

- **Lupus: Molecular Mechanisms of Brain Changes Revealed**

  Researchers supported by NIAMS have focused on the involvement of the nervous system in some people with lupus, and have reported significant advances in our understanding of the molecular mechanisms involved in changes that can occur in the brains of people with lupus. These researchers reported that the antibodies that attack the DNA of people with lupus can also attack the molecules that bind a particular neurotransmitter (glutamate) involved in nerve cell activity. These same antibodies can cause death of the nerve cells, and they are present in the fluid of the brain and spinal cord (cerebrospinal fluid), possibly affecting brain function. While researchers had previously documented cognitive dysfunction in some patients with lupus, it was not clear what mechanism was involved in dysfunction. This new research finding not only helps us to understand the nervous system complications in lupus, which also provides some new therapeutic possibilities for these aspects of lupus that can be quite challenging for patients, their families, and their health care providers.

- **Potential Gene Therapy Treatment for Lupus**

  In basic research on lupus, scientists have recently issued the first report describing the application of gene transfer technologies to experimental models of lupus. In this report, investigators describe the therapeutic application of intramuscular injection of DNA encoding a protein that blocks lupus onset in lupus-prone mice. These results highlight the value of DNA transfer for the treatment of autoimmune diseases.

- **Genetic Differences Found in African American and European American Lupus Families**

  Among the many mysteries of health disparities is the fact that no one knows why more African Americans die of lupus and develop more severe complications, such as kidney failure, compared with people of European descent. NIAMS-supported researchers are studying the inherited component of lupus in order to identify the specific genes that predispose African Americans to develop lupus. Using DNA, researchers have investigated the linkage patterns in African American and European American families, and have determined that African Americans have different genetic risks for developing lupus B, a region of chromosome 1 is associated with the development of lupus in African American families. They also identified two regions of chromosome 11 associated with lupus in subsets of the African American families. In European American families, researchers found a genetic linkage near the top of chromosome 4 that contributes to lupus. These results suggest that the genetic origins of lupus may differ in African Americans and European Americans, and may help explain why sometimes the disease has a more severe prognosis in African Americans.

- **Ethnicity and Disease Activity**

  A person's ethnicity does influence his or her experience with lupus. Ethnicity includes race, as well as cultural values and beliefs and practices, which in the United States are associated with a certain socioeconomic status. Ethnicity, in fact, may affect patients with lupus. This information comes from the study **LU**pus in **MI**norities: **NA**ture versus Nurture (LUMINA), conducted by NIAMS-supported researchers. The study, which includes over 300 African American, Hispanic, and Caucasian lupus patients aged 20 to 50 years, is designed to identify the relative contribution of genetic and socioeconomic

factors on the course and outcome of lupus among these three ethnic groups. LUMINA researchers are investigating features such as socioeconomic-demographic characteristics (e.g., age, gender, marital status, income, health insurance); clinical attributes (e.g., disease onset and duration, clinical manifestations, treatments); behavioral-psychosocial factors (e.g., social support, abnormal illness-related behaviors, feelings of helplessness, acculturation [Hispanics only]); immunologic factors (e.g., autoantibodies); and genetic factors. To date, the LUMINA study reveals that ethnicity, more than several other factors, does make a significant impact on some aspects of the disease. Both African American and Hispanic lupus patients tend to develop lupus earlier in life, experience greater disease activity at the time of diagnosis (including kidney problems), and have more severe disease overall than Caucasian patients. Further, African American patients have a higher frequency of neurologic problems such as seizures, hemorrhage and stroke, while Hispanic patients experience cardiac disease more frequently. Although LUMINA results, to date, do not implicate genetic influences as commonly responsible for differences in the early course of disease among these ethnic groups, researchers believe there are relevant genetic factors to be identified. NIAMS is also supporting several groups of investigators who are attempting to identify the complex genetic factors that contribute to lupus susceptibility.

- **Patient and Physician Perceptions of Disease Activity in Lupus**

  Additional insights into health disparities came from a recent report from NIAMS-supported, long-term study of patients in the LUMINA study. In this report, researchers compared the patient's and the physician's assessment of disease activity in a multiethnic (Hispanic, African American, and Caucasian) group of patients with lupus. Researchers in this study reported that a discrepancy was exhibited by 58 of the patients, meaning that patients and their physicians rate disease activity in lupus differently. Physicians appear to place more emphasis on laboratory features, while patients place more emphasis on function. Ethnicity did not account for the discrepancies in perception of disease activity.

- **Coping Skills among Ethnic Groups**

  Researchers have documented differences in the damage caused by lupus in studies of Hispanic, African American, and Caucasian individuals with this disease. Patients from these three populations had similar disease duration, but the proportion of patients accruing any organ damage was higher among Hispanics than among the other two groups, confirming the greater negative impact of lupus among members of this ethnic group. The association of damage with poor coping skills was reported for the first time, and it suggests that approaches designed to modify patients' behaviors and attitudes to their illness could reduce the damage to the body caused by lupus.

### *Osteoarthritis*

Osteoarthritis, or degenerative joint disease, is the most common form of arthritis. It is a slowly progressing disease characterized clinically by pain, deformity, enlargement of the joints, and limitation of motion. The disease usually occurs late in life and most commonly affects the hand and large weight-bearing joints. Approximately 20.7 million adults have physician-diagnosed osteoarthritis. Additionally, more women than men suffer from severe osteoarthritis, and African Americans have higher rates of hip and knee osteoarthritis.

- **Osteoarthritis Initiative**

  NIAMS and NIA have joined with several other institutes and centers and four pharmaceutical companies, in launching the Osteoarthritis Initiative, a public-private partnership aimed at developing clinical research resources

that support the discovery and evaluation of biomarkers and surrogate endpoints for osteoarthritis clinical trials. This is a 7-year project that will recruit 5,000 men and women, aged 50 and above, who are at high risk for developing symptomatic knee osteoarthritis. Four clinical sites and one data coordinating center have been selected to establish and maintain a natural history database that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification. It is expected that this consortium can serve as a model for future endeavors linking the public and private sectors.

- **Genetic Regions Linked to Inherited Hand Osteoarthritis**

  Specific chromosomal areas are likely to play a role in the inheritance of hand osteoarthritis, a form of degenerative joint disease that is a major cause of disability in people age 65 and over. NIAMS-supported researchers have reported the first large-scale study of hand osteoarthritis in the general U.S. population. The project was a search for genetic markers that are linked to the amount of hand osteoarthritis in parents and children participating in the Framingham Heart Study. Half of the participants, and 30 percent of their children, had at least one joint affected by osteoarthritis. Results suggest eight genetic regions may be linked to susceptibility for hand osteoarthritis. In the future, a test to determine who carries osteoarthritis susceptibility genes could help people reduce their risk for osteoarthritis with lifestyle adjustments. In addition, an understanding of how genes cause osteoarthritis could enhance the development of new treatments.

### *Scleroderma*

Scleroderma, often referred to as a single disease, is actually a symptom of a group of diseases that involves the abnormal growth of connective tissue, which supports the skin and internal organs. In some forms of scleroderma, hard, tight skin is the extent of the disease. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as the heart, lungs, and kidneys. Currently, there is no treatment that controls or stops the underlying problem: the overproduction of collagen.

- **Scleroderma Research Receives a Boost from Multiple NIH Grants**

  Ten new research grants on scleroderma have been funded by NIAMS. The grants, totaling more than $2 million per year, include both basic and clinical research studies. ORWH co-funded two of the grants. Projects included research in: 1) cellular and molecular pathways in scleroderma, 2) cell transfer between mother and child in scleroderma, and 3) innovative therapies in scleroderma. Currently there is no treatment that controls or stops the underlying problem of scleroderma – the overproduction of collagen.

- **Specialized Center of Research in Scleroderma**

  Although the causes of scleroderma are unknown, many researchers are investigating the possibility of both genetic and environmental influences. This center focuses on molecular approaches to better understand the pathogenic mechanisms of scleroderma, especially genetic factors, and the predictors of outcomes in scleroderma. One specific aim of the center is the evaluation of potential demographic, clinical, autoantiboty, and genetic predictors of disease outcomes in Caucasians, African Americans, and Mexican Americans.

## Initiatives

*Requests for Proposals (RFPs)*

- **Data Coordinating Center for Osteoarthritis Initiative**

  NIAMS issued this RFP in July 2001 to solicit proposals for a Data Coordinating Center for the Osteoarthritis Initiative that would be responsible for assimilating, storing, organizing, and coordinating the dissemination of data and x-ray images and the storage of biological specimens from 5,000 individuals enrolled. (NIH-NIAMS-BAA-02-02)

- **Clinical Centers for Osteoarthritis Initiative**

  This contract was for a Clinical Center that would be enrolling subjects and collecting data for the Osteoarthritis Initiative. This RFP was issued by NIAMS in July 2001. (NIH-NIAMS-BAA-02-3)

*Requests for Applications (RFAs)*

- **Specialized Centers of Research in Systemic Lupus Erythematosus and in Osteoarthritis**

  The purpose of this RFA, issued in January 2001 by NIAMS, invited applications for Specialized Centers of Research in osteoarthritis or in systemic lupus erythematosus. This RFA was established to foster a coordinated research effort that strongly emphasizes basic disciplines, but also involves significant interaction between basic research and clinical investigations in one of these two disease areas. (AR-01-005)

- **Neuropsychiatric Systemic Lupus Erythematosus**

  The purpose of this RFA, issued in July 2001 by NIAMS, is to encourage exploratory/developmental research on the pathogenesis of neuropsychiatric manifestations of systemic lupus erythematosus and on the development of innovative therapeutic approaches and diagnostics for this form of lupus. (AR-01-007)

*Comferences and Workshops*

- **Health Disparities in Arthritis and Musculoskeletal and Skin Diseases**

  The goals of this conference, which was held in December 2000, were to review current knowledge about health disparities in arthritis and musculoskeletal and skin diseases and promote new research opportunities and approaches to eliminating disparities in the frequency and course of these diseases in ethnic groups at increased risk. The meeting focused on four areas: measuring and interpreting observed disparities, genetic and environmental factors leading to disparities, social and behavioral factors influencing disease frequency and impact, and strategies to eliminate disparities. Cosponsors included: NIAMS, NCMHD, ORWH, ODP, OBSSR, CDC, the Arthritis Foundation, the American College of Rheumatology, the American Academy of Orthopaedic Surgeons, and the American Academy of Dermatology.

- **SLE: Targets for New Therapeutics**

  The purpose of this conference, held in February 2002, was to facilitate the exchange and integration of scientific information between scientists working in disparate areas relating to systemic lupus erythematosus (SLE), and to identify novel strategies for clinical intervention. The conference was sponsored by the S.L.E Foundation of New York, NIAMS, the Lupus Research Institute, ORWH, NIAID, and Merck & Company, Inc..

*Position and Component in Women's Health Research*

- **Program Director for Health Disparities and Women's Health Research**

  Charisee Lamar, Ph.D., M.P.H., is the new Program Director for Health Disparities and Women's Health Research, a newly created position

in the Centers Program which is part of NIAMS' Extramural Program. Dr. Lamar is overseeing 11 Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health for ORWH, the primary sponsor of this new program for which NIAMS provides administrative support. In addition, Dr. Lamar will develop and oversee extramural initiatives under the NIAMS strategic plan for research on health disparities.

## National Institute of Biomedical Imaging and Bioengineering

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest of the research institutes within the National Institutes of Health and was established by law in December 2000. NIBIB received its first appropriation and grant funding authority in FY 2002. As the NIBIB continues to grow and structure programs, new initiatives will be developed to support a variety of scientific areas, including programs aimed at fostering women's health research.

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

During FY 2002, NIBIB funded grant awards that were focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to new drug delivery systems designed specifically for women health diseases, disorders, and conditions such as breast cancer, osteoporosis, and temporomandibular joint diseases (TMJ). NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. NIBIB-supported researchers 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 researchers are working on novel drug delivery treatments that will promote bone resorption for women suffering from osteoporosis.

To identify advanced imaging technologies for specific biomedical applications, including TMJ research, NIBIB sponsored a workshop entitled "Thermographic Approaches to Medical Diagnosis and Therapy" with the Department of Energy in December 2001, and held a major international conference with the Institute of Electrical and Electronics Engineers in July 2002. The NIBIB also conducted a biosensor symposium coordinated by the NIH's Bioengineering Consortium (BECON) (administered by NIBIB) to identify advanced biosensor technologies for biomedical research applications including mechanical sensing appropriate for TMJ research. In September 2002, NIBIB was also a cosponsor of the Medical Implant Information Performance and Policies workshop which promoted biomaterials development. Several initiatives addressing TMJ, as well as other medical implants, will be undertaken as a result of the recommendations from this workshop. In addition, NIBIB participates on the NIH Temporomandibular Disorders Interagency Working Group and will collaborate with the National Institute of Dental and Craniofacial Research on the initiative, "Research Registries and Repositories for the Evaluation of the Temporomandibular Joint Implants" and the upcoming conference on "Joint and Muscle Dysfunction of the Temporomandibular Joint" in May 2002.

NIBIB also participated in the National Institute of Child Health and Human Development's (NICHD) Small Grants Program that provides support for research in population science, reproductive science, pregnancy and birth, human growth and nutrition, normal and atypical development, pediatric, adolescent and maternal HIV/AIDS, genetics and teratology, developmental biology, and medical rehabilitation research. Through this partnership with NICHD, NIBIB funded a project aimed at improving the resolution of an ultrasound imaging method for testicular perfusion in children, a condition that often causes infertility when not diagnosed early. This new methodology will offer a faster and more accurate diagnostic tool.

As NIBIB continues to grow, new multidisciplinary research and training programs will be developed which will bridge the fields of bioengineering and bioimaging. Consistent with these goals, NIBIB has conducted several meetings in areas relevant to the NIBIB mission and has plans for future meetings to request input from the extramural community on program directions. As programs are developed in response to the needs of the national community, they will include the needs of the female population and research areas, such as TMJ and breast cancer, that require a multidisciplinary approach.

## Highlights

Dr. Roderic Pettigrew, NIBIB Director, began his tenure at NIH in September 2002. Since his arrival, NIBIB has been working to reorganize the institute to facilitate the support of research in areas of relevance to NIH and NIBIB missions. Currently, NIBIB does not have an office dedicated to research on women's health.

## Initiatives

In FY 2002, NIBIB participated in a number of initiatives that address technology development related to biomedical imaging and bioengineering that may have applications in different disease areas relevant to women's health ranging from bioinformatics development to advances in imaging technology. Examples of these initiatives include the following:

- ***Mathematical Models of Cytokine/Chemokine Networks in HIV-associated Lung Disease***

  Cofunded with NHLBI, the objective of this Request for Application is to develop and validate mathematical models of cytokine/chemokine networks associated with immunodeficiency virus type 1 (HIV1)-associated lung disease. These computational models would offer new approaches to complex reactions and clarify existing data and theories on the pathogenesis of HIV1 in the lung. (RFA-HL-02-009)

- ***Innovation Grants for AIDS Research***

  Cofunded with NIAID, NICHD, NIDCR, NIDDK, and NIMH, the objective of this Program Announcement is to encourage novel and significant hypotheses that would have a substantial impact on current understanding of HIV/AIDS or projects that develop innovative techniques or methods with *in vivo* relevance that will provide new insights into HIV pathobiology. This could include mitigating the sided effects of antiretroviral therapies in pregnant women and children. (PA-02-046)

## Supporting Research

NIBIB recognizes the significance of supporting research to address health disparities. In FY 2003, NIBIB plans to fund projects to specifically target technology development that would address these public health needs. Medical imaging is critical for quality health care, yet due to its expensive nature, it remains widely unavailable to large segments of the population. The goal of a recently published Request for Applications (RFA-EB-03-006) is to stimulate research in the area of novel investigations for reduced-cost imaging

devices that can be broadly applied to research on biological or disease processes. Novel imaging tools, such as portable ultrasound machines or radiographic devices, could be cheaply and widely distributed; thereby, increasing access and affordability. In addition, NIBIB recently published another RFA (RFA-EB-03-005) that will support the design and development of novel telehealth instrumentation or technologies that can be applied to a broad spectrum of disorders or diseases. Development and/or improvements to telehealth technologies will also likely promote access to healthcare for rural or underserved populations.

## National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) has a broad research mission dedicated to understanding the processes governing the growth and development upon which the health of infants, children, youth, and families depends. Based on this mission, part of the institute's research portfolio is also dedicated to advancing women's health. NICHD is home to much of the nation's leading science related to reproductive processes, pregnancy and childbirth, and women with disabilities. As such, basic research and studies on health conditions such as endometriosis, uterine fibroids, premenstrual syndrome, menopause, polycystic ovary syndrome, premature ovarian failure, pelvic floor disorders, and HIV/AIDS are part of the institute's research portfolio.

### IC Offices, Divisions, or Working Groups Focused on Women's Health Research

While research on women's health is an integral part of the NICHD mission, a significant portion of the institute's research in this area is supported by the Pregnancy and Perinatology Branch and the Pediatric and Maternal AIDS Branch, both located in the NICHD Center for Research on Mothers and Children, as well as by the Reproductive Sciences Branch and the Contraceptive and Reproductive Health Branch, located in the NICHD Center for Population Research.

### Accomplishments

Highlighted below are some of the many NICHD research accomplishments related to women's health.

#### *Adolescent Health*

**HIV/AIDS: The Changing Faces of an Epidemic**

As the face of HIV grows increasingly younger, NICHD continues its focus on HIV in the adolescent population through its new Adolescent Medicine Trials Network (ATN). In FY 2001, NICHD established the network to conduct HIV-related research involving American youth in the areas of prevention, drug development, and clinical management. Now that this infrastructure is in place, ATN researchers will partner with the HIV Vaccine Trials Network to launch a clinical trial of a vaccine candidate to determine its effectiveness in teens.

**Reach for Health**

To address the challenge of reducing the high rates of unplanned pregnancy, sexually transmitted diseases, and HIV infection among minority youth, scientists have developed an intervention program called "Reach for Health." This program combines comprehensive health education with community service. The young adults who participated in the service-learning program were less likely to report engaging in sexual activity than were the students who participated in only the health education program. The scientists also found that this type of program could influence student behavior for as long as 2 years after completing the program. These findings

show that this kind of creative, research-based intervention, which promotes active and positive community involvement, can alter behavior by delaying sexual activity in young, vulnerable teenagers.

**Mothers' Attitudes and Daughters' Sexual Behavior**

Family characteristics, including parent-teen relationships, parental attitudes toward sex, family values, education, and economic status, are all known to influence young peoples' decisions about sexual behavior. However, much of what is currently known reflects only what adolescents themselves report about their families' attitudes and characteristics. Findings from a new data analysis of a major national survey indicates that 14- and 15-year-old girls are more likely to delay having sex if their mothers report satisfactory relationships with them, strong disapproval of their daughters having sex, and frequent communication with parents of their daughters' friends. NICHD led the study, which was also supported by eight other NIH institutes, the Centers for Disease Control and Prevention, other Department of Health and Human Services agencies, and the National Science Foundation.

## *Hormone Therapy, Contraceptives, and Health Risks*

**Hormones and Breast Cancer**

Scientists have long suspected that the balance between female and male hormones influences breast development. However, the roles that these hormones play are not clearly understood in the normal growth of breast tissue and in the abnormal growth that leads to breast cancer, the most common form of cancer among women. Previous research has shown that exposure to estrogen increases the risk of breast cancer, possibly by stimulating the growth of breast tissue. Scientists believe that extended exposure to estrogen may underlie the risk of breast cancer that is associated with hormone therapy. This notion is complemented by new evidence suggesting that male hormones, called androgens, are critical in the process and may inhibit the development of breast tissue. In more recent studies, scientists have clearly shown in an animal model that hormone therapy with estrogen causes breast tissue to grow. At the same time, they also showed that adding the male hormone, testosterone, to the therapy significantly reduced breast tissue growth. These findings suggest that combined estrogen and androgen hormone therapy might reduce the risk of breast cancer associated with estrogen replacement. These findings provide researchers with the foundation to develop a treatment that will reduce estrogen's stimulation of breast tissue while providing other benefits, such as increased bone and muscle strength and improved sexual function for many women.

**Breast Cancer and Oral Contraceptives**

Oral contraceptives are the most widely used method of family planning among women in their 20s. However, scientific research has produced conflicting information on whether taking oral contraceptives increases a woman's risk of breast cancer during her mature years, the period of highest risk. Recently, a very large study showed that women who took oral contraceptives at some point in their lives were no more likely to develop breast cancer between the ages of 35 and 64 than other women. The study also showed that oral contraceptives do not pose a higher risk of breast cancer for African American women or for women whose nearest female relatives had breast cancer. The large scale of the study, conducted through the NICHD Women's Contraceptive and Reproductive Experiences Study (Women's CARE), increases confidence in the results and helps resolve conflicting information from previous and smaller studies.

**Osteoporosis and Injectable Contraceptives**

Osteoporosis, a disease that thins and weakens bones to the point that they break easily, is a major health risk for 28 million Americans, especially women. More than 1.5 million fractures annually are related

to osteoporosis and, in older individuals, fractures may end the ability to live independently or even lead to death. Injectable contraceptives have been implicated in osteoporosis, but evidence has been inconclusive. In the largest and longest study to date of the relationship between injectable contraceptives and bone density, the scientists followed women for 4 years as they used, and then stopped using, the injectable contraceptive, DMPA. The study showed that while women lost bone density while using DMPA, a large majority recovered most of their bone mass within 2 years of stopping use of the contraceptive. These findings may reassure women who have used DMPA and may prefer to continue its use, because of its convenience and reliability. But the findings indicate more research is needed with the youngest women (ages 18 to 21) using DMPA because their recovery of lost bone mass after stopping DMPA was less clear.

## *Genetic Disease*

### A Genetic Disorder in Girls

Rett syndrome (RTT) is a severe genetic disorder that gradually halts healthy development in infant and toddler girls. Girls with RTT lose the ability to talk, to interact with other people, and to move independently. They may experience seizures and behavior disorders. Scientists do not know how to cure RTT or halt its progression. Recently, NICHD-supported researchers created a genetically modified mouse with RTT-like symptoms that should help scientists understand how RTT develops over time. The experimental mouse may lead to better understanding of the molecular events that contribute to certain stages of RTT and may enable researchers to identify genes involved in regulating motor function, involuntary movements, seizures, and anxiety disorders. The new mouse model is superior to earlier experimental models of RTT and may enable scientists to test medications and other treatments for the disease.

## *Treatments and Technology to Maintain Reproductive Health*

### Obesity, Infertility, and Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a complex disorder affecting 6 to 7 percent of women in their childbearing years. Women with PCOS often fail to ovulate. Failure to ovulate is estimated to cause 40 percent of female infertility. Women with PCOS also tend to have other health problems such as obesity and insulin resistance, the inability of cells to respond to insulin properly. Treatment with clomiphene citrate (CC), the drug most commonly used to induce ovulation, is often unsuccessful in obese women with PCOS. Now, a new treatment may help such women overcome infertility. A recent study showed that CC treatment, combined with metformin, a drug used to treat insulin resistance, increases the chances of ovulation and pregnancy among obese women with PCOS who are resistant to CC alone. Because this promising combination therapy is also less expensive and less likely to result in multiple pregnancies than other infertility treatments, it may reduce health care costs and improve the health of both mothers and their children.

### Hormones and Polycystic Ovarian Syndrome

In another study, scientists examined the role of hormones in controlling ovulation in women with PCOS. Ovulation is regulated by the rise and fall of both male and female hormones within a woman's body. For example, androgens stimulate the secretion of luteinizing hormone (LH), which suppresses ovulation. By contrast, the female hormones, estrogen and progesterone, inhibit LH secretion and stimulate ovulation. Scientists investigated whether the higher-than-normal levels of androgens and LH seen in women with PCOS blocked the ability of estrogen and progesterone to stimulate ovulation. They found that adding flutamide, an androgen-blocking drug, to the therapy of women with PCOS

reduced the levels of LH. This finding suggests that blocking androgens can restore the normal regulation of LH secretion by estrogen and progesterone in women with PCOS. With this important finding, scientists can develop new treatments to restore regular ovulation and fertility in women with PCOS.

**Assessing Risks of Cervical Ectopy**

Scientists are developing tools that will help them better understand conditions that threaten the physical and reproductive health of many women. For instance, scientists developed a new computer technique to determine whether cervical ectopy increases a woman's susceptibility to sexually transmitted diseases (STDs). Cervical ectopy is a condition in which blood-rich cells migrate from the inner to the outer areas of the neck of the womb, or cervix, and is commonly seen in adolescent girls, pregnant women, and women who use oral contraceptives. Findings from previous studies report an association between cervical ectopy and certain STDs. However, researchers have not clearly established whether a larger area of cervical ectopy increases a woman's susceptibility to STDs, nor have they identified how hormonal contraceptives affect the extent of cervical ectopy. Conclusive evidence is lacking, in part because of difficulties in documenting the extent of cervical ectopy that physicians observe during pelvic examinations. To address this issue, the scientists developed a more accurate technique, called computerized planimetry, for measuring the area of cervical ectopy. They used a standard reference dot placed on the cervix, a special camera to photograph the cervix, and an analytic software program to obtain objective measurements that are more reliable than visual assessments. When this new technology is refined, researchers will be able to use it in large-scale longitudinal studies to determine whether oral contraceptives or other prescription drugs that women might use directly affect their risk of STD infections and any associated infertility.

## *Reproductive Organ Disorders*

**Endometriosis and the Immune System**

Endometriosis is a complex gynecological disorder associated with pelvic pain and infertility that affects more than 5.5 million women in North America alone. Endometriosis occurs when tissue like that which lines the uterus grows outside of the organ, usually on surfaces in the pelvic and abdominal areas. A single, clear explanation for the cause of this disease has eluded scientists. Recently, scientists reported that women with endometriosis are more likely than others to have autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, in which the body's immune system attacks its own cells, tissues, and organs. These diseases affect millions of Americans and some disproportionately affect African Americans, Hispanics, or Native Americans. The researchers also found that women with endometriosis were more likely than others to have a variety of other conditions, including chronic fatigue syndrome (strong, lasting fatigue) and fibromyalgia (recurrent muscle, tendon, and ligament pain). The findings of multiple conditions that seem to relate to endometriosis and immune system function could yield clues to the causes and better treatment of the associated conditions, as well as endometriosis itself.

**Endometriosis and Immune Response**

For many women with endometriosis, treatment with progestins (hormones that prepare the lining of the uterus for implantation of a fertilized egg) can relieve pelvic pain and certain other symptoms. But scientists have questioned the utility of progestin therapy on a long-term basis, and some women with endometriosis do not gain pain relief from this treatment. Scientists have long recognized that immune cells and the products they secrete, known as cytokines, play an important role in the cellular events that occur as endometriosis develops, particularly as the disease process relates

to pain. Recently, scientists reported that progestin reduces the pain associated with endometriosis by suppressing the natural inflammatory response that occurs when endometrial tissue invades the pelvic cavity. Understanding the way that progestins work provides insight into both the disease process of endometriosis and the reason that progestin does not always relieve endometriosis-related pain. This knowledge could help researchers improve therapies for endometriosis.

**Uterine Fibroids and Genes**

More than a quarter of U.S. women may develop uterine fibroids, the most common non-cancerous tumors found in women of childbearing age. The tumors can cause infertility, pain, and uterine bleeding. Treatment options are limited to hormone therapies and surgery, with fibroid tumors accounting for an estimated 200,000 hysterectomies each year. African American women are at greater risk for surgery because they are more likely to develop large or multiple-fibroid tumors. Recently, scientists, using a new technology that permits very rapid analysis of multiple genes, were able to identify genes involved in the development and growth of fibroid tumors. Identifying genes specific to the condition will help scientists better understand how the tumors grow and, ultimately, could lead to the development of new therapies for this condition. The researchers plan further genetic studies to identify a "master regulator" of tumor growth and to develop drugs that could shrink fibroids, sparing women from surgery and the side effects of other current therapies.

**Pelvic Floor Disorders Network**

In July 2001, NICHD established the Pelvic Floor Disorders Network (PFDN), which consists of seven clinical sites and one data coordinating center. Major research projects within the network include examining standards and treatments for incontinence, and determining the prevalence of pelvic symptoms after childbirth.

## *The Basics of Healthy Pregnancies*

**Helpful Hormone**

Considering the sensitivity of the human immune system, pregnancy can be viewed as a paradox since a pregnant woman's body can perceive her embryo as a foreign body. What prevents a woman's immune system from attacking the embryo similar to the way her body fights off foreign organisms that cause illness? Findings from a new study offer an answer. Scientists found that a stress hormone known as a corticotropin-releasing hormone (CRH) is directly involved in the process that prevents a pregnant woman's immune system from destroying the embryo. Furthermore, the study revealed that early embryonic cells, called trophoblasts, which develop into the placenta, produce CRH. In turn, CRH causes the trophoblasts to secrete a protein called Fas ligand, or FasL, which activates a process that destroys special immune, or "T," cells before they can attack the developing embryo. With these findings, scientists can now focus on the CRH/FasL relationship to pinpoint factors that might disrupt its ability to suppress a woman's immune system. A better understanding of this delicate relationship may provide insights into unexplained miscarriages and infertility, as well as preeclampsia, a potentially life-threatening condition for a pregnant woman. Moreover, some observable similarities between trophoblast cells and certain cancer cells might lead to clues that could help design new cancer treatments.

**Enzymes and Premature Rupture of Membranes**

Premature rupture of membranes (PROM) is already known to be one of the most common causes of premature birth in the United States. It occurs when the membranes surrounding a fetus break apart, often leading to premature labor. In previous studies, scientists discovered that an association exists between PROM and bacteria present in the membranes. They were uncertain, however, whether enzymes

produced by the bacteria directly caused the membranes to rupture, or whether they ruptured because of an immune response to an infection by the mother or by the developing fetus. To answer these questions, scientists studied a family of enzymes, matrix metalloproteinases (MMPs), which can cause the membranes to break apart. They found that the bacteria do not produce the enzymes, but rather the womb and fetus produce them, most likely in response to an infection in the membranes. Also, while it has been suggested that giving antibiotics to women with membrane infections may prevent PROM and premature labor, these scientists showed that antibiotic treatment is not effective and, in some cases, may make the situation worse by killing protective bacteria. Further research is needed to identify the factors that predispose some women to PROM. In turn, the findings can pave the way for developing new methods to prevent the condition and premature labor.

**Uterine Contractions Do Not Predict Preterm Birth**

One way to find the most relevant clues as to why a condition or biological process occurs is to distinguish between factors that are only associated with it versus factors that can actually predict the condition or process. Recently, scientists clarified this distinction for a longstanding debate about whether the frequency of uterine contractions in the third trimester of pregnancy actually predicts, or only relates, to preterm birth. They found that women who delivered before 35 weeks of pregnancy had more contractions compared with women who delivered at or after 35 weeks. However, the difference in frequency was too small to predict preterm birth. In addition, some pregnant women had frequent contractions and did not deliver preterm. For physicians and mothers, this means that even though contraction frequency is significantly related to preterm birth, it is not a useful screening test to identify patients who will deliver preterm.

**Antiretroviral Drugs and Birth Complications**

The standard of care for a pregnant woman with HIV, the virus that causes AIDS, includes ongoing treatment with antiretroviral (anti-HIV) drugs. This approach avoids interrupting treatment of the woman while also helping to prevent transmission of the virus to the fetus. But doubts about this approach arose when several studies, involving relatively small numbers of women, suggested that treatment during pregnancy with combination antiretroviral therapy increased the risk of premature delivery. Recently, scientists reviewed multiple clinical trials and concluded that women who continued antiretroviral therapy (standard combination drug therapies and single-drug therapy) during pregnancy were no more likely to give birth prematurely than those who either stopped combination therapy or took only one antiretroviral drug. These scientists also found that antiretroviral drugs did not generally increase the risk of other complications, including low birthweight, stillbirth, or poor newborn responses, as indicated by a standard test (Apgar test) at birth. A subgroup of women did appear to have a slightly higher risk of having very low birthweight infants; however, the researchers suggest that factors other than drugs, such as alcohol or tobacco use, could be responsible. The new findings permit more informed treatment choices by pregnant, HIV-positive women and their physicians.

**Repeated Miscarriage and Genes**

Repeated miscarriages, without a known cause, affect 1 to 2 percent of couples who wish to have a child. Women experiencing multiple miscarriages may undergo exhaustive and expensive diagnostic tests that fail to identify the cause of their miscarriages. Scientists have long assumed that a large percentage of unexplained repeated miscarriages is caused by genetic problems, but they have been unable to identify a specific gene as a cause. Recently,

scientists reported that 14 to 15 percent of women with a history of unexplained repeated miscarriages have a genetic flaw in one of their two X chromosomes. Also, these women are more likely to miscarry male than female fetuses. The percentage of women with the genetic aberration combined with its selective effect on male fetuses means that the flawed gene may account for up to 40 percent of previously unexplained repeated miscarriages. Identifying this trait is expected to lead to blood tests to determine the risk of miscarriage in future pregnancies.

**Miscarriage and an Anti-Diabetes Drug**

Polycystic ovary syndrome (PCOS) can make it difficult for a woman to become pregnant or to carry a fetus through the early months of pregnancy. In fact, women with PCOS are three times more likely than other women to miscarry. They also have a condition, insulin resistance, that precedes diabetes. From continuing studies on the use of an anti-diabetes drug, metformin, to help treat PCOS, researchers found that the drug also helped to reduce the risk of a miscarriage in the first trimester of pregnancy. The investigators had already demonstrated that the drug increases blood flow in the uterus and brings about changes in the uterine lining. Further research could confirm the drug's positive effects in relation to miscarriage and evaluate its safety through the full course of pregnancy.

**Preeclampsia and Insulin Resistance**

Preeclampsia, a dangerous condition that complicates 3 to 4 percent of pregnancies, strikes without warning and is a leading cause of maternal and fetal death. Delivery is the only known cure for preeclampsia and surviving infants are likely to have suffered a hemorrhage before birth, be small for gestational age, be premature, and have serious disorders requiring neonatal intensive care. Currently, physicians lack a reliable method of identifying women at risk for preeclampsia. Recently, however, scientists reported that women with heightened resistance to the hormone insulin in the early months of pregnancy are at risk of later developing preeclampsia. This finding suggests that physicians may be able to initiate early measures to help prevent preeclampsia in pregnant women with insulin resistance. This could be done by improving insulin sensitivity in at-risk women before, or soon after, they become pregnant.

## Initiatives

***Requests for Applications (RFAs) and Program Announcements (PAs)***

Training and Career Development

- **Specialized Cooperative Centers Program in Reproduction Research**

  This program is a national network of centers designed to foster multidisciplinary collaborations among basic and clinical scientists conducting reproduction research. The goal is to improve human reproductive health by speeding the transfer of basic science findings into clinical practice. (HD-01-023 and HD-02-029)

- **Midcareer Investigator Award in Patient-oriented Research for Researchers in Female Pelvic Floor Disorders**

  In collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NICHD plans to increase the number of trained clinical scientists studying female pelvic floor disorders. To accomplish this, NICHD and NIDDK will support clinician researchers to devote time to patient-oriented research, and to mentor new clinical investigators. (PAR-01-085)

**HIV/AIDS**

- **Microbicide Preclinical Development Program**

  NICHD and the National Institute of Allergy and Infectious Diseases encourage research to discover and

develop preclinical novel microbicides to prevent sexual transmission of HIV1. (HD-00-018)

- **Integrated Preclinical/Clinical Program for HIV Topical Microbicides**

  NICHD is cosponsoring this NIAID-led initiative. The goal is to advance novel topical microbicides and microbicide combination strategies, from preclinical to clinical studies, to prevent sexual transmission of HIV. (PA-01-075)

- **HIV Pathogenesis in Women's Interagency HIV Study**

  In collaboration with the NIH Office of Research on Women's Health and other ICs, NICHD is supporting this NIAID-led initiative to continue an ongoing cohort study of HIV-infected and at-risk, HIV-negative women living in six cities in the United States. (PA-01-084)

### Treatments and Technology to Maintain Reproductive Health

- **Progestin Contraception and Endometrial Bleeding**

  This initiative will help identify effective agents that prevent and treat endometrial breakthrough bleeding in women using progestin-only contraception. (HD-01-016)

- **Reproductive Genetics**

  NICHD will support new research on how genes and genetic mechanisms influence sex determination, human fertility, and the role of differential expression of parental alleles in reproduction. (PA-01-005)

- **Vulvodynia – Systematic Epidemiologic, Etiologic, or Therapeutic Studies**

  NICHD, in collaboration with ORWH, plans to support experienced basic scientists, epidemiologists, and clinical investigators to examine the epidemiology, etiology, prevalence, criteria for accurate diagnosis, underlying pathophysiology and pain mechanisms, as well as treatment strategies for vulvodynia. (PA-02-090)

### Contraception

- **Cooperative Contraceptive Research Centers**

  NICHD plans to support scientists to conduct studies in an ongoing multicenter cooperative research program designed to speed the development of new methods to regulate fertility. The goal is to develop knowledge that may lead to clinically useful products. (HD-01-011)

### Fertility and Infertility

- **Cooperative Infertility Research Centers**

  The goal of this initiative is to speed the development of preclinical and clinical research that may lead to promising new approaches for diagnosing and treating infertility in women and men. To accomplish this, NICHD will support scientists to conduct studies in a multicenter cooperative research program, National Cooperative Program for Infertility Research. (HD-01-001)

- **Female Health and Egg Quality**

  NICHD will also support scientists to conduct studies in the multisite National Cooperative Program on Female Health and Egg Quality. The goal is to better understand how poor nutrition, extreme exercise, smoking, certain assisted reproductive technologies, and other adverse health conditions affect the developing egg before and during the fertilization process. (HD-02-018)

### The Basics of Healthy Pregnancies

- **Cooperative Program on Trophoblast-Maternal Tissue Interactions**

  The goal of this initiative is to help women establish healthy pregnancies by preventing or alleviating problems

linked with abnormal implantation. Such complications can result in preeclampsia or ectopic pregnancy, leading causes of maternal mortality in African American women. (HD-01-012)

INTERNATIONAL HEALTH

- **Global Network for Women's and Children's Health Research**

  NICHD, in collaboration with the NIH Fogarty International Center, and in partnership with the Bill and Melinda Gates Foundation, will expand support for U.S. scientists partnered with foreign researchers to conduct studies in the Global Network for Women's and Children's Health Research (Global Network). The goal is to enhance the existing Global Network by adding new research units from Eastern Europe and Africa to improve health, and to prevent premature disease and death among women and children, primarily in developing countries. (HD-01-024)

MAINTAINING HEALTH

- **Biology of the Menopausal Process and Associated Health Conditions during and after Menopause**

  NICHD is one of several institutes cosponsoring this initiative led by the National Institute on Aging. The goal is to clarify the molecular and cellular mechanisms underlying the menopausal process, and better understand how the pathophysiology of this process relates to various women's health problems during and after menopause. (PA-01-067)

- **Women's Health in Sports and Exercise**

  With support from NICHD and ORWH, the National Institute of Arthritis and Musculoskeletal and Skin Diseases is leading an initiative to stimulate and foster a wide range of basic, translational, and patient-oriented clinical studies to improve the basic knowledge of how sports injuries affect other underlying physiological mechanisms in women. The purpose is to help solve the puzzle of why female athletes are more susceptible to certain types of injury. Understanding women's pathophysiology during injury may also be applicable to women with disabilities. (PA-02-115)

*Conferences and Workshops*

CAREER TRAINING

- **Specialized Cooperative Centers Program in Reproduction Research Meeting**
  **May 14-16, 2001**

  The meeting highlighted significant advances in research, technology and resource development, and bioinformatic efforts supported by the Specialized Cooperative Centers Program in Reproduction Research. This program is a national, multicenter, research effort to promote collaborations between basic and clinical scientists conducting research on a wide range of reproductive issues.

- **Informational/Technical Assistance Workshop for the Specialized Cooperative Reproductive Science Research Centers at Minority Institutions**
  **May 20, 2002**

  This workshop brought together potential minority applicants and partners interested in reproductive science. NICHD staff provided information and technical assistance to help these individuals develop proposals in response to the Request for Application, "Specialized Cooperative Reproductive Science Research Centers at Minority Institutions."

- **Women's Reproductive Health Research Career Development Centers**
  **July 25-26, 2002**

  This workshop established investigators and scholars from the Women's Reproductive Health Research Career

Development Centers to discuss and identify emerging issues or continuing gaps in knowledge, and to explore future opportunities for research. The program supports research career development of obstetrician-gynecologists by bridging clinical training with basic, translational, and clinical research relevant to women's reproductive health.

### Reproductive Organ Disorders

- **Chronic Pelvic Pain: Pathogenic Mechanisms, Treatment Innovations, and Research Implications**
  **April 8-9, 2002**

  With ORWH support, NICHD held a workshop that brought together clinicians, and basic and translational scientists to develop a multidisciplinary research agenda in chronic genital and pelvic pain in women. Participants discussed the current state of knowledge, identified emerging issues, and explored future research opportunities.

- **Endometriosis: Emerging Research and Intervention Strategies**
  **April 9-10, 2001**

  In collaboration with ORWH and the National Institute of Environmental Health Sciences, NICHD held this conference where clinicians, endocrinologists, immunologists, and reproductive and developmental biologists discussed new methods to diagnosis and treat endometriosis. In addition, the scientists identified research gaps and explored future directions for research in endometriosis.

### Reproductive Health across the Lifespan

- **Potential Clinical Uses of GnRH Antagonists**
  **January 31-February 1, 2001**

  This NICHD workshop examined how GnRH antagonists could be used clinically in women to induce ovulation and enhance fertility, and to treat endometriosis, polycystic ovary syndrome, and breast cancer. The conferees also examined the potential use of these antagonists in men for contraception, treating prostatic carcinoma, and protecting testes during radiation or chemotherapy.

- **NICHD Workshop: The Role of Genetics in the Health Disparity of Premature Birth and Low-birthweight Infants**
  **May 4, 2001**

  A racial and ethnic health disparity exists in the incidence of premature birth and low-birthweight (LBW) infants. To address this issue, NICHD held a workshop to develop a research agenda to examine the role of genetics as a potential factor that contributes to the high number of premature and LBW babies in minority populations.

- **Sixth International Conference of the Extracellular Matrix of the Female Reproductive Tract**
  **May 12-14, 2001**

  NICHD hosted this international meeting where scientists discussed how the extracellular matrix plays fundamental roles in tissue remodeling, signal transduction, and cell cycle and cell death cascades. The goal was to stimulate further research of how the extracellular matrix affects developmental biology, ovulation events, the menstrual cycle, implantation, tissue remodeling of the uterus and cervix during gestation, and development and rupture of the fetal membranes in pregnancy.

- **Reproductive Genetics, Genomics, and Proteomics: Advances in Genetics, Molecular, and Statistical Techniques**
  **June 29-July 10, 2001**

  To stimulate the use of cutting-edge technology in the field of reproductive genetics, NICHD brought together experts in genetic techniques and

reproductive biology. The goal was to encourage genetics experts to turn their attention to reproductive issues, and reproductive biologists to take advantage of using powerful genetic techniques to address reproductive health problems.

- **Staging System for Reproductive Aging**
  **July 23-24, 2001**

  NICHD cosponsored this NIA-led meeting to identify and categorize hypothalamic-pituitary-ovarian function in women into stages that researchers could use and apply in clinical studies. By developing a systematic view of these stages as women age, scientists can better compare study populations and increase confidence in scientific findings.

- **Dietary Supplement Use in Women of Reproductive Age: Current Status and Future Directions**
  **January 28-29, 2002**

  With support from ORWH, NICHD held a meeting where participants identified research gaps in understanding how dietary supplements interact with drugs, affect women's nutrition, and affect their risk for certain adult diseases.

- **Primary and Secondary Ovarian Insufficiency in Adolescents and Young Women**
  **May 23-24, 2002**

  NICHD, with ORWH support, held this meeting to define the conditions that may lead to primary or secondary ovarian insufficiency in adolescents and young women, and to determine its prevalence. Participants also discussed: 1) the extent to which each type of ovarian insufficiency in adolescents and young women contributes to the development of osteoporosis, and 2) the state of the science in terms of diagnosing and replacing sex steroids in this population.

- **Evidence-based Assisted Reproductive Technologies**
  **September 18-19, 2002**

  NICHD participated in a meeting to discuss current scientific data concerning assisted reproductive technologies (ART), identified ethical issues specific to ART, and assessed the usefulness of animal models and laboratory science for human ART.

### The Basics of Healthy Pregnancies

- **NIH Consensus Development Conference on Phenylketonuria: Screening Management**
  **October 16-18, 2000**

  NICHD held a conference to discuss the incidence and prevalence of phenylketonuria (PKU), newborn screenings for PKU, treatments to prevent adverse outcomes of PKU, and research needs for the future to optimize outcomes for individuals with PKU and their families. Participants also discussed the special needs of women with PKU who are of childbearing age or pregnant.

- **Stress, Placental Corticotropin-releasing Hormone, and Human Parturition**
  **October 26-27, 2000**

  A growing body of scientific evidence suggests that stress and placental corticotropin-releasing hormone (CRH) may adversely affect neuroendocrine processes early in pregnancy, and may result in preterm delivery. NICHD hosted a symposium at a satellite meeting of the International Congress on Endocrinology to bring together leading experts in the area of stress, CRH, and the birthing process to discuss this hypothesis.

- **Endocrine Disorders and Fetal Development**
  **November 3-5, 2000**

  The purpose of this NICHD meeting was to begin developing a consensus

in the medical community concerning when and how to treat mothers with hypothyroidism and maternal diabetes. If not properly managed, these conditions can adversely affect a developing fetus.

- **The Neurobiology of Prenatal Stress: Implications for Fetal Development and Health**
  (Presented at the First World Congress on Fetal Origins of Adult Disease)
  **February 2, 2001**

  NICHD sponsored this symposium to bring together leading biobehavioral experts in the area of perinatal stress and fetal development. The participants discussed genetic models of early development and its implications for the risk of developing adult disease.

- **Effects of Maternal Health on Reproductive Events Leading to Adult Diseases and Disorders in Offspring**
  **February 28, 2001**

  To help ensure every child grows into a healthy adult, NICHD held a conference to encourage scientists to examine how poor nutrition and other adverse health situations in girls and women, both before and after conception, may lead to the birth of children who have an increased risk of developing a range of diseases and chronic conditions.

- **International Conference on Maternal Phenylketonuria**
  **April 11-12, 2002**

  NICHD and the NIH Office of Rare Diseases organized an international conference to share scientific findings on maternal phenylketonuria (MPKU). Participants discussed fetal brain development, obstetrical aspects of MPKU, how phenylalanine hydroxylase gene affects MPKU, biopterin therapy, barriers to successful dietary control of MPKU, and the developmental profile of children born to MPKU mothers.

#### Gender

- **NICHD Research Planning Workshop in Intersex Research**
  **May 19-20, 2002**

  To address whether patients were satisfied with sex assignment and/or genital reconstructive surgery, NICHD held a workshop to identify data sets in the United States and abroad that could be used to shed light on this important issue. Participants included pediatric endocrinologists, pediatric urologists, psychologists, ethicists, and biostatisticians, who have a strong interest and a depth of experience in this sensitive area.

#### HIV/AIDS and Sexually Transmitted Diseases

- **Natural Product Development in Microbicidal and Non-Microbicidal Contraceptives: Trends and Needs Workshop**
  **September 10-11, 2001**

  This meeting provided learning and networking opportunities for scientists conducting studies that use natural products to develop microbicidal and non-microbicidal contraceptives. Participants discussed the chemistry, processing, and testing of natural plant compounds. In addition, they discussed the current status and future directions of studies that use and test natural products as potential contraceptive agents and compounds to prevent transmission of sexually transmitted diseases, including HIV.

## Health Disparities among Special Populations of Women

### *Scientific Advances*

#### Childhood Origins of Health Disparities in African Americans

Scientists have made substantial strides in discovering what leads to the high rates of obesity, diabetes, high blood pressure,

stroke, and other cardiovascular disease in African Americans. Previous studies have shown that African American girls are more likely to become obese, and that African American women are much more likely to be a victim of stroke than their white counterparts. To isolate factors leading to these conditions, scientists examined African American and white children to determine whether changes in glucose and insulin activity led to changes in body fat as the children reached puberty. They found that the levels of circulating insulin were higher in the African American children and that these children were less responsive to the effects of insulin. These findings suggest that circulating insulin can be used as a marker to predict later obesity or diabetes in African Americans. With this information, scientists can develop specific pharmacological interventions that help to modify insulin levels and the body's response to them.

**Fetal Origins of Adult Hypertension and Increased Risk for Cardiovascular Disease**

Scientists are also investigating other mechanisms that may explain why some health conditions are more prevalent in minorities. It has been suggested that certain environmental factors predispose a woman to give birth to a child who develops health disorders later in life, such as adult hypertension and cardiovascular disease. Although this hypothesis remains controversial, accumulating research findings support it. Recently, scientists showed in an animal model that, by restricting protein in the diet of pregnant animals, the offspring had a reduced birth weight and impaired kidney development. The latter condition could result in poor kidney function, high blood pressure, or other cardiovascular diseases. This impairment is caused by the suppression of the kidney's renin-angiotensin system (RAS) during the development of the fetus. The RAS, a hormonal system that regulates blood pressure and blood volume in adults, establishes the number of nephrons, tiny filtering devices, in the kidney and helps determine normal blood pressure. These findings will allow scientists to identify pathways in the fetal environment that may lead to poor health conditions later in life and, in turn, modify these pathways to ameliorate or prevent these health conditions.

## Initiatives

- **Cooperative Reproductive Science Research Centers at Minority Institutions**

  This is a major NICHD cooperative program, cosponsored by the National Center for Research Resources and ORWH, to link researchers at existing networks in women's health, reproductive medicine, and infertility with researchers at minority institutions. Specifically, this reissued Request for Applications increases the number of minority investigators who are trained in biomedical issues concerning racial and ethnic populations, and will serve as an important step towards addressing reproductive conditions that adversely affect minority women. As a result of the initial solicitation, the Morehouse School of Medicine, in partnership with the University of Pittsburgh, received the first award in September 2001. Through this partnership, scientists are examining how certain hormones and genes affect various aspects of egg and sperm development. The newest request will allow additional partnerships to be formed, and lay the foundation for future clinical applications to reduce health disparities in minority populations. (HD-02-012)

- **The Role of Gene-Environmental Interactions Underlying the Health Disparity of Premature Birth**

  NICHD, in collaboration with NIEHS and the National Institute of Nursing Research, encourages research examining the role of gene-environmental interactions underlying the health disparity of premature birth in the United States.

The goal is to better understand how adverse societal, behavioral, and environmental conditions alter gene expression and interact with diverse genetic backgrounds to increase a woman's susceptibility for premature birth in high-risk racial and ethnic groups. (PA-02-102)

# National Institute of Dental and Craniofacial Research

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

## Accomplishments

### *Gender and Pain Research*

Pain conditions, including those that primarily affect women, have been an active area of NIDCR-supported research for a number of years. Findings from studies indicate that gender-based differences in pain conditions are due, in part, to biological differences between women and men.

#### Understanding the Role of Gender in Pain

NIDCR-supported studies are uncovering the basis for gender differences in pain perception through several basic and clinical approaches. For example, one study is elucidating the unique analgesic effects of kappa opioid receptor activation in women. Such research may aid in the development of analgesic drugs whose pharmacological activity is optimized for a specific patient population. In addition, other extramural scientists are studying the effects of the menstrual cycle on pain sensitivity. This study is in response to findings that suggest a role of sex hormones on the heightened sensitivity to pain in women in their reproductive years. Finally, functional imaging studies are revealing gender-specific differences in the central nervous system distribution of opioid receptors.

#### Female Sex Steroids and Pain Response

Intramural scientists have been using rodent models to study gender-related pain response. Comparative studies using estrous cycle females as experimental subjects and male and ovariectomized females as controls revealed that production of dynorphin, an opoid peptide, is significantly increased in response to

inflammation and hyperalgesia in ovulating females. In contrast, males and ovariectomized females produced less dynorphin under identical test conditions. Data suggest that mammals respond to pain in a gender-based fashion and that the models provide a venue for assessing the relationship between pain and hormone levels.

### *Temporomandibular Muscle and Joint Disorders*

Temporomandibular muscle and joint disorders (TMJDs) are important chronic pain conditions of particular interest to NIDCR. NIDCR researchers are presently conducting basic and clinical research addressing the origin of the gender differences associated with TMJDs. For example, a series of clinical studies are evaluating the effects of gender, the menstrual cycle, female hormone levels, and other gender-related factors, including pregnancy, on the appearance and severity of TMJDs. These studies could demonstrate relationships between generalized pain sensitivity, gender and hormonal status, and the development of TMJDs. Basic studies are investigating the effects of female hormones on the temporomandibular joint. These hormones, specifically estrogen and relaxin, have a set of actions that "softens" and loosens the pelvic girdle of women during pregnancy (in order to ease delivery). Current work seeks to determine if these hormones can promote systemic joint laxity and the development of disease in other joints, specifically the TMJ.

NIDCR recognizes that for the design and development of new implant materials, it is necessary to understand the success and failure of TMJ implants when used in patients. Thus, NIDCR supports a *TMJ Implant Registry and Repository*. This contract supports: 1) the collection of medical information from health care provider records and interviews; 2) the collection of clinical and laboratory data on the genotypic immunological profile (e.g., MHC, cytokines) of the enrollees; 3) the establishment and maintenance of a registry and repository of TMJ retrieved implants; and 4) a registry of biological materials (e.g., synovial fluid, blood, tissue specimens, DNA). Findings from this registry will provide insight into the strengths and weaknesses of TMJ implants' design, and enable improvements for future implant designs. Moreover, the availability of well-characterized biological materials and retrieved implant materials should help in basic and clinical studies focused on the pathobiology of TMJ diseases and disorders.

In addition, several other NIDCR-funded studies are exploring the relationship between fibromyalgia and TMJDs. One investigator is studying the relationship of TMJDs with fibromyalgia and factors associated with the two conditions. This study offers a unique opportunity to look at multiple risk factors thought to be associated with different types of chronic pain. Participants in this longitudinal cohort study of women of various ethnic origins are being followed through the most vulnerable period of life for developing such conditions. Another study is examining several hypotheses concerning the relationship between TMJDs and fibromyalgia, including whether TMJDs is a regional manifestation of fibromyalgia, or whether TMJDs associated with fibromyalgia has a different etiology and pathogenesis than TMJDs appearing in isolation.

### *Osteoporosis and Basic Bone Biology*

The study of bone and other mineralized tissues has been a mainstay of NIDCR-supported research since the institute's inception, not only because of its importance as it relates to teeth and jaws, but also as it relates to the growth and development of the entire craniofacial complex.

Bone is an active and dynamic tissue that continuously remodels throughout life. The process of bone remodeling consists of the cycled bone formation and resorption performed respectively by osteoblasts and osteoclasts. An imbalance between bone formation and resorption will lead to a change in bone mass. In young or developing (< 20 years old) bone, bone

formation dominates resorption, resulting in bone growth and development. In healthy adult (20 to 40 years old) bone, the processes of bone formation and resorption are delicately equilibrated; no increase or decrease in bone mass occurs. However, in aging bone, an imbalance of resorption over formation often induces loss of bone mass, and can lead to osteoporosis, a skeletal disease that affects bone architecture and increases the risk of fracture. Recent research findings indicate that oral bone can be affected as well, leaving the mandible and maxilla less able to support teeth, especially during periodontal infection.

It is estimated that the overall lifetime risk of osteoporotic fractures in women in the United States is on the order of 30 to 40 percent, and that the health care expenditures for osteoporosis-related fractures total an estimated $13.8 billion per year in direct costs. In most women, accelerated loss of bone begins at menopause, and total bone loss can be as much as 15 to 25 percent of premenopausal bone mass.

**Role of Estrogen**

Estrogen is one of the most important factors regulating the bone remodeling process and preventing osteoporosis. Extensive clinical investigations and basic studies have demonstrated that postmenopausal osteoporosis is induced primarily by a decrease in estrogen levels. Ovariectomized animals and postmenopausal women experience increased bone resorption and decreased bone mass. On the other hand, estrogen replacement therapy inhibits bone loss and prevents osteoporosis. Recent studies have established the cellular and molecular mechanisms for estrogen action on bone. Estrogen acts directly on osteoblasts (bone-formation cells), stimulating their proliferation and inducing the synthesis of growth factors. Estrogen also regulates the synthesis of bone matrix proteins that construct the organic structure of bone. Estrogen deficiency increases the production of cytokines, such as interleukin-1, -6, and tumor necrosis factor, which mediate bone resorption. In addition, estrogen inhibits the activity of osteoclasts (bone-destructing cells) and increases apoptosis (programmed cell death) of osteoclasts.

**Oral Bone Loss in Postmenopausal Women**

NIDCR is funding a study with the aim of determining if systemic and mandibular bone loss are associated with increased prevalence and severity of periodontitis among postmenopausal women that are part of the Women's Health Initiative (WHI). As part of the study protocol, comprehensive medical history and examination data from the core WHI, including hip bone mineral densities (BMD), as determined by dual energy x-ray absorptiometry, are linked with results from an oral examination and severity of periodontal diseases, which are measured by gingival attachment level and computer-assisted radiographic measurement of interproximal alveolar bone.

Based on previous studies, osteoporosis has been associated with decreased BMD. The main cause for a decreased BMD in postmenopausal women is estrogen E2 deficiency. In a longitudinal NIH-supported clinical trial, a loss of alveolar crestal bone height and density in postmenopausal E2-deficient women with a history of periodontitis was observed when compared to E2-sufficient women, as well as in osteoporotic/osteopenic women versus women with normal lumbar spine BMD. Because of the relationship between estrogen deficiency and oral bone loss, a study is testing the effects of low-dose doxycycline in postmenopausal osteopenia and periodontitis.

Further studies are needed to determine the clinical implications of an association between oral and skeletal bone status, and whether oral cavity examination and radiographic findings may be useful signs of extra-oral bone diminution. Although preliminary studies

along these lines have met with promising results, it is too early to know the value of routine dental visit information in signaling the need for skeletal bone evaluations.

**Pathogenesis of Osteoporosis**

NIDCR supports a number of research projects on the mechanisms of osteoporosis. These projects include the regulatory mechanisms of parathyroid hormone in the mechanical threshold in osteoblasts, the effects and mechanisms of cytokines inhibiting osteoblast differentiation, and intracellular signaling systems regulating osteoclast formation. For example, tumor necrosis factor (TNF) is a major contributor to osteoporosis. While the role of TNF in causing bone resorption has been demonstrated, the effect of TNF on bone-formation cells, osteoblasts, remains unclear. These projects should provide much clearer insights into the pathogenesis of osteoporosis and potential new preventive and therapeutic measures.

**Transplantation (Restoration) of Bone Tissue Cells**

NIDCR intramural scientists have defined the role of nutritional supplements in supporting the *ex vivo* expansion of bone marrow stromal cells and their subsequent ability to form bone upon *in vitro* transplantation. This study indicated that human bone marrow stromal cells can be grown during the late stages of *ex vivo* expansion in serum-free medium. Upon transplantation, these cells actually form more bone than cells grown continuously in fetal bovine serum. These studies are laying the foundation for producing large numbers of healthy replacement bone cells outside of the donor for the purpose of replacing damaged or diseased bone tissue in the same patient.

### *Bone Stromal Cells and Tissue Regeneration*

An enhanced understanding of the differentiation potential of bone stromal cells may lead to new approaches in tissue regeneration.

**Preliminary Steps In Understanding the Tissue Regeneration Process**

Populations of bone marrow stromal cells contain stems cells that possess the ability to form bone, cartilage, myelosupportive stroma, adipocytes, and perhaps cells with other functions. In this study, several clones were isolated and characterized to determine the nature of this heterogeneity. It was found that all clones expressed many different markers at varying levels, and that the levels also changed with time in culture. Upon *in vivo* transplantation, some clones were multi-potent, capable of forming bone, myleosupportive stroma, and fat, whereas other clones had specialized forming only bone or fibrous tissue. Irrespective of the pattern of differentiation, all clones expressed the osteogenic master gene, cbfa-1, which has been shown to be absolutely required for bone formation. This work indicates that the bone marrow stromal cell population contains both multi-potent and uni-potent clonogenic cells, and further supports the notion that all of the phenotypes arise from a committed osteogenic cell, as demonstrated by the expression of cbfa-1.

### *Cancer*

Oral mucositis, a severe inflammation of the mucosal tissues in the mouth, develops in many patients undergoing chemotherapy and who have a bone marrow transplant. These types of treatments are given to women for breast and other forms of cancer. Many health care providers and patients may not be aware of this side effect and how it may be managed. Thus, NIDCR is leading a national media campaign, "Oral Health, Cancer Care and You," designed to raise awareness of oncologists, dentists, and patients about the oral complications of cancer therapy and how these complications can be prevented and managed.

### *Autoimmune Disease*

Autoimmune disorders disproportionately affect women and result in the unintended destruction of the body's own tissues. In the oral cavity the disorder is manifested

in Sjögren's syndrome (dry mouth), a dysfunction of the salivary gland that results in a reduced or permanent cessation of saliva secretion. It is the second most common autoimmune disease in the United States estimated to affect 1 to 2 million people with a female:male ratio of 9:1. The inability to moisten foods and initiate the digestive process results in considerable morbidity and has a marked impact on affected individuals' quality of life. NIDCR researchers have played a major role in developing drugs like pilocarpine that improve salivary flow in affected glands. More recently, gene replacement therapy to restore lost salivary gland function is being tested for eventual application in humans. An alternative approach is the modeling of an "artificial" salivary gland that can be implanted into various oral tissues.

### *Salivary Hypofunction*

Saliva is the most important factor in the maintenance of oral health. Lack of adequate saliva causes severe impairments in oral heath. These include difficulty in swallowing, chewing, and speaking, as well as loss of enjoyment of food; increases in oral diseases such as dental caries, periodontal diseases, and other infections; nutritional deficiencies; and reduced quality of life. Many diseases and conditions can induce salivary gland hypofunction (dry mouth). For example, autoimmune diseases such as Sjögren's syndrome (SS) and rheumatoid arthritis often cause dry mouth. Most patients with these autoimmune diseases are women. The etiology and pathogenesis of autoimmune disease-induced salivary hypofunction remain unclear, and effective prevention and treatment are still lacking. To better understand the pathogenesis of this autoimmune disease of the salivary and lachrymal glands, NIDCR researchers are using NOD mice, which spontaneously develop SS. The mouse model allows the researchers to employ state-of-the-science techniques to selectively remove (i.e., knockout) specific parts of the immune system in order to determine the relevance of each to the disease. SS appears to require local production of IgM and IgG, however, remarkably, the antibodies are not produced by the B cells infiltrating the glands, but rather the B cells in regional lymph nodes or in the bone marrow. This finding changes the concept of where to target treatment to reduce autoantibody production in the glands. Another study is trying to identify the mechanism for salivary epithelial injury in SS by quantifying and characterizing salivary gland epithelial cell apoptosis.

### *Human Immunodeficiency Virus*

The study of the oral manifestations of human immunodeficiency virus (HIV) infection has been of great interest to NIDCR because oral lesions in HIV-infected individuals are frequent and varied, and are among the first symptoms of infection. Moreover, the presence of pseudomembranous oral candidiasis and oral hairy leukoplakia indicates a strong likelihood that the HIV infection is progressing towards AIDS.

The impact of HIV/AIDS on women has grown substantially since the beginning of the epidemic, and NIH launched a national cohort study of HIV infection among women in 1995. The study is known as the Women's Interagency HIV Study (WIHS) and is conducted at six sites throughout the United States. Building on the opportunity to enhance the study's scientific yield, and because a detailed oral examination was not part of the core physical examination, NIDCR took steps to integrate an oral health component into the WIHS protocol. The overall goal of the WIHS oral sub-study is to assess the course of oral conditions (caries, periodontal diseases, soft tissue lesions etc.) over time in HIV-infected and -uninfected women. As of September 30, 2001, the oral sub-study enrolled 123 HIV-negative women and 503 HIV-positive women. The retention rate among HIV-negative women is 67 percent, and among HIV-positive women 76 percent, which is analogous to the core WIHS study retention rate. The specific objectives of the oral sub-study are to:

- Determine the prevalence and incidence of oral diseases in HIV-positive women receiving HAART therapy.

- Identify, in a prospective cohort, the oral adverse effects related to HAART therapy because an increased incidence of oral warts, salivary gland disease, and caries have been suggested in cross-sectional studies.
- Describe the periodontal disease experience between HIV-positive HAART-naive, HIV-positive HAART, and HIV-negative women.
- Describe the pathogenic synergy between viruses prevalent in HIV-positive women and the bacteria implicated in periodontal diseases.
- Determine differences in caries prevalence/incidence in HIV-positive HAART-naive, HIV-positive HAART, and HIV-negative women.

NIDCR researchers have expanded their studies of the role and significance of oral manifestations of HIV infection to sub-Saharan African women. Because serologic tests to measure HIV infection are rarely accessible due to their costs in sub-Saharan African countries, visual diagnosis of selected oral mucosal lesions may represent a useful tool to monitor HIV disease progression in this setting. The immediate objectives of this small project are:

- To estimate oral disease incidence among Zimbabwean women in relation to CD4 count controlling for potential confounders, such as current sexually transmitted diseases.
- To estimate the sensitivity and specificity of detecting oral mucosal lesions by *visual* inspection of the mouth by trained nurses in a family planning/gynecology clinic in Harare, Zimbabwe.

Long-term objectives of this project are to explore specific hypotheses such as:

- The occurrence of HIV-related oral lesions (mainly candidiasis) is associated with the development of *Pneumocystis carinii* pneumonia.
- The occurrence of HIV-related oral lesions (mainly candidiasis) is associated with the reactivation of tuberculosis.

## Health Disparities for Special Populations of Women

NIDCR funds research projects that are pursuing links between the health of mothers and their infants and toddlers. One study, supported jointly by the National Institute of Child and Human Development and NIDCR, is testing interventions for promoting positive changes in health behaviors in low-income mothers receiving foods through the federally funded Supplemental Food Program for Women, Infants, and Children (WIC). Low-income women were randomly assigned to receive either the standard WIC program or low-cost, enhanced interventions involving monthly motivational phone calls, and several home visits from community-based paraprofessionals. At four intervals postpartum (4 weeks up to 18 months), the women are being evaluated to determine whether the groups differ in dietary practices, child feeding practices, physical activity levels, weight gain or loss, and preventive health care utilization for themselves and their children. This research has the potential for identifying effective, practical interventions tied to ongoing WIC programs, which could help reduce health risks for both low-income mothers and their children.

Also, NIDCR is funding a project that is characterizing biological and environmental predictors of early childhood caries in low-income Hispanic children. Early findings indicate that mothers who have untreated dental caries themselves, and inadequate access to oral health care, are particularly likely to have children who develop early childhood caries. These findings are not surprising because dental caries arise when infections destroy tooth surfaces; mother-child transmission of these microbial agents has been demonstrated. One implication is that programs providing improved dental

health care for disadvantaged infants and children may not yield optimal results if the children's care givers have untreated oral infections or lack adequate preventive dental health care themselves.

## *Craniofacial Anomalies*

Clefts of the lip and palate are common human birth defects of multifactorial etiology; approximately 70 percent are non-syndromic. NIDCR researchers have identified three candidate genes – TGFA, TGFB, and MSX1 – which contribute significantly to the causes of this disorder. Environmental factors, particularly smoking by the mother, may act in conjunction with candidate genes to increase risk factors. Currently, a funded study is expanding case ascertainment using surveillance systems in the United States and overseas with the purpose of identifying the cleft lip and palate locus at 6p23 by using a high resolution genetic mapping and by evaluating the relevant candidate genes in this region.

Another craniofacial malformation being studied by NIDCR researchers is hemifacial microsomia (HFM). A dearth of epidemiological studies about the risk factors of HFM exists although experimental evidence suggests a vascular etiology. A multicenter, case-control study of HFM is obtaining data on: 1) maternal exposure to decongestants, 2) maternal exposure to other vasoactive agents (such as alcohol, coffee, cigarette smoking, aspirin, and ibuprofen), and 3) maternal exposure to other environmental risk factors (such as other medications, illness, and nutritional factors). Data will provide information on possible gene/environment interactions.

## *Periodontal Diseases and Systemic Effects*

Several researchers have been studying the relationship between pregnancy outcomes and the mother's periodontal status. An example is the Obstetrics and Periodontal Therapy Study. The goal of this multicenter, randomized clinical trial is to determine if non-surgical therapy for pregnant women with periodontitis would reduce the incidence of preterm birth. Despite significant efforts to prevent preterm birth, it remains a major cause of neonatal morbidity and mortality. Human, animal, and bacteriologic studies have linked periodontal disease with preterm delivery and low birthweight, and preliminary data indicate that periodontal therapy may reduce the incidence of preterm birth. This clinical trial will enroll 816 women who are 13- to 16-weeks pregnant. Volunteers will be recruited from four populations in Minnesota, Mississippi, Kentucky, and New York (Harlem). Participants will be randomly assigned to receive non-surgical mechanical periodontal therapy or will have periodontal therapy delayed until after delivery. Both groups will be followed until delivery, and the primary birth outcome variable will be gestational age at birth.

### Periodontal and Cardiovascular Diseases

Cardiovascular diseases (CVD) account for 57 percent of all deaths among American women. Several epidemiological studies are trying to determine the independent contribution of periodontal infections to the risk of arteriosclerosis and cardiovascular diseases. The primary outcome variable of these studies is changes in the carotid wall thickness and its relationship to periodontal diseases assessed by a clinical, radiological, microbiological, and markers of inflammation. These studies are addressing whether or not periodontal diseases are a risk factor for CVD in women.

### Periodontal Diseases and Diabetes

Periodontal infection may be an aggravating factor for diabetes in women. An epidemiological study is conducting an oral examination of participants of the Epidemiology of Diabetes Complication Study with the purpose of evaluating the prevalence, incidence, and disease progression rates for tooth loss, periodontal diseases, dental caries, soft tissue pathologies, salivary dysfunction, and oral health behaviors of a type 1 diabetic cohort.

## Initiatives

*Requests for Applications (RFAs)*

- **Pathobiology of Temporomandibular Joint Disorders**

  The purpose of this initiative is to stimulate cross-cutting, integrative research aimed at delineating the mechanisms underlying the etiology and pathogenesis of the orofacial structures associated with temporomandibular joint disorders. (DE-03-005)

*Progran Announcements (PAs)*

- **Management of Chronic Pain**

  The National Institute of Nursing Research and cosponsoring institutes and centers encourage research proposals in the management of chronic pain across the life span. Pain is a subjective experience influenced by gender, age, race and ethnicity, and psychosocial factors. The management of pain is influenced by patient, health care provider, and system factors. Research is needed to determine the most effective interventions to remove barriers to effective treatment; to determine the most effective pharmacological and non-pharmacological therapies, including complementary and alternative therapies; to identify assessment tools for patients unable to verbalize their pain; and to identify effective pain management strategies for individuals with disabilities and underserved populations. (PA-01-115)

- **New Approaches to the Pathogenesis and Treatment of Orofacial Pain**

  The National Institute of Dental and Craniofacial Research and the Office of Research on Women's Health invite research grant applications for innovative basic research investigations to study the pathogenesis of orofacial pain, in particular temporomandibular disorders. A broad range of research proposals on pathogenic mechanisms, new animal models, and interventions to halt and reverse disease processes is encouraged. (PA-01-108)

*Request for Proposals (RFPs)*

- **International Research Registry Network for Sjögren's Syndrome**

  The National Institute of Dental and Craniofacial Research is interested in establishing an International Research Registry Network for Sjögren's Syndrome (SS). The Broad Agency Announcement includes the following technical objectives: 1) to design and implement an International Research Registry Network for SS; 2) to establish a set of standardized diagnostic criteria for the recruitment of SS patients; 3) to collect, process, store, ship and analyze clinical information and biological specimens from patients and families with SS; and 4) to disseminate to researchers clinical information and biological specimens from patients with SS. (BAA-DR-03-01)

- **NIDCR International Patient Registry and Repository for Temporomandibular Muscle and Joint Disorders' Natural History**

  This international registry will enroll patients at high-risk of developing TMJDs by using a standard inclusion and exclusion criteria to be established in the first year of the contract. In addition, the registry will collect, process, and store patient information and biological specimens, and serve as a resource for providing well-characterized patient populations and biological specimens for TMJ research by qualified scientists. This information, and the subsequent research derived from it, will play a major role in gaining a fuller understanding of the etiology, pathogenesis, and treatment of TMJDs. Also, it will provide systematic information about the incidence and prevalence of the disorders. Together, this information can lead to an informed approach

in developing new and more effective diagnostic and prognostic indicators, as well as treatments and prevention modalities for TMJDs. (BAA-DR-04-06)

*Conferences, Workshops, and Working Groups*

- **Second Annual Scientific Meeting of the TMJ Association: Moving TMJ into the 21st Century**
  **May 6-8, 2002**

  The meeting was organized by the TMJ Association, Inc. and sponsored by NIDCR, ORWH, NIBIB, and NIAMS. The program consisted of five scientific sessions and involved 24 speakers. The five scientific sessions were: Osteoarthritis and Inflammatory-immune Processes in Joints; Cartilage Degradation (Mechanics/Biochemistry/Metabolism); Microvascular Structure/Function of Synovial Joints and Mechanisms/Implications of Angiogenesis for Arthritis; Clinical Symptoms and Current and Emerging Therapeutic Approaches and Skeletal Muscles; and the Jaw – Fatigue and Remodeling in Response to Loading.

- **Analgesic Drug Development Workshop: Translating Scientific Advances Into Improved Pain Relief**
  **March 13-14, 2002**

  The workshop was jointly sponsored by NIDCR and FDA. The purposes of the workshop were to define the unmet clinical needs in pain management; delineate the ways in which clinical research methods have failed to address these needs; explore the ways in which new technologies can expand therapeutic options, as well as improve safety and effectiveness of future therapies; determine whether it is more efficient and economical to develop analgesic drugs for specific as opposed to broad pain indications; and delineate the promises and limitations of therapies for chronic pain and suffering.

- **TMD Interagency Working Group**
  **July 1998**

  NIDCR has convened a TMD Interagency Working Group (TMDIWG) that held the first of a series of meetings. TMDIWG facilitates cooperation, communication, and collaboration among agencies that conduct or support TMD-related activities. These activities range from support for biomedical and behavioral research to direct provision of health care services. TMDIWG provides both a forum for sharing information and scientific advances, initiating collaborative projects, and a mechanism for tracking their progress.

  The working group is comprised of representatives from four agencies in the Department of Health and Human Services. At NIH, representatives come from NIDCR, NINDS, NINR, NIAMS, NCCAM, NIAID, NHLBI, and ORWH. Other agencies represented include the Agency for Healthcare Research and Quality (formerly Agency for Healthcare Policy and Research), the Food and Drug Administration, and the Centers for Disease Control and Prevention. In addition, the working group includes representatives from patient advocacy groups, academia, and the Department of Defense.

## NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

The research mission of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) includes the conduct and support of basic and clinical research on diabetes, endocrinology (including growth factors), and metabolic diseases (including fundamental research important to bone diseases such as osteoporosis); digestive diseases and nutrition; and kidney,

urologic, and hematologic diseases. In FY 2001 and 2002, the institute has made progress in the following areas of women's health, which are summarized in this report: diabetes, breast cancer, osteoporosis, irritable bowel syndrome, primary biliary cirrhosis, obesity and nutrition, lupus nephritis, end-stage renal disease, urinary tract infections, urinary incontinence, and interstitial cystitis. The following paragraphs highlight a few of these areas, which span all the divisions of the institute.

## Diabetes

An estimated 17 million Americans have diabetes, a disease which has a major impact on women's health. It is the leading cause of new-onset adult blindness, kidney failure, and non-traumatic lower-extremity amputations. It also increases the risk of stoke, heart attack, and premature death. Women, in particular, are at a much greater risk of heart disease due to diabetes, and older minority women are affected disproportionately by end-stage renal disease as a result of diabetes. Diabetes also disproportionately affects minorities. To address this major health problem, the institute is conducting several major clinical trials, both in type 1 and type 2 diabetes. The Office of Research on Women's Health has worked with NIDDK in supporting specific women's health studies in association with the institute's major trials aimed at preventing or delaying the onset of diabetes in populations at risk. At the same time, advances in basic research are providing clues to the underlying etiology and pathogenesis of both type 1 and type 2 diabetes, and may provide targets for intervention.

## Obesity

Obesity is increasing dramatically in the U.S. population and is now considered an epidemic. The problem is particularly severe for minority women. Obesity is a risk factor for cardiovascular disease, diabetes, stroke, gallstones, and certain forms of cancer. NIDDK is expanding its support for basic and clinical research to address this problem, and has established an Office of Obesity Research to coordinate efforts in this area. The institute, with support from ORWH and other ICs, has launched the Look AHEAD (Action for Health in Diabetes) clinical trial to examine the effects of weight loss in obese individuals with type 2 diabetes. The institute, ORWH, and other ICs are also supporting innovative studies in obesity prevention and intervention. Basic research supported by NIDDK is generating important discoveries about the underlying causes of obesity, and is leading to the identification of likely targets for development of pharmaceutical interventions for prevention and treatment.

## Urologic Diseases

Lack of knowledge of the urinary bladder has hampered insight into several major diseases affecting the bladder, including interstitial cystitis, urinary incontinence, and urinary tract infections, which are major health problems for women of all ages. NIDDK continues to support both basic and clinical research in these important areas of women's urologic health. In addition to NIDDK-led efforts, the institute has worked with ORWH to fund Specialized Centers of Research (SCORs) performing research on these diseases. The recently issued report from the NIDDK-established Bladder Research Progress Review Group, "Overcoming Bladder Disease: A Strategic Plan for Bladder Research," is guiding NIDDK as it plans new initiatives in basic and clinical research on the bladder and lower urinary tract.

## Accomplishments

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 or predominantly affect women include gestational diabetes; obesity (especially in minority populations); coronary artery disease; urinary disorders;

cardiovascular and end-stage renal disease associated with diabetes; eating disorders; irritable bowel syndrome (IBS); osteoporosis; thyroid diseases (including Graves disease, goiter, and hypothyroidism); hyperparathyroidism; gallstones; primary biliary cirrhosis; interstitial cystitis (IC); urinary tract infections (UTIs); urinary incontinence; and lupus nephritis (the kidney disease of systemic lupus erythrematosus). Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other ICs, such as the importance of hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease.

NIDDK supports research that directly addresses the important women's health questions cited above – through basic research directed to understanding underlying disease processes, and through clinical research that translates this understanding into therapies and preventive interventions.

### *Diabetes*

Diabetes mellitus is one of the leading causes of disability and death in the United States. It affects an estimated 17 million Americans, about one-third of whom do not even know that they have the disease. Diabetes affects 9.1 million women, or 8.9 percent of women over the age of 20. The causes of diabetes are not precisely known, but both genetic and environmental factors play a role. Although there are several interventions currently available to help reduce the burden of this disease, there are no methods to cure or prevent it. The most common forms of the disease are type 1 diabetes, in which insulin-producing capacity is totally destroyed, and type 2 diabetes, in which the body is resistant to insulin, even though some small amount of insulin may be produced. Ninety to 95 percent of diabetes cases are type 2. Both forms of diabetes can lead to serious and costly complications, including kidney failure, blindness, amputations, heart disease, and stroke; diabetic women are at greater risk for the latter two complications. Furthermore, some women develop a reversible state of diabetes during pregnancy, termed gestational diabetes, which puts them at increased risk for developing type 2 diabetes later in life. Five to 10 percent of women with gestational diabetes are diagnosed with type 2 diabetes immediately after pregnancy; women who have had gestational diabetes have a 20 to 50 percent chance of developing type 2 diabetes within the next 5 to 10 years. Gestational diabetes occurs more frequently among women who are African American, Hispanic/Latino American, or American Indian – minority groups already at disproportionately high risk for type 2 diabetes. According to the American Diabetes Association (ADA), diabetes and its complications cost an estimated $132 billion annually.

NIDDK supports a large number of basic and clinical research programs for extramural and intramural scientists aimed at increasing our 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. Because of women's disproportionate risk of death from diabetes, particularly from cardiovascular disease, and their unique risk of gestational diabetes and its link to later type 2 diabetes, research in all of these areas – particularly disease prevention – is extremely important to women's health.

#### Informational and Strategic Activities in Diabetes that Benefit Women

NIDDK supports the National Diabetes Information Clearinghouse (NDIC) to increase the knowledge and understanding about diabetes among patients, health care professionals, and the general public. NDIC is currently developing and publishing new information booklets on gestational diabetes. NIDDK and the Centers for Disease Control and Prevention together support the National Diabetes Education Program (NDEP). NDEP includes both public and private partners in an initiative to improve

the treatment and outcomes for people with diabetes, to promote early diagnosis and, ultimately, to prevent the onset of diabetes. Information about diabetes and risks for diabetes complications is available from NDEP in English, Spanish, and Asian language versions. NDEP has also launched a health awareness campaign, "Si Tiene Diabetes, Cuide su Corazon" ("If You Have Diabetes, Take Care of Your Heart") to increase awareness of diabetes and cardiovascular disease among Hispanic and Latino Americans.

Recently, NIDDK organized the trans-NIH report to Congress on progress in diabetes research, "Conquering Diabetes – A Scientific Progress Report on the Diabetes Research Working Group's Strategic Plan." This report highlights recent advances and outlines research directions for the future. It contains a section on "Special Needs for Special Problems – Diabetes in Women, Children, the Elderly, and Minority Populations." The report can be found at *http://www.niddk.nih.gov/federal/dwg/2002/dwg02.htm*.

**Clinical Studies in Prevention of Type 1 Diabetes**

Type 1 diabetes is an autoimmune disease in which the insulin-producing beta cells of the pancreas are targeted and destroyed by immune system T cells. Maintaining even a small amount of insulin-producing capacity can delay disease onset and hence the onset of debilitating complications, thus preserving health. NIDDK is supporting numerous basic and clinical research efforts aimed at delaying, preventing, or reversing onset of type 1 diabetes. Notably, women are disproportionately affected by a number of autoimmune disorders, so knowledge gained in studies of type 1 diabetes may have broader implications for women's health. In a major clinical trial, NIDDK-supported researchers tested the efficacy of an antigen-based approach to type 1 diabetes prevention, through injection of insulin. The results of the Type 1 Diabetes Prevention Trial (DPT-1) showed that injecting individuals at high risk for the disease with low doses of insulin does not prevent disease onset. Importantly, however, the set of immunologic, genetic, and metabolic methods used to identify the high-risk group were validated through this trial – leaving researchers better poised to diagnose those at risk, which will be critical for implementing successful prevention strategies in the future. Another trial testing oral insulin as a therapy to prevent or delay disease onset is ongoing. It is being conducted through the Type 1 Diabetes TrialNet, a consortium of 14 clinical centers, a data coordinating center, and laboratory facilities in the United States and Canada. NIDDK established TrialNet to conduct rapid, preliminary clinical trials for therapies that may delay, reverse, or prevent type 1 diabetes, thus facilitating the large-scale testing of the most promising therapies for this disease. This network will also provide an important shared resource of biologic samples and data for the research community at large.

In another clinical trial, researchers tested whether disease progression could be halted or delayed in patients with newly diagnosed diabetes. Patients were given a new agent to modify the immune system to dampen its attacks on the insulin-producing beta cells in the pancreas. Encouragingly, most of the patients in this small-scale trial who received the treatment with the anti-CD3 monoclonal antibody maintained or improved the ability to produce their own insulin during the first year after diagnosis, whereas the majority of the control group did not. This approach will now be expanded in larger trials through the Immune Tolerance Network (ITN), a research effort spearheaded by NIAID with support from NIDDK and the Juvenile Diabetes Research Foundation International (JDRF). The purpose of ITN is to accelerate the development of new tolerance therapies to treat human conditions – including transplant rejection, autoimmunity, and asthma – and allergic diseases. If it proves effective in new-onset patients in larger trial, anti-CD3 treatment will then be studied in individuals at high risk for type 1 diabetes to determine whether it can actually prevent development of the disease. Other promising immune system

tolerizing agents, including other antibody-derived agents and MHC-derived molecules, are arising from ongoing research.

**Islet Transplantation and Beta Cell Biology**

NIDDK researchers have also had some success with islet transplantation, a possible treatment modality for type 1 diabetes. Pancreatic "islets" are the discrete cell clusters that contain insulin-producing beta cells. NIDDK has long maintained a strong research program in islet transplantation. In the past few years, the first American patients have undergone the experimental islet transplantation procedure that has been the most successful to date, the "Edmonton protocol," developed by researchers in Edmonton, Canada. These patients were treated by NIDDK intramural clinical research physicians. Encouragingly, several patients no longer depend upon injected insulin to survive. Research on the long-term effects and success of this procedure is still ongoing, as is research on how to reduce side effects of immunosuppressive medications. Intramural NIDDK researchers have succeeded in developing a primate model for islet transplantation, which will facilitate further evaluation and refinement of this procedure. NIDDK is also working to address other obstacles, including the availability of a sufficient number of islets for transplantation, and the means to prevent their rejection without long-term drug treatment to suppress the immune system.

To enhance future opportunities to develop alternative sources of functioning beta cells, NIDDK has established major research consortia. The Functional Genomics of the Developing Endocrine Pancreas Consortium is generating important genomic and bioinformatics tools from studies of developing mouse and human pancreatic tissue. Another group, the Beta Cell Biology Consortium, was established to facilitate interdisciplinary approaches to advance understanding of pancreatic islet development and regeneration, and is exploring new ways of producing differentiated islet cell types from multiple mouse sources and human stem cell sources eligible for NIH-funded research. The hope is that an increased basic understanding of the islets and the beta cells within them will accelerate clinical efforts to replace, preserve, or even "re-program" them, benefiting both type 1 and type 2 diabetes patients.

**Type 2 Diabetes Can Be Prevented or Delayed Through Physical Activity and Weight Loss – Important Implications for Women**

In addition to the estimated 16 million Americans with type 2 diabetes, another 16 million Americans have "pre-diabetes," a condition of impaired glucose metabolism and insulin sensitivity that places them at high risk for developing the disease. Overweight and obesity are strongly associated with pre-diabetes and diabetes; an estimated 34 percent of non-pregnant American women, compared with 27.7 percent of men, are obese. The landmark Diabetes Prevention Program (DPP) clinical trial, spearheaded by NIDDK and supported by ORWH, as well as by NICHD, NIA, NCMHD, NCRR, OBSSR, CDC, ADA, and industry, tested whether type 2 diabetes could be prevented or delayed in persons with pre-diabetes. The study enrolled over 3,200 overweight, pre-diabetic participants. Sixty-eight percent of the study participants were women, and 45 percent were from minority groups that suffer disproportionately from type 2 diabetes: African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and American Indians. The trial also recruited other groups at higher risk for type 2 diabetes, including individuals age 60 and older, persons with a first-degree relative with type 2 diabetes, and women with a history of gestational diabetes (16.1 percent of all female participants); ORWH support for DPP facilitated recruitment and retention of the latter group. After an average 2.8 years of followup, the study showed that patients randomized into an intensive lifestyle change group – which focused on moderate weight reduction and exercise – reduced their risk of developing type 2 diabetes by 58 percent. The intervention worked equally well in women and men and in all ethnic groups, but particularly

well in patients 60 and older, who reduced their risk by 71 percent. Participants randomized to receive metformin, a drug used to treat diabetes, also reduced their diabetes risk, by an average of 31 percent; this treatment was most effective in younger and heavier patients. NIDDK is establishing a long-term followup study to the DPP, the "Post-DPP Outcomes Study." Also supported by ORWH, this study will examine longer-term effects of the trial intervention on the development of type 2 diabetes and its complications, particularly cardiovascular disease, in DPP participants. It will also compare outcomes for women and men, and by age and ethnicity. The results of a number of ancillary studies to the original DPP that were supported by ORWH will also be invaluable in continued analysis of the DPP. These studies include assessing the correlation between glucose intolerance, insulin resistance, and androgenic profile, as well as the various treatment modalities on pre- and perimenopausal women of different ethnic backgrounds; and examining serum lipid measurements as an outcome measure to assess cardiovascular risks and the effects of the DPP intervention on CVD risk in trial participants. (The outcomes of a third ancillary study supported by ORWH are highlighted under "Eliminating Health Disparities in Type 2 Diabetes Prevention.")

DPP results are particularly important for women in light of recent NIDDK-supported studies of diabetes risk using data from the Nurses' Health Study I (NHS I), a large prospective cohort including over 120,000 women currently aged 56 to 81. Because of NHS's large size, high response rate to detailed biennial questionnaires on health and lifestyle, and the availability of biological samples (including blood), NIDDK has supported many studies using this cohort to examine diabetes risk, complications, and susceptibility factors for disease onset in women. One study followed over 84,000 women from NHS I for 16 years and found that, of five lifestyle and physical variables studied, excess body fat was the single most important predictor of diabetes risk in women. Encouragingly, even in overweight and obese women, a reduced risk of diabetes was associated with exercise, a healthy diet, and abstinence from smoking.

The extraordinarily valuable message of the DPP study – that type 2 diabetes can be delayed or prevented in individuals at high risk through lifestyle intervention or through medication – is being disseminated through NDEP. It is at the core of a new campaign, "Small Steps, Big Rewards: Prevent Type 2 Diabetes." This campaign is providing informational materials about the risk factors for type 2 diabetes and emphasizing implementation of small lifestyle changes – particularly diet and exercise – to prevent the disease. These materials are available at *http://ndep.nih.gov/get-info/dpi.htm.*

**Preventing Diabetes Complications – Persistent Benefits of Blood Sugar Control**

Both type 1 and type 2 diabetes lead to serious and potentially deadly complications, including cardiovascular disease and stroke, kidney disease and irreversible kidney failure, eye and nerve damage, and lower limb amputations. Relative to diabetic men, diabetic women experience a much greater increase in their risk for cardiovascular disease and stroke. Major clinical trials have demonstrated that good control of blood sugar is crucial to preventing diabetes complications. Excess blood sugar damages endothelial cells of the macro- and microvasculature, interfering with normal circulation and reducing oxygen delivery to vital tissues and organs. The Epidemiology of Diabetes Interventions and Complications (EDIC) study is a long-term followup study of patients with type 1 diabetes originally enrolled in the Diabetes Control and Complications Trial (DCCT). A recent report from the EDIC study has shown that the benefits of intensive blood sugar control for these patients, initially demonstrated in the DCCT, persist for at least 7 years. At the same time, another study has pointed out that overly tight blood glucose control can put type 1 diabetes patients at higher risk for bouts of hypoglycemia (low blood sugar). Both of these studies are important for adjusting and adopting more precise standards for

blood glucose monitoring. To facilitate better blood sugar control, NIDDK is supporting efforts to develop better, non-invasive methods of measuring blood sugar, to replace the current method of using finger pricks to obtain blood samples. This method is not only painful and burdensome, but can also cause patients to miss dangerous episodes of hypoglycemia, especially at night. Recent NIDDK-supported evaluations of non-invasive devices developed through multidisciplinary basic and clinical research studies are quite promising.

**Risk Assessment and Prevention of Cardiovascular Complications in Diabetic Women**

Cardiovascular disease (heart disease and hypertension) is the leading cause of death in patients with diabetes. The risk of death due to heart disease is increased two- to fourfold in all patients with diabetes as compared to their age-matched, non-diabetic counterparts. In women, the risk is even higher – four- to sixfold. This dramatically increased risk of heart disease was derived from analysis of data from the Nurses' Health Study I (NHS I). These data have been fleshed out by a recent NIDDK-supported study of over 121,000 women from NHS I, demonstrating that coronary heart disease (CHD) prior to diabetes, in combination with long-term duration of clinical diabetes (15 years or more), can increase a woman's risk of death due to CHD by thirtyfold. Even more ominously, another health survey of 117,000 women from NHS I showed that the risk of cardiovascular disease (CVD) began to rise at least 15 years before a clinical diagnosis of type 2 diabetes. These studies emphasize the importance of both diagnosing and managing pre-diabetes, not just to try and prevent onset of type 2 diabetes, but also to reduce CVD risk factors in the event of frank diabetes. Relevant to this, another recent NIDDK-supported study has shown that moderate exercise, such as walking, can markedly reduce the risk for cardiovascular events in diabetic women. Assessing and managing CVD risk is at the core of the NDEP's "Be Smart About Your Heart – Control the ABCs of Diabetes" campaign, which stresses the importance of not only controlling blood glucose levels (through the A1C test), but also blood pressure and cholesterol.

NIDDK has launched an important clinical effort to determine if lifestyle intervention can improve cardiovascular outcomes in obese patients with type 2 diabetes. Cosponsors include NHLBI, NINR, ORWH, NCMHD, and CDC. The LookAHEAD (Action for Health in Diabetes) clinical trial may prove especially beneficial for women. The trial expects to enroll 5,000 patients, including an estimated 60 percent women and 35 percent members of minority groups. This trial will compare the effects of behavioral intervention to achieve and maintain long-term weight loss versus diabetes education alone on incidence of heart attack, stroke, and cardiovascular-related death in these patients. Other health outcomes will also be assessed. The total followup period will be 9 to 11.5 years. In addition to 15 extramural clinical centers across the United States, a Southwest American Indian Look AHEAD clinical center has been formed at the NIDDK Phoenix Epidemiology and Clinical Research Branch in Arizona. Ancillary studies to LookAHEAD will elucidate additional topics, such as fatty liver disease and eating disorders in Look AHEAD participants.

**Genetic Markers of Diabetes and Susceptibility to Complications**

Finding the genes that confer increased susceptibility to type 1 and type 2 diabetes will help researchers understand why some people develop diabetes and others do not. This is particularly important in light of the differing effects some genes may have on diabetes risk in different racial and ethnic populations. For example, researchers have further elucidated the role of the previously identified *calpain-10* gene as a susceptibility factor for type 2 diabetes in different ethnic and racial groups. In addition to its effect in Pima

Indian and Mexican American populations, one research group has determined that a particular polymorphism in *calpain-10* may contribute to 25 percent of genetic susceptibility to type 2 diabetes in African Americans. As part of ongoing efforts to identify other diabetes susceptibility genes, NIDDK, NIAID, NHGRI, and JDRF are supporting the International Type 1 Diabetes Genetics Consortium, which is striving to identify type 1 diabetes susceptibility genes by "scanning" human genome sequences in families from the United States, Europe, and Australia. NIDDK has also expanded its efforts in the International Type 2 Diabetes Genetic Linkage Analysis Consortium, by enhancing its data set with more samples from African Americans, due to their disproportionately high risk of type 2 diabetes. There are also genetic influences on susceptibility to diabetes complications, such as kidney disease. Researchers have found that a polymorphism of the apolipoprotein E gene, which encodes a protein important for cholesterol transport, confers a threefold increased risk of kidney disease to persons with type 1 diabetes. NIDDK is currently supporting a study, Family Investigation of Nephropathy of Diabetes (FIND), to identify other genes that confer increase risk for kidney disease and progression in 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, Arizona. Working closely with the Pima Tribal Council, NIDDK is also studying the development of complications and the genes that predispose to diabetic kidney disease, which is highly prevalent among the Pimas. Because the Pima population is relatively homogeneous, studies could identify factors that would not only shed light on the genetics of diabetes in the Pimas, but also on genetic propensities for developing the disease that may exist in other populations.

**Basic Biology of Diabetes**

To develop better agents to address the metabolic dysfunctions of diabetes, NIDDK-supported researchers are pursuing basic research to more precisely define the targets of insulin action and downstream activities on a cellular and tissue level. Several important findings have recently emerged. For example, researchers working in mice have found that the absence of the glucose transporter protein GLUT4 in mouse fat cells led to insulin resistance in fat, muscle, and liver. From these and other results, it appears that the fat cells may be communicating with liver and muscle cells to help regulate insulin response in those tissues. This research opens up a window to identifying agents that may help increase insulin sensitivity in patients with diabetes. Insulin sensitivity, especially in the liver, is crucial for maintaining blood glucose levels within a narrow range – when the liver perceives less insulin stimulation, it increases release of glucose into the bloodstream. In another study in mice, researchers identified a pivotal protein that acts as an "on-off switch" to glucose production by the liver in response to insulin. Knowledge about the PGC-1 protein may enable researchers to learn more about how the drug metformin and other antidiabetes drugs act to shut down glucose production by the liver, and to propel the development of better drugs to control blood glucose.

**Diabetes and Disease Risk for Mother and Child – Intrauterine Exposure**

Gestational diabetes increases a woman's risk for developing type 2 diabetes later in life. It also affects diabetes risk for the child. Babies born to mothers with diabetes have an increased risk of becoming diabetic and obese themselves, but it has not been clear whether this is solely due to the genes inherited by the children, or whether the diabetic condition of the mother also plays a role. In a new study in the Pima Indians of Arizona, researchers looked at families in which one child was born before and another after their mother's diagnosis with type 2 diabetes – which is metabolically similar to the reversible gestational diabetes. The children born after their mothers had developed diabetes were more likely to be diabetic and obese themselves. Thus, the diabetic condition

of the mother during pregnancy appears to affect a child's risk of diabetes and obesity. Since type 2 diabetes is occurring more frequently in younger women, the results of this study are particularly important, suggesting that prevention of diabetes in women of child-bearing age improves not only their own health, but the health of their offspring.

**Positive Outcomes of Improved Diabetes Care for Both Women and Men**

Improved care for diabetes and its complications is translating into improved life expectancy. A recent study of type 1 diabetics, the Allegheny County Study, surveyed mortality rates within the Allegheny County Registry of patients. The patients were divided into three groups based on time of diagnosis. The study found a major improvement in long-term survival of both women and men diagnosed with type 1 diabetes in more recent years. Both Caucasians and African Americans experienced improvements, but the death rates remained substantially higher in African Americans. The improvements roughly correlate with the introduction of better methods of assessing glucose control and self-monitoring equipment, and with advances in blood pressure therapy in the 1980s. Follow-up studies will document whether survival continues to improve over time. If so, the results could suggest strategies to further increase survival, and address racial disparities in survival.

## *Endocrinology*

**Breast Cancer**

NIDDK supports a substantial amount of biomedical research related to breast cancer. Most of this 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, normal cells are 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 resistance to hormone action and continue to thrive. For example, the drug tamoxifen acts initially to curtail unwanted cancerous cell growth in the breast, but after a period of time, cell growth again becomes activated.

Mutations in the breast cancer-related protein, *BRCA1*, have been linked to development of cancer. *BRCA1* appears to be a central player in many biological pathways, including regulating cell growth and maintaining the integrity of the genome through repair of DNA damage. While the precise role of *BRCA1* has not been fully determined, scientists at NIDDK, NHGRI, and NCI have bred a strain of mouse that may increase understanding of the particular role of *BRCA1* in breast cancer. The mouse harbors a tissue-specific deletion of *BRCA1* in mammary epithelial cells and develops mammary tumors following a long latency period. This conditional mutant offers a model to study molecular changes arising from *BRCA1* deficiency, to identify genetic modifiers and exogenous factors that influence the onset of tumor formation, and to validate potential therapeutic strategies. In a collaborative study using this mouse strain, researchers appear to have uncovered an important mechanism for *BRCA1* activity. They found that the mice lacking *BRCA1* exhibit widespread programmed cell death (apoptosis), likely in response to DNA damage that remained unchecked in the absence of *BRCA1*. Surprisingly, this massive cell death was not seen in mice that both lacked *BRCA1* and had an impaired tumor suppressor gene p53; however, most of the female mice went on to develop mammary tumors. These results are particularly significant for human cancer because *BRCA1*-associated tumors have a relatively high frequency of p53 mutations. Researchers are continuing to examine this very important mouse model of breast cancer development, which could potentially be an important model to test therapies.

**Osteoporosis**

Osteoporosis has been reported in people of all ethnic backgrounds and the chances of developing osteoporosis are four times greater in women. Osteoporosis is characterized by low bone mass and bone deterioration. A comprehensive treatment program includes a focus on proper nutrition, exercise, and safety measures to prevent falls that may result in fractures. In addition, medication may be prescribed that will slow or stop bone loss and increase bone density. According to the National Osteoporosis Foundation, approximately 10 million people in the United States have osteoporosis, and 34 million more have low bone mass, placing them at increased risk for developing the disease. Direct and indirect expenditures for osteoporosis and related fractures are estimated at $17 billion each year, and the cost is rising.

Progress is continuing in efforts to prevent or stop bone loss. Building upon recent research advances demonstrating that low doses of synthetic parathyroid hormone (PTH) can increase bone mass, researchers are currently evaluating ways to introduce synthetic PTH into therapeutic regimens for osteoporosis. For example, glucocorticoid-induced bone loss is the most common cause of drug-related osteoporosis. It is especially severe in patients over 50 and in postmenopausal women. The important anti-inflammatory and immunosuppressive properties of glucocorticoids have prompted their extensive use; however, side effects are many, and bone loss resulting in vertebral fractures is the most incapacitating. Attempts to treat glucocorticoid-induced osteoporosis include calcium; vitamin D3 replacement; and anti-resorptive agents, such as bisphosphonates, calcitonin, and estrogen. All of these therapies seem to slow further bone loss, but none has been able to increase bone mass. NIDDK investigators are conducting a study in women with glucocorticoid-induced osteoporosis to determine whether a regimen alternating between 1) low doses of synthetic parathyroid hormone fragment, and 2) treatment with an anti-resorptive agent to inhibit bone loss could provide a useful new therapeutic regimen. In another ongoing study to prevent osteoporosis, researchers are examining whether calcium supplementation in women who have attained peak bone mass can prevent the subsequent loss of bone that occurs prior to menopause; this study is supported by ORWH.

## *Digestive Diseases*

**Informational Activities in Digestive Diseases That Benefit Women**

NIDDK continues to support the National Digestive Diseases Information Clearinghouse (NDDIC). NDDIC was established in 1980 to increase knowledge and understanding about digestive diseases (including liver disease) among people with these conditions and their families, health care professionals, and the general public.

**Irritable Bowel Syndrome**

The intestinal disorder irritable bowel syndrome (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. One research group has found that, in response to anticipated or actual rectal stimuli, IBS patients show more activity in regions of the brain that process negatively charged emotions and have reduced blood flow to specific circuits of the brain. This research group is now participating in an ORWH Specialized Center of Research for Women's Health, cofunded by NIDDK. The goal of this SCOR is to examine both interstitial cystitis – a painful bladder disorder – and IBS, focusing on the role of the brain, stress, and emotions in these disorders, which often occur in the same individual.

**Primary Biliary Cirrhosis**

Primary biliary cirrhosis is an uncommon autoimmune liver disease that primarily affects women. Although treatment is available and the disease progresses slowly, it can ultimately resist treatments and lead to liver failure. Researchers recently surveyed patients, their siblings, and their friends for medical and lifestyle information to uncover potential risk factors. Based on the information obtained, the disease may be influenced by genetic susceptibility, and infection may help trigger the disease; primary biliary cirrhosis is also associated with smoking. From another study, researchers have also learned more about the disease pathology. They found that cytotoxic CD8+T cells, targeting a particular liver cell protein, likely play an important role in liver destruction in patients with primary biliary cirrhosis. These findings will help direct ongoing and future research toward better understanding the causes of this disease.

## *Obesity and Nutrition*

Overweight and obesity have risen dramatically in the past 3 decades. Using the body mass index measurement, a calculation based upon height and weight, an estimated 64 percent of the U.S. adult population is overweight or obese. An estimated 34 percent of all non-pregnant women are obese, as compared to 27.7 percent of men. Moreover, it is estimated that over half of non-Hispanic African American women and 40.1 percent of Mexican American women are obese. Obesity places these individuals at increased risk for numerous life-threatening complications, including coronary heart disease, diabetes (and its complications), stroke, and some forms of cancer; it also causes morbidity by increasing the risks for osteoarthritis, gallstones, and urinary incontinence. Basic and clinical research on multiple fronts – including nutrition, physical activity, epidemiology, behavioral intervention, surgery, neuroendocrinology, and fat cell biology – will help to determine how best to prevent overweight and how to effectively maintain a healthy weight.

**Informational and Strategic Activities in Obesity and Nutrition that Benefit Women**

NIDDK spearheads obesity research at NIH. NIDDK supports eleven basic and clinical research programs related to weight regulation and obesity, including support for two types of university-based core centers, the Clinical Nutrition Research Units (CNRU) and the Obesity/Nutrition Research Centers (ONRC). To strengthen its efforts in obesity research, NIDDK has recently established an Office of Obesity Research that will coordinate various obesity efforts within the institute. In addition, NIDDK leads the National Task Force on the Prevention and Treatment of Obesity. This panel of mostly external scientific experts assists the institute in developing science-based information for the public and in framing new initiatives. NIDDK also supports the Weight-control Information Network (WIN). WIN was established in 1994 to provide health professionals and consumers with science-based information on obesity, weight control, and nutrition. WIN is coordinating with the Look AHEAD (Action for Health in Diabetes) clinical trial to provide information on healthy eating and physical activity to participants. WIN has also developed the "Sisters Together: Move More, Eat Better" pilot program that encourages African American women to achieve and maintain a healthy weight through increasing physical activity and eating healthier food. WIN is currently publishing a new series of booklets, "Healthy Eating and Physical Activity Across Your Lifespan," to encourage better eating and physical activity habits.

**Clinical Studies in Obesity Prevention and Intervention for Women**

NIDDK is supporting numerous approaches to preventing and reducing overweight and obesity, including the previously described LookAHEAD trial. Epidemiological studies have observed that specific stages of life confer high risk for the development of obesity in susceptible individuals, including adolescence, marriage, postpregnancy, and menopause. In response to a research

solicitation, "Innovative Approaches to the Prevention of Obesity," NIDDK, ORWH, NHLBI, NICHD, NIA, NCMHD, ODP, and CDC provided funding for pilot studies for obesity prevention primarily in the populations most alarmingly affected by overweight and obesity – women and children, particularly in minority groups. ORWH has provided support for several studies, including ones targeting pregnant women, weight control in peri- and early menopausal women, primary care office management of weight in African American women, and a mentor-based approach to long-term weight loss. In workshops held since the studies were launched, investigators have met to discuss preliminary data from the different projects and possibilities for integrating successful obesity prevention strategies into broader prevention research. NIDDK recently issued another research solicitation, "Environmental Approaches to the Prevention of Obesity," which was cosponsored by NHLBI, NIEHS, NCMHD, ORWH, ODP, and CDC. The studies funded under this solicitation emphasize approaches that modify the environment to promote healthful eating, increase physical activity, and decrease sedentary behaviors. Such approaches offer the potential for safe and effective programs for obesity prevention that could be widely disseminated. Projects include an ORWH-supported study aimed at reducing community barriers to physical activity in medically underserved women.

For some persons with morbid obesity, surgery to reduce stomach size and intestinal absorption of nutrients can be the only feasible way to achieve and maintain weight loss. NIDDK has sponsored meetings and workshops to determine how best to implement clinical studies of bariatric surgery, also known as gastric bypass surgery. Another goal was to identify areas of scientific opportunity pertaining to bariatric surgery and its impact on obesity and comorbid conditions. The institute plans to establish, through a recent research solicitation, a Bariatric Surgery Clinical Research Consortium that will accelerate clinical research and progress in understanding the pathogenesis of severe obesity and its complications. The consortium will also spur increased understanding of the risks and benefits of bariatric surgery as a treatment modality.

**A Genetic Locus for Severe Obesity in Women**

While sedentary lifestyles and unhealthful diets contribute to obesity, heredity also plays a role. However, the search for predisposing genes has been hampered by the genetic complexity of obesity – no single gene is responsible for all human weight gain. In an NIDDK-supported collaboration between academia and industry, a team of investigators has found a chromosomal region (locus) linked to severe obesity in women; it is not clear whether it is also linked to obesity in men. The industrial partner in the collaboration recently announced identification of the responsible gene within the locus, although this has not yet been published in a peer-reviewed scientific journal. It is anticipated that understanding how the gene functions could lead to drug development to modulate its effects on obesity. Continuing efforts to identify genes that contribute to obesity involve NIDDK-funded studies of the Pima Indians of Arizona, and new initiatives now being formulated to support genetic studies of obesity in animal models and humans.

**Basic Biology of Overweight and Obesity**

NIDDK has spearheaded basic research on the neuroendocrine pathways and metabolic factors influencing energy balance, metabolism, and weight regulation. Scientists now have a model for control of body energy balance, a model that includes an "appetite control center" in the brain's hypothalamus integrating information about energy stores and needs in order to regulate appetite, eating, and physical activity. Such information is provided by levels of hormones and other molecules, such as the fat hormone leptin, which acts on key neurons in the hypothalamus to suppress eating. As new discoveries are made, the model continues to evolve, and more targets for possible

therapeutic interventions arise. For example, researchers have made exciting new discoveries about the influence of gut hormones on appetite and weight. One of these hormones, ghrelin, increases appetite and is produced by the stomach and small intestine. Researchers have found that ghrelin not only stimulates appetite just before meals, but it also regulates body weight over the long term in ways that thwart dieters' best intentions for keeping off extra pounds. In one study, a group of obese individuals followed a 6-month dietary program, leading to a healthy weight loss. However, this weight change boosted the dieters' levels of ghrelin – a signal to eat more. By contrast, obese individuals who underwent gastric bypass surgery, a treatment for severe obesity, not only lost weight, but their ghrelin levels decreased. The effect of this surgical procedure on ghrelin levels may in part explain its success. In a related study, scientists found that patients with Prader-Willi syndrome, a genetic syndromic obesity disorder, have elevated ghrelin levels. Ghrelin may thus contribute to their weight gain. Another gut hormone, $PYY_{3-36}$, has the opposite effect of ghrelin – it suppresses appetite. In a recent study, people given infusions of $PYY_{3-36}$ had reduced appetite and decreased their calorie intake – even when presented with a free-choice buffet meal. Understanding the nature of hormones such as ghrelin and $PYY_{3-36}$ may lead to new therapies to control appetite and achieve sustained weight loss.

In other studies, NIDDK-supported investigators are continuing to uncover important links between metabolic and signalling pathways that are derailed in both obesity and diabetes, which may explain the association between these two conditions. For example, visceral fat in the abdomen, rather than total body fat, is the best predictor of obesity-associated diseases, such as diabetes. Researchers have now determined that the stress hormone cortisol plays a key role in determining where fat is deposited in the body. In humans, high cortisol production has been found in visceral fat cells. Mice genetically engineered to have fat cells containing extra amounts of a cortisol-producing enzyme ate more than normal, carried much of their increased weight around their middles, and developed insulin resistance and other metabolic conditions that are harbingers of type 2 diabetes. Notably, metformin, a drug already in use to treat type 2 diabetes, reduces the activity of this cortisol-producing enzyme. The development of new strategies to target the enzyme may lead to new therapies for both obesity and diabetes.

**Novel Approaches To Treating Obesity**

New opportunities to develop treatments for the serious problems of overweight and obesity are emerging from increased understanding of normal weight regulation, and from innovative experiments with compounds that promote weight loss. One new study was based on knowledge that the hormone insulin reduces food intake and body weight when injected into the brain of animals, but it does not have this effect when given systemically. Scientists tested the effects of small molecules that mimic insulin and found that these insulin "mimetics" decreased obesity, not only when injected into the brain, but also when given orally to rodents. Insulin mimetics might thus be useful therapeutically. Another research team investigated how the drug dexfenfluramine reduces food intake in animals. They discovered that it works through molecular pathways in the central nervous system. These findings may help in the design of improved weight loss drugs that act along these pathways, but that do not cause the side effects that led to the removal of dexfenfluramine from the market. In other studies in animals, scientists demonstrated the importance of proteins called beta-adrenergic receptors in regulating appetite and energy expenditure to prevent obesity. Continued exploration in these diverse areas of research may lead to novel therapies for obesity.

## *Kidney Disease and End-stage Renal Disease*

### Informational and Strategic Activities in Kidney Disease That Benefit Women

NIDDK has launched a new information campaign, the National Kidney Disease Education Program (NKDEP). The NKDEP message is targeted at doctors and other primary healthcare providers, at people at high risk for kidney disease – especially those with diabetes, hypertension, and/or a family history of kidney failure – and at insurers and others responsible for paying for healthcare. Currently in its first phase, NKDEP is recruiting volunteers to conduct educational campaigns for at-risk African Americans and health care providers in four pilot sites with high African American populations. The message focuses on identifying risk factors for kidney disease, screening those at risk, and providing appropriate treatment for those who are diagnosed with kidney disease. After completing campaigns in these sites, NKDEP will be able to identify and refine successful strategies and launch a broader national campaign. In its next phase, NKDEP will target its message to American Indians, Hispanics, and Latinos. The ultimate goal of this educational campaign is to reduce complications and death due to kidney disease and kidney failure among all Americans.

### Lupus Nephritis

Kidney disease represents one of the common and often serious manifestations of systemic lupus erythematosus (SLE), an inflammatory connective tissue disease that affects different organ systems in varying combinations. The majority of patients afflicted with SLE are young women of childbearing age. Most people with SLE have some degree of renal disease, and many have kidney failure. The importance of renal involvement, as a major cause of both morbidity and mortality of SLE, has been well established. Thus, an understanding of the causal mechanisms and treatment is of significant interest to NIDDK. Ongoing research seeks to develop a better understanding of the immunologic events leading to immune deposit formation in the glomerulus of the kidneys. Results of ongoing studies should identify disease-relevant glomerular antigens for pathogenic lupus autoantibodies and provide insights into overall pathogenic relevance of autoantibody-glomerular cell surface interactions in lupus nephritis. NIDDK intramural researchers are also recruiting patients for a new clinical trial to investigate a highly successful immunosuppressive agent (sirolimus), currently approved for use in kidney transplant operations to prevent organ rejection, to see if it can reduce kidney damage in lupus nephritis.

### New Insights into Hemodialysis

Racial and ethnic minorities suffer a far higher incidence and prevalence of end-stage renal disease (kidney failure) than Caucasians. Rates of kidney failure are disproportionately greater in African Americans, American Indian and Alaska Natives, Native Hawaiians and other Pacific Islanders, and Hispanic Americans. Diabetic kidney disease is the most common cause of kidney failure in all of the aforementioned minority groups except for African Americans, for whom diabetic kidney disease runs a close second after kidney failure caused by hypertension. Middle-aged and older African American and American Indian women are affected disproportionately by kidney failure due to diabetes. To survive, persons with end-stage renal disease must either have a kidney transplant, or have toxins removed from their blood at least three times weekly through hemodialysis. However, current dialysis regimens enable only a 26.3 percent probability of survival for 5 years – a grim statistic. In a large-scale randomized clinical trial, investigators tested whether standard hemodialyis regimens could be improved by making dialysis "doses" more intense or by using a different "high-flux" filter. The HEMO trial demonstrated that these changes to the standard protocol did not provide benefit to trial participants as a whole. However, the study also found in sub-group analyses that women who received a more intensive dose had improved survival

and reduced hospitalizations, suggesting that there may be sex- or gender-based differences in response to different dialysis regimens; these results can now be explored in future studies of hemodialysis outcomes in women. In another effort to improve dialysis outcomes, NIDDK has issued a research solicitation to initiate pilot trials examining whether daily dialysis regimens may offer improved outcomes for patients.

## *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. It has been estimated that 35 million Americans of all ages suffer from bladder disease and most have chronic conditions. Bladder problems have been reported to cost Americans more than $16 billion per year in health-related expenses. Women are disproportionately affected by urological diseases. Through its basic, clinical, and epidemiological research programs in urology, NIDDK is continuing efforts to improve interventions and treatments for these diseases, and to better understand their underlying causes.

### Informational and Strategic Activities in Women's Urologic Health

The NIDDK-supported National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC) continues to disseminate information to the general public on women's urologic disorders, including urinary incontinence and IC. Many patient- and clinician-focused brochures are available on the NIDDK website. NKUIDC provides easy-to-read and culturally sensitive publications on bladder control targeted to women, including *Bladder Control for Women*; *Exercising Your Pelvic Muscles*; *Menopause and Bladder Control*; and *Pregnancy, Childbirth, and Bladder Control.* As part of a coordinated information program to reach minority women (African American, Hispanic, and Latino American), who are disproportionately affected by urinary incontinence, many of these publications have been translated into Spanish.

To accelerate research on the normal and diseased bladder, NIDDK formed a Bladder Research Progress Review Group (Bladder Research PRG) in early 2000. This independent group of advisors consisted of scientists and medical professionals prominent in clinical and basic research and professional and lay organizations related to the bladder. They were asked to evaluate the research portfolios of NIDDK and NIH, identify research opportunities, and define unmet needs in bladder research. The ultimate objective of the Bladder Research PRG was to develop a national "strategic plan" for bladder research – a document outlining goals and recommendations for future research and its implementation, to be used by NIDDK, NIH, and other entities as a guide for future initiatives. The report, *Overcoming Bladder Disease: A Strategic Plan for Bladder Research*, has been issued and will serve as a guidepost for NIDDK program planning for basic and clinical research studies of the bladder and lower urinary tract. The report is available at *http://www.niddk.nih.gov/fund/other/brprg_book.pdf*.

### Urinary Tract Infections – Insights into Causes and Treatments

Urinary tract infections (UTIs) are among the most common infectious diseases acquired by humans; in fact, only respiratory infections occur more often. Women are especially prone to UTIs, primarily due to differences in female and male anatomy of the urinary tract. UTIs caused by the bacterium *Escherichia coli* (*E. coli*, normally found in the colon) affect 11 percent of women annually, and many women suffer from frequent infections. If a UTI is not treated promptly, bacteria may travel to the bladder, which can lead to a relatively serious infection of the kidneys.

NIDDK-supported researchers have made several important discoveries about UTIs. For example, NIDDK-supported researchers have recently demonstrated that asypmtomatic UTIs are relatively

common and rarely persist for a long period of time. Thus, bacteria in the urine do not automatically lead to clinically overt UTIs. However, asymptomatic infections are strong predictors of subsequent, symptomatic UTIs. Because UTIs are a recurrent problem for a large number of women, there has also been interest over the years in determining whether it may be beneficial for women to self diagnose and self medicate with antibiotics as a valid approach to treating these chronic, recurrent infections. Researchers studying women in a university-based primary health care clinic found that self diagnosis was highly accurate, with 94 percent of 172 self-diagnosed cases subsequently confirmed by laboratory analysis. Self treatment of uncomplicated recurrent UTIs was also very effective in curing infection in this study, as the cure rate exceeded 90 percent. Self diagnosis, followed by self treatment, may thus simplify the care of women with recurrent UTIs; however, it will still be important to involve physicians and other health care professionals in the management of these infections, especially in light of the growing problem of drug-resistant bacteria. Researchers recently identified a new drug-resistant strain of *E. coli*, called clonal group A, in urine samples from women with UTIs in California, Michigan, and Minnesota. Clonal group A was responsible for both 10 percent of the total UTIs and 38 to 51 percent of the drug-resistant UTIs observed in the patient groups, a surprisingly high prevalence for a single strain. Importantly, the distinct geographic clusters of the patient groups studied suggest a common route of dissemination of clonal group A, possibly through food. Thus, molecular typing of the *E. coli*-causing, drug-resistant UTIs may provide important information about the origins and spread of these bacteria within communities, thus enhancing opportunities to prevent further transmission of drug-resistant infections.

As part of its continued support for research to prevent and treat UTIs, NIDDK is cofunding with ORWH a Specialized Center of Research supporting three major, interlocking projects devoted to elucidating the molecular and epidemiologic bases of acute and recurrent UTIs. Special emphasis will be placed upon better defining the epidemiology of UTIs, determining the presence of persistent bladder and vaginal reservoirs following acute symptomatic UTI in women, and elucidating the molecular factors involved in host-pathogen interaction. Results of this research may lead to new means of evaluating UTIs and new and better ways to treat infection.

**Improvements in Understanding Basic Bladder Biology**

Results from NIDDK-supported research on bladder genes and proteins are providing insights into normal bladder function that could, in turn, lead to better tests, treatments, and prevention strategies for bladder disease. Recent studies have elucidated the functional importance of a class of four proteins, called uroplakins, found only in the urinary tract. These proteins form "plaques" that are a vital part of the permeability barrier that protects the bladder from infectious agents and prevents leakage of waste products into the body. In animal studies, NIDDK-supported researchers have learned more about the functional interactions between the uroplakin proteins, and found a developmental defect in the bladder-ureter junctions as a result of "knocking-out" the uroplakin III protein; in the animal model, this defect resembles the human disease vesicoureteral reflux. In another study, NIDDK-supported researchers found that the bladder can secrete a number of different proteins that go directly into the urine rather than forming part of the bladder lining. The proteins, which include both enzymes and enzyme inhibitors, may have important physiological or protective functions in the lower urinary tract. Importantly, this finding also suggests that the bladder may play a more dynamic role in responding to its environment. For example, the inappropriate secretion of bladder proteins in response to factors encountered in the urine could act as a trigger for bladder dysfunction. These new findings are providing great momentum to bladder

research at the cellular level. By exploiting these discoveries, scientists can propel bladder research even further to reveal, with greater precision, how the bladder functions, and how bladder diseases can be optimally treated and prevented.

**Interstitial Cystitis**

Interstitial cystitis (IC), one of the chronic pelvic pain disorders, is a condition resulting in recurring discomfort or pain in the bladder and the surrounding pelvic region. The cause(s) of IC are not yet known, but are the subject of active investigation by NIDDK-supported researchers. IC is far more common in women than in men. Of the more than 700,000 Americans estimated to have IC, 90 percent are women. Epidemiological studies using data from the Nurses' Health Study cohorts I and II have indicated that prevalence may be increasing, and that IC may be more common in younger women than in older women. Continued NIDDK-supported research on both IC and basic bladder biology has led to advances in determining the scope of the problem and in understanding some basic mechanisms that may be significant in the disease process.

In 1999, NIDDK began its first clinical trial to test treatments for IC. This trial is comparing two oral medications, one already FDA-approved for IC treatment (pentosan polysulfate sodium) with a new one (hydroxyzine hydrochloride) for possible combined use to bring more potent relief of IC symptoms; this trial is nearing completion. The IC Clinical Trials Group (ICCTG) is also testing whether administering the bacterium Bacillus Calmette-Guérin (BCG) in a bladder wash will relieve the pelvic pain and frequent urination that are hallmarks of IC. Exactly how BCG works in the bladder is still a mystery, but research suggests it may stimulate a protective immune response and downplay a harmful one in the IC bladder. ICCTG researchers are also conducting an ancillary study to the trial to evaluate promising new biomarkers for IC in urine, which emerged from NIDDK-supported research. ORWH has provided support to the ICCTG through its Research Enhancement Awards Program. NIDDK hopes to fund a second 5-year clinical trials group through a recent research solicitation, with enhanced opportunities to develop ancillary studies in conjunction with the clinical trials. As noted previously, NIDDK is also cofunding with ORWH a Specialized Center of Research on IC and Irritable Bowel Syndrome (IBS), two conditions which often occur in the same individual. This center will conduct both clinical research studies in patients with IC and IBS, and basic research studies using animal models of IC and IBS.

NIDDK has already planned several initiatives to promote basic and clinical research on or relevant to IC. It is anticipated that a recent research solicitation for basic research related to interstitial cystitis will greatly expand research in this area. This solicitation was drafted with the aid of the Bladder Research PRG report and publicized to the IC community in cooperation with the Interstitial Cystitis Association. Another planned initiative will request studies on the basic biology of the bladder.

**Urinary Incontinence**

About 13 million Americans, most of them women, suffer from urinary incontinence, a problem often associated with pregnancy, childbirth, and aging. After pregnancy and childbirth, about 30 percent of women develop problems with bladder control, and it can also be precipitated by estrogen loss in menopause. Research is ongoing, but treatment options for urinary incontinence are currently limited to physical therapy to improve muscle tone and bladder control, and to surgical procedures. In FY 2000, NIDDK, in collaboration with NICHD, established the Urinary Incontinence Treatment Network (UITN) to ascertain the long-term effectiveness of common surgical approaches for the treatment of urinary incontinence (stress and mixed) in women. This much-needed assessment will provide both physicians and patients with information necessary to make well-informed decisions about the best treatment options. In FY 2001, NIDDK

increased the number of clinical centers in the UITN to enhance the ethnic and racial diversity of trial participants. Currently, NIDDK, with cosponsorship from NICHD, supports eight clinical Continence Treatment Centers and a data coordinating center; ORWH has also provided support for the establishment of clinical centers. NIDDK intends to provide additional funds to expand the scope of UITN.

Further insights into the normal functioning of the bladder and its response to trauma and aging may provide improved alternatives to surgical treatment for urinary incontinence. In this vein, NIDDK has cofunded a Specialized Center of Research with ORWH for work on urinary incontinence in women. The focus of this center is to expand basic knowledge about female urethral, bladder, and pelvic floor function; improve understanding of the natural history of incontinence; and provide information for the development of novel treatments for female urinary incontinence. Both basic and clinical research projects will be pursued at this center, including one project addressing the impact of diabetes on urinary incontinence. Such studies are highly responsive to the recommendations made by the Bladder Research PRG for research in this area.

## Initiatives

*Requests for Applications (RFAs)*

- **George M. O'Brien Kidney Research Centers**

  NIDDK supports seven George M. O'Brien Kidney Research Centers as part of an integrated program of kidney-related research support within the institute. The overall goal of the centers is to sustain and maintain state-of-the-art research that will contribute to improved detection, diagnosis, treatment, and prevention of kidney disease and to bring together, in a cooperative, multidisciplinary, and integrative manner, basic science and clinical investigators to enrich the effectiveness of research into causes, treatment, and cure of ESRD. (DK-02-028, DK-01-015)

- **Digestive Diseases Research Development Centers (DDRCCs)**

  This goal of this RFA is to establish DDRDCs, which will enhance capabilities for conducting basic, clinical, and/or translational digestive diseases research. The major purpose of this initiative is to increase the availability of core resources, with the goal of fostering research, collaborations, and new directions in digestive and liver disease research. (DK-01-030)

- **Hepatotoxicity Clinical Research Network**

  This purpose of this RFA is to invite applications for the establishment of a Clinical Research Network that will focus upon the elucidation of the clinical features and pathogenesis of drug- and toxin-induced liver injury, a common cause of acute liver disease, morbidity, and mortality. (DK-02-033)

- **George M. O'Brien Urology Research Centers**

  This RFA, cosponsored by NCI, invites new applications for this centers program. These centers emphasize attracting new scientific expertise into the study of the basic mechanisms of urological diseases and disorders, multidisciplinary approaches, exploration of new basic research areas that may have clinical research application, and the pursuit of pilot and feasibility studies in urology. (DK-02-032)

- **Diabetes-based Science Education in Tribal Schools**

  Diabetes is increasingly a devastating disease in the American Indian communities. This RFA, cosponsored by NCMHD, CDC, and IHS, invites the tribal colleges and universities of the American Indian Higher

Education Consortium to apply for a grant to develop an educational program to enhance understanding and appreciation of diabetes and related science in tribal elementary, middle, and high schools. (DK-02-030)

- **Obesity/Nutrition Research Centers (ONRC)**

  The purpose of this RFA is to invite applications for Obesity/Nutrition Research Centers (Core Centers) grants, continuing support for this program. ONRC grants provide a focus for increasing collaboration and improving the cost-effectiveness of supported research among groups of successful investigators at institutions with an established, comprehensive, federally supported research base involving both basic and clinical research related to obesity. (DK-02-007)

- **Consortium for Identification of Environmental Triggers of Type 1 Diabetes**

  This RFA, cosponsored by NIAID, NICHD, NIEHS, and CDC, solicits applications for establishment of a clinical research consortium to participate in the development and implementation of studies to identify environmental factors which trigger the development of type 1 diabetes in genetically susceptible individuals. The primary objective(s) of this investigation will be identification of infectious agents, dietary factors, or other environmental factors that are associated with increased risk of type 1 diabetes, with specific phenotypic manifestations such as early age of onset or rate of progression, or with protection from the development of type 1 diabetes. (DK-02-029)

- **Imaging Early Markers of Diabetic Microvascular Complications in Peripheral Tissue**

  Early detection of changes in perfusion or oxygenation may help to identify those patients that are at risk for the microvascular complications of diabetes, enabling them to be specially flagged for intensive treatment in hopes of preventing complications. The purpose of this RFA, cosponsor by NIAMS, is to solicit applications for studies designed to apply imaging techniques that measure perfusion or tissue oxygenation at the level of the microvasculature to the study of diabetes and its complications. (DK-02-001)

- **Environmental Approaches to the Prevention of Obesity**

  The purpose of this RFA is to invite applications to study primary and secondary prevention approaches targeting environmental factors that contribute to inappropriate weight gain in children, adolescents, and adults. Cosponsors include NHLBI, NIEHS, NCMHD, OBSSR, ORWH, ODP, and CDC. (DK-02-021)

- **Training Programs in Diabetes Research for Pediatric Endocrinologists**

  To foster development of a diverse and highly trained workforce of pediatric endocrinologists to assume leadership roles related to the Nation's biomedical and behavioral research efforts in the area of pediatric diabetes, this RFA invites applications for the establishment of joint programs for the research training and career development of pediatric endocrinologists. Cosponsors are the American Diabetes Association and the Juvenile Diabetes Research Foundation International. (DK-02-024)

- **Bench to Bedside Research on Type 1 Diabetes and its Complications**

  This RFA, cosponsored by NIAID, NEI, and NHLBI, invites applications involving partnerships between clinical and basic biomedical researchers with the goal of translating advances in our understanding of the molecular basis of type 1 diabetes and its complications

into new therapies for the prevention, treatment, and cure of this disease. In these "bench to bedside" research partnerships, a team of clinical and basic scientists will conduct collaborative research that, if successful, will bring basic research advances from the laboratory to a point where a potential new therapy can be tested in patients or in preclinical studies in animal models. (DK-02-022)

- **NIDDK Progenitor Cell Genome Anatomy Projects**

  The purpose of this RFA is to support the development of the necessary biological procedures and reagents for characterization of tissue-specific progenitor cells and to characterize gene expression patterns in these cells using advanced technologies and bioinformatic techniques. The focus of the projects supported through this RFA will be on progenitor cells of the gastrointestinal tract, liver, pancreas, kidney, and genitourinary tract in both human and murine systems. (DK-02-027)

- **Innovative Partnerships in Type 1 Diabetes Research**

  The purpose of this RFA, cosponsored by NIAID, NEI, NINR, and NHLBI, is to attract new research talent to type 1 diabetes research, strengthen the ongoing efforts of type 1 diabetes researchers by providing access to specialized expertise or technologies relevant to their research, and facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes. (DK-02-023)

- **Depression and Mental Disorders in Diabetes, Renal Disease, and Obesity and Eating Disorders**

  Few studies have addressed the natural history and consequences of co-existent mental disorders on chronic diseases such as diabetes mellitus, chronic renal disease, and obesity and eating disorders, and vice versa. The purpose of this RFA is to increase research activity in the field of mental disorders in relationship to diabetes mellitus, chronic renal disease, and obesity and eating disorders. Cosponsored by NIMH. (DK-02-009)

- **Gene Transfer Approaches to Enhance Islet Transplantation**

  Gene transfer approaches could be one method to engineer beta-cells or alter islets to enhance viability that could have advantages for islet transplantation. The purpose of this RFA, cosponsored by NIAID, is to solicit pilot and feasibility studies to develop gene transfer approaches to enhance islet transplantation. (DK-02-020)

- **Feasibility Projects to Test Strategies for Preventing or Slowing the Progression of Diabetic Nephropathy**

  This RFA invites clinical research applications for trials using novel agents or drug combinations in patients to prevent the appearance or slow the progression of diabetic nephropathy. The goal of this initiative is to evaluate therapies that might potentially be taken to large, phase III interventional trials. (DK-02-025)

- **Barrett's Esophagus, Gastroesophageal Reflux Disease, and Adenocarcinoma of the Esophagus**

  This initiative, cosponsored by NCI, is designed to stimulate and solicit studies to broadly address the problem of Barrett's esophagus (a pre-malignant condition) and its etiology and relationship to gastroesophageal reflux disease and its link to the rising incidence of adenocarcinoma of the esophagus. (DK-02-015)

- **Diabetes Research and Training Centers (DRTCs)**

  DRTCs are intended to facilitate progress in research with the goal of developing new methods to treat, prevent and, ultimately, cure diabetes mellitus and its complications. DRTCs support Research Cores that provide shared resources to enhance the efficiency of biomedical research and foster collaborations within and among institutions with established, comprehensive bases of research relevant to diabetes mellitus; a Pilot and Feasibility Program; and an Enrichment Program. DRTCs must also have a substantial base of research on translation of research advances into clinical practice. (DK-02-005)

- **Diabetes Endocrinology Research Centers (DERCs)**

  DERCs are intended to facilitate progress in research with the goal of developing new methods to treat, prevent and, ultimately, cure diabetes mellitus and its complications. DERCs support Research Cores that provide shared resources to enhance the efficiency of biomedical research and foster collaborations within and among institutions with established, comprehensive bases of research relevant to diabetes mellitus; a Pilot and Feasibility Program; and an Enrichment Program. (DK-02-004)

- **Surrogate Endpoints for Diabetic Microvascular Complications**

  This RFA invites basic and clinical research applications to develop biochemical, cellular, physiologic, or genetic surrogate endpoints that can be used to predict risk, aid in early diagnosis, and assess progression of the microvascular complications of diabetes. Cosponsored by NEI and NINDS. (DK-02-016)

- **Comprehensive Programs in Beta Cell Biology**

  This initiative is intended to support large, multicomponent projects consisting of innovative, high-impact studies focused on the beta cell and the adult pancreatic islet; to attract established investigators who can bring novel or advanced techniques, tools, and concepts from other areas of research to the study of beta cell biology; and to foster interdisciplinary approaches to the study of beta cell biology. The ultimate goal is to use this increased understanding of the biology of the pancreatic islet to develop novel approaches to the treatment of diabetes. (DK-02-014)

- **Imaging Pancreatic Beta Cell Mass, Function, Engraftment, or Inflammation**

  This RFA is intended to further stimulate the development of techniques or reagents leading to the ability to image or otherwise noninvasively detect pancreatic islet beta cells *in vivo*, and measure their mass, function, or evidence of inflammation, or to monitor engraftment of transplanted isolated pancreatic islets. (DK-02-002)

- **New Approaches to Prevent Hypoglycemia in Patients with Diabetes**

  Episodes of severe hypoglycemia may complicate treatment to control blood sugar and are often a major obstacle to the achievement of euglycemia in many patients. This RFA solicits clinical studies to 1) define and characterize hypoglycemia in diabetic individuals, and 2) develop new approaches to prevent the development of hypoglycemia or to ameliorate its effects in individuals with diabetes. Cosponsors include NINDS, NICHD, NINR, and the Juvenile Diabetes Research Foundation International. (DK-01-032)

- **Understanding Hypoglycemia Unawareness in Patients with Diabetes**

  This RFA complements DK-01-032 and solicits basic and clinical studies to 1) define the mechanisms underlying the loss of hypoglycemia awareness in patients with diabetes, and to 2) develop novel approaches to prevent or reverse hypoglycemia unawareness. Cosponsors include NINDS, NICHD, NINR, and the Juvenile Diabetes Research Foundation International. (DK-01-031)

- **Inflammatory Bowel Disease Genetics Research Consortium**

  The purpose of this RFA is to establish a consortium to participate in the development and implementation of studies to identify genes which are associated with the inflammatory bowel diseases, Crohn's disease, and ulcerative colitis. (DK-02-01)

- **Treatment of HAART-associated Metabolic Changes in Patients with HIV Infection**

  HAART treatment for HIV/AIDS has been associated with a variety of metabolic complications – including dyslipidemia, insulin resistance, and abnormal distribution of body fat (lipodystrophy) – all of which are major risk factors for the development of other serious diseases, such as diabetes and cardiovascular disease. This RFA, cosponsored by NHLBI, solicits clinical studies to 1) test the efficacy, in patients infected with HIV, of agents currently approved for the treatment of dyslipidemia, insulin resistance, or diabetes, and osteoporosis; and 2) develop and test novel treatment approaches to HAART-associated metabolic changes, including lipodystrophy. (DK-02-006)

- **Adult-to-Adult Living Donor Liver Transplantation Cohort Study (LDLT)**

  Adult-to-adult LDLT is a relatively new procedure increasingly used at major transplantation centers. The objective of this RFA is to establish and maintain the infrastructure required to accrue and follow sufficient numbers of patients being considered for and undergoing LDLT to provide generalizable data on donor and recipient outcomes. (DK-02-010)

- **Multicenter Clinical Trial of Focal Glomerulosclerosis in Children and Young Adults**

  This purpose of this RFA is to establish support for a randomized clinical trial of cyclosporin or novel immunomodulatory agents in children and young adults with the kidney disease focal segmental glomerulosclerosis. (DK-02-013)

- **Functional Atlas of Orphan Nuclear Receptors**

  Members of the nuclear receptor protein superfamily play a variety of roles in gene expression. Alterations in gene expression over the long-term can play a role in many diseases, including cancer, osteoporosis, and obesity. The purpose of this initiative, cosponsored by NIA, is to develop a functional atlas of orphan nuclear receptors emphasizing understanding and cataloging of structure, tissue distribution, specificity, and function of this sub-group of the nuclear receptor superfamily. (DK-01-026)

- **Polycystic Kidney Disease Clinical Trials Network**

  This RFA invites cooperative agreement applications to establish a network to design and implement clinical trials to slow the progressive loss of renal function in polycystic kidney disease (PKD). The network, consisting of a Data Coordinating Center and Participating Clinical Centers, will develop and execute both pilot and feasibility trials and a large, randomized controlled clinical

trial on blockade of the renin-angiotensin axis in patients with PKD. (DK-01-029)

- **Silvio O. Conte Digestive Diseases Research Core Centers**

  The Silvio O. Conte Digestive Diseases Research Core Centers are part of an integrated program of digestive diseases-related research support provided by NIDDK. The centers have provided a focus for increasing collaboration and improving the cost effectiveness of supported research among groups of successful investigators at institutions with an established, comprehensive digestive diseases research base. (DK-01-027)

- **Planning Grant for Diabetes and Science Education in Tribal Schools**

  This RFA invites the tribal colleges and universities to apply for a planning grant to develop an educational program to enhance understanding and appreciation of diabetes and related science in elementary, middle, and high schools serving American Indian/Alaska Native communities. Cosponsors include NCMHD, CDC, and IHS. (DK-01-033)

- **Clinical Research Network in Non-Alcoholic Steatohepatitis (NASH)**

  NASH is a common, but poorly understood, liver disease that is characterized by accumulation of fat in the liver (steatosis), accompanied by inflammation, cell injury, and fibrosis (hepatitis) that closely resembles alcoholic liver disease but occurs in patients who drink little or no alcohol. NASH is most common in adults above the age of 40 who are overweight or have diabetes, insulin resistance, or hyperlipidemia, but also occurs in children and in adults who are not obese or diabetic. This RFA invites applications for establishment of a Clinical Research Network that focuses upon the etiology, contributing factors, natural history, complications, and therapy of NASH. (DK-01-025)

- **Non-Human Primate Immune Tolerance Cooperative Study Group (NHPCSG)**

  The NHPCSG is a multicenter, cooperative research program focused on the study of immune tolerance in non-human primate models of kidney and islet allograft rejection, asthma and allergic diseases, and autoimmune diseases. The ultimate purpose of this RFA is to develop candidate tolerogenic approaches for the treatment of immune-mediated diseases in humans. Cosponsored by NIAID (lead). (AI-01-006)

- **Cooperative Multicenter Research Network to Test Glucose Sensors in Children with Type 1 Diabetes Mellitus**

  This RFA, cosponsored by NICHD (lead), invites cooperative agreement applications for participation in a collaborative research consortium that will utilize new continuous glucose monitoring devices to: 1) evaluate glycemic control and the incidence, magnitude, and duration of hypoglycemia in a contemporaneous population of children with type 1 diabetes mellitus; and 2) to evaluate glucose homeostasis in children without diabetes. This research consortium may also evaluate the value of providing data from these devices to health care professionals with regard to achieving glycemic control and minimizing hypoglycemia in children with type 1 diabetes mellitus. (HD-01-009)

- **Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection**

  The purpose of this RFA is to solicit applications for research projects that propose developing novel technologies

or improving established technologies to enhance the ability to identify and validate the role of microbial pathogens in chronic diseases and cancer for which an infectious etiology is suspected. Areas of particular interest are studies using recent technological approaches in genomics, molecular biology, proteomics, and computational biology. Cosponsors include NIAID (lead), NCI, and ORWH. (AI-01-004)

- **Mouse Models of Diabetic Complications Consortium**

  The intent of this initiative is to assemble a cross-disciplinary Mouse Models of Diabetic Complications Consortium to develop innovative mouse models that closely mimic the numerous human complications of diabetes, including diabetic kidney disease, micro- and macrovascular disease, urinary tract infection, and altered gastrointestinal and bladder function. Cosponsors include NHLBI, NEI, NIDCR, and the Juvenile Diabetes Research Foundation International. (DK-01-009)

- **NIDDK Biotechnology Centers**

  The purpose of this RFA is to make comprehensive gene expression technologies widely available to researchers working in areas supported by NIDDK. This RFA seeks to establish Biotechnology Centers that will provide genomic profiling resources to investigators working in research areas within the NIDDK's mission. (DK-01-019)

- **Urinary Incontinence Treatment Network (UITN): Continence Treatment Centers**

  The primary goal of UITN is to assess the long-term outcomes of the most commonly applied treatments for women with the diagnoses of stress and mixed urinary incontinence. The purpose of this solicitation is to add up to four Continence Treatment Centers to the UITN to increase the number of patients enrolled and to enhance the ethnic and racial diversity of the study population. (DK-01-018)

- **Beta Cell Biology Consortium**

  This RFA seeks applications to establish a Beta Cell Biology Consortium for the purpose of intensifying research; encouraging interdisciplinary; fostering the application of basic research to generate new research tools and approaches for the diagnosis, treatment, and cure of diabetes; and establishing a comprehensive database for the beta cell. Through the consortium, individual Beta Cell Biology Programs will have access to information, resources, technologies, expertise, and reagents that are beyond the scope of any single research effort. (DK-01-014)

- **Type 1 Diabetes Trialnet: Clinical Centers and Core Support Facilities**

  These RFAs seek applications for clinical centers and a coordinating center to perform and facilitate intervention studies to preserve pancreatic beta cell function and prevent type 1 diabetes. The TrialNet will complete the ongoing Diabetes Prevention Trial for Type 1 Diabetes and participate in the design and execution of pilot and expanded studies of new agents to prevent or ameliorate type 1 diabetes, and in natural history and genetics studies in populations screened for or enrolled in these studies. Cosponsors include NIAID and NICHD. (DK-01-003, DK-01-004)

- **Prevention and Treatment of Type 2 Diabetes in Children and Adolescents – Clinical Centers and Coordinating Center**

  Type 2 diabetes has been traditionally viewed as a disease of adults; however, recent epidemiological data reveal an increasing number of cases of type 2

diabetes in the pediatric population, especially among adolescents and in certain minority populations. The purpose of these RFAs is to: 1) solicit proposals for clinical trials for the prevention and treatment of type 2 diabetes in the pediatric population; 2) create an infrastructure for the conduct and analysis of such clinical trials; and 3) provide administrative, analytical, and statistical support for the clinical studies. (DK-01-010 and DK-01-011)

*Program Announcements (PAs)*

- **Race and Ethnic Disparities in the Incidence of Diabetes Complications**

  This PA, cosponsorsed by NINDS, NEI, NINR, and NHLBI, seeks research to understand racial and ethnic disparities in the development of the microvascular (nephropathy, retinopathy, and neuropathy), and macrovascular (cardiovascular disease and stroke) complications of diabetes. Investigation of both biologic and non-biologic (environmental and lifestyle) factors through metabolic, genetic, and/or epidemiologic studies in representative populations is encouraged. (PA-02-165)

- **Intestinal Failure, Short Gut Syndrome, and Small Bowel Transplantation**

  The purpose of this PA is to encourage research studies on the pathogenesis, natural history, treatment, and complications of intestinal failure and its therapies, including parenteral nutrition and small bowel transplantation. (PA-02-163)

- **Development of the Endocrine Pancreas**

  This program announcement is intended to stimulate the application of advances in developmental biology, specifically in developmental genetics, embryology, and stem cell biology, to study pancreatic development. (PA-02-161)

- **Translational Research for the Prevention and Control of Diabetes**

  The purpose of this PA is to solicit research to translate recent advances in the prevention and treatment of type 1 or type 2 diabetes into clinical practice for individuals and communities at risk, particularly in minority populations, and among children and adolescents. Cosponsors include NEI, NINR, OBSSR, AHRQ, CDC, and the American Diabetes Association. (PA-02-153)

- **Development of Cell-selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract**

  The purpose of this PA, cosponsored by NCI and NICHD, is to promote the development of research tools and innovative methods that may be applied to studies of individual cell types of the bladder, prostate, and genitourinary tract. Elucidating the function of physiologically relevant, specialized cell types in humans and in rodent models will enhance the understanding of the function of these organs under healthy and pathological states. (PAR-02-143)

- **Racial and Ethnic Differences in the Etiology of Type 2 Diabetes in the United States**

  This PA seeks research applications to enhance understanding of the underlying metabolic and physiologic mechanisms that contribute to the racial and ethnic differences in the incidence and pathophysiology of type 2 diabetes in the United States. (PA-02-117)

- **Complex Formation in Hormonal Regulation of Gene Expression**

  The purpose of this PA is to stimulate basic research to address the fundamental mechanisms effecting hormonal regulation of gene expression. Of interest is the potential role(s) these mechanisms

may play in the development of endocrine organs or of diseases such as diabetes, obesity, osteoporosis, and prostate cancer. Cosponsors include NIMH, NIA, and NCI. (PA-02-100)

- **Ancillary Studies on Control Groups in Clinical Trials**

  The purpose of this PA, cosponsored by NCCAM, is to invite ancillary studies to NIH-funded interventional clinical trials to address the biological, behavioral, and statistical issues related to the control or comparison group used in these trials and the effects of inclusion of a placebo group on clinical trial design. (PA-02-094)

- **Secondary Analyses in Diabetes, and Digestive and Kidney Diseases**

  This PA invites applications to support the secondary analysis of existing data sets relevant to diabetes and endocrine and metabolic diseases; digestive diseases and nutrition, including obesity and eating disorders; and kidney, urological, and hematological diseases. The goal of this NIDDK program is to facilitate performance of short-term projects that explore innovative approaches that are not readily supported by other funding mechanisms and that can be conducted using existing data sets. (PA-02-077)

- **Liver and Pancreatic Disease in HIV Infection**

  This PA, cosponsored by NIAID, solicits clinical and basic research applications that focus on the pathogenesis and therapeutics of the liver and pancreatic disease associated with coinfections that occur in patients with HIV infection (such as hepatitis B and C), or the metabolic complications associated with treatment of HIV infection (including hepatic drug toxicity and pancreatitis). (PA-01-117)

- **The Role of Antioxidants in the Prevention of Diabetic Complications**

  This PA solicits applications to: 1) determine the efficacy of vitamin E or other antioxidants in preventing, delaying, or ameliorating the micro- or macrovascular complications of diabetes; and 2) provide insight into the mechanism(s) by which antioxidants might prevent or influence the development of diabetic vascular disease. Cosponsors include NEI, NHLBI, NIA, NINDS, and ODS. (PA-01-112)

- **Physical Activity and Obesity Across Chronic Diseases**

  This PA invites applications from investigators for research studies that will address the relationship between physical activity and obesity, including studies to test intervention approaches that incorporate physical activity for obesity prevention or treatment related to chronic diseases. Cosponsors include NCI, NHLBI, NIA, NIAMS, NICHD, and NINR. (PA-01-017)

*Conferences and Workshops*

- **Genetic Modifiers of Mendelian Diseases**
  **September 9-10, 2002**
- **Hereditary Calcium Oxalate Stone Disease Registry Planning Meeting**
  **August 9, 2002**
- **2nd Investigators Workshop on Innovative Approaches to Obesity Prevention**
  **August 12-13, 2002**
- **Strategic Planning for Polycystic Kidney Disease**
  **July 10-11, 2002**
- **NIH Consensus Development Conference on Management of Hepatitis C: 2002**
  **June 10-12, 2002**
- **Hepatocyte-based Therapies for Oxalosis**
  **June 9, 2002**

- **Perspectives on Conjugated Linoleic Acid Research: Current Status and Future Directions**
  **May 15-16, 2002**
- **Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century**
  **April 8-9, 2002**
- **Congenital Urinary Tract Obstruction: State-of-the-Art Strategic Planning Workshop**
  **March 11-12, 2002**
- **Kidney Disease Clinical Trials Task Force Workshop**
  **March 7-8, 2002**
- **NIH Consensus Development Conference on Endoscopic Retrograde Cholangiopancreatography for Diagnosis and Therapy**
  **January 14-16, 2002**
- **Encapsulation and Immunoprotective Strategies of Islet Cells**
  **December 6-7, 2001**
- **Beta Cell Biology in the 21st Century**
  **November 26-28, 2001**
- **Etiology and Epidemiology of Early Autoimmune Type 1 Diabetes in Humans**
  **October 25-26 , 2001**
- **Pancreatic Development, Proliferation, and Stem Cells**
  **October 18-19, 2001**
- **A Review of Endocrinology, Diagnosis, and Treatment (CME course)**
  **October 17-21, 2001**
- **Preparing for a Clinical Research Career in Nephrology**
  **September 8-10, 2001**
- **Bladder Research Progress Review Group Report Meeting**
  **July 20-22, 2001**
- **Genomics and Proteomics for Kidney and Urologic Diseases**
  **July 8-10, 2001**
- **National Kidney Disease Education Program Strategic Development and Planning Meeting**
  **June 28-29, 2001**
- **Workshop on Noninvasive Measurement of Iron**
  **April 17, 2001**
- **Task Force on Daily Dialysis**
  **April 11-12, 2001**
- **Lipoatrophic Diabetes and Other Syndromes of Lipodystrophy**
  **March 22-23, 2001**
- **Diabetes Science Education in American Indian Tribal Middle and High Schools**
  **March 15-16, 2001**
- **Diabetes and Aging**
  **February 12-13, 2001**
- **Depression and Mental Disorders in Patients with Diabetes, Renal Disease, and Obesity and Eating Disorders**
  **January 29-30, 2001**
- **Living Donor Liver Transplantation**
  **December 4-5, 2000**
- **The Science of the Placebo**
  **November 19-21, 2000**
- **Oxalosis and Calcium Oxalate Stone Disease**
  **November 16-17, 2000**
- **Cell Biology and Pathophysiology of Peptide Hormone Processing, Secretion, and Action**
  **October 26-28, 2000**
- **Interstitial Cystitis and Bladder Research**
  **October 19-20, 2000**
- **New Directions in Drug-induced Liver Injury: Mechanism and Test Systems**
  **October 17-18, 2000**
- **Familial Investigation of Nephropathy of Diabetes**
  **October 2, 2000**

*Health Disparities Research*

- **Eliminating Health Disparities in Type 2 Diabetes Prevention**

  Important progress is being made toward eliminating health disparities in diabetes prevention. An ancillary study to the DPP, supported by ORWH, focused on drug intervention in over 230 Hispanic women with a history of gestational diabetes. In this study, the incidence of type 2 diabetes in women who received the drug was reduced by at least 50 percent. Furthermore, the protective effect persisted for at least 8 months after the end of therapy, and was associated with preservation of beta cell function. The drug used is one of a class of agents that improve the body's sensitivity to insulin; although the specific drug used in this study (troglitazone) is no longer on the market, other drugs in this class are approved for diabetes treatment and are being evaluated for diabetes prevention. Researchers have also recently found that Filipina American women are at much higher risk for type 2 diabetes than Caucasian women. However, Filipinas differ from Caucasians in that body mass index, typically used to assess overweight and obesity, did not correlate well with diabetes in this study. Instead, waist circumference and cholesterol measures were more useful for predicting diabetes in Filipina women.

  Diabetes is a major health concern among Native American communities, and NIDDK is supporting many clinical studies in these populations. One recent study showed that high insulin levels, which precede the development of type 2 diabetes, are associated with a skin condition called acanthosis nigricans in Cherokee Indians. These findings confirm and extend previous reports associating this skin condition with type 2 diabetes. Screening for this readily visible skin condition would provide a simple, inexpensive and non-invasive way to predict risk for type 2 diabetes, providing an opportunity for early intervention. An ongoing research project that has received past support from ORWH, through the REAP program, focuses on diabetes prevention and education in urban Native American women in New Mexico. The Family Centered Diabetes Project has developed the "Sharing Wisdom" program, a culturally appropriate, lifestyle-specific intervention and outreach effort. The intervention hopes to reduce diabetes risk factors in urban Native American communities by targeting Native American women between 18 and 40 who do not have diabetes. In addition to its support of extramural studies, NIDDK maintains the NIDDK Phoenix Epidemiology and Clinical Research Branch in Arizona. Researchers at this branch work with the Pima Indians of Arizona, who have the highest rates of type 2 diabetes in the world. Studies in this population are uncovering susceptibility genes, metabolic factors, and other factors that contribute to the development of type 2 diabetes and its complications.

## National Institute of Environmental Health Sciences

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

regulators can better define standards that protect women from environmental triggers of these diseases.

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

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

## Highlights

### *Working Groups Focused on Women's Health*

NIEHS' Laboratory of Women's Health focuses on important diseases in women, such as breast cancer, ovarian cancer, uterine leiomyoma, ovarian dysfunction, and pregnancy and parturition dysfunctions. The laboratory studies how these diseases develop and occur over the life span of a woman, and how environmental toxins and stresses cause these diseases. The ultimate goal is to reduce the burden of environmentally related diseases. The laboratory has initiated a clinical study, the Uterine Leiomyoma Longitudinal Intervention Study designed to define the growth dynamics of uterine leiomyomas, through time, and develop markers for growing and/or clinically relevant leiomyomas that will be important in future studies of the etiology, therapy, and prevention of these tumors. The Laboratory of Women's Health also is developing genetically defined animal models that provide links between molecular medicine, human epidemiology, and experimental studies. These models provide opportunities to identify key genes and signaling mechanisms of the reproductive systems that interact with the environment, over time, at different stages of life. The overall goal is to integrate genetics, endocrinology, immunology, pathology, epidemiology, and clinical research to study diseases in women in order to discover new ways to prevent environmentally related diseases.

## Accomplishments

### *Breast Cancer*

#### Breast Cancer Susceptibility Genes, *BRCA1* and *BRCA2*

Women with mutations in the *BRCA1/2* genes carry an increased risk for developing breast cancer. However, there is substantial variation in the incidence of breast cancer in *BRCA1/2* mutation carriers. Other risk factors may include hormone-related exposures; reproductive status, such as age at first birth or never giving birth; and other genetic variations. The gene AIB1 was identified in a search of genes that are amplified in breast tumors. AIB1 enhanced estrogen-dependent gene transcription suggesting that altered expression of AIB1 may influence the progression of steroid-dependent cancers. As in some other hormone-related genes, AIB1 has a region that repeats three nucleotides (CAG) that code for the amino acid glutamine. The purpose of this study was to determine whether AIB1 variation was associated with *BRCA1/2*-associated breast cancers. A matched case-control study of 448 women with *BRCA1/2* mutations was conducted. Women who had their first live birth at a later age or women who had never given

birth had increases in *BRCA1/2*-associated breast cancer risk. Also, women with 28 or 29 polyglutamine repeats in AIB1 were at increased risk for *BRCA1/2*-associated breast cancer risk compared to women with genes with fewer polyglutamine repeats. These results support the idea that pathways that involve endocrine signaling, as measured by AIB1 genotype and reproductive history, may have a substantial role in *BRCA1/2*-related breast cancer. The ability to effectively apply risk-prediction and reduction strategies in *BRCA1/2* carriers may depend on the knowledge of additional risk factors in addition to *BRCA1/2* mutation status.

**Hormonal Factors Modulate Risk of Developing Breast Cancer in Women with *BRCA1/2* Mutations**

Inheritance of germ-line mutation in the *BRCA1/2* genes is associated with increased risk of developing breast cancer. However, inheriting one of these defective genes may not be sufficient for breast cancer development. Many women who inherit the susceptibility genes never develop the disease, whereas others do. This fact suggests that other genetic or environmental factors modify the risk. Recent studies, cofunded by NIEHS, the National Cancer Institute, and the Department of Defense, showed that hormonal factors may modulate *BRCA1*-associated breast cancer risk. These results suggest that exposure to endogenous hormones or exogenous synthetic chemicals, with hormone-like activity, can influence the risk of developing cancer in women who inherit the *BRCA1* susceptibility gene.

**Intervention to Delay and Prevent Breast Cancer**

Breast cancer is one of the most common cancers in women and is the second leading cause of cancer deaths of women in the United States. Animal models are useful for understanding the biology of breast cancer and for evaluation of prevention strategies and therapeutic approaches. The transgenic mouse model Tg.NK with c-neu, the human breast cancer oncogene homologue of erbB2, develops mammary cancers early in life (e.g., by 6 months). Recent study with the Tg.NK mouse model indicated that low doses of soy isoflavones may have the potential to delay the development of mammary tumors. However, higher doses (five to ten times) may have the potential to promote mammary cancer. Mice were exposed starting at 4 weeks of age, which is close to adult exposure. However, the normal human exposure to soy isoflavones will be during all stages of life including *in utero*, neonatal, prepuberty, and adult. Therefore, it is necessary to expose the Tg.NK mice to different concentrations of soy isoflavones (by diet), during all stages of life, to determine the beneficial effects and adverse effects of soy isoflavones on mammary cancer. Some components of diet, dietary supplements, vitamin A – and its analogues (retinoids) – and therapeutic agents, such as tamoxifen, may delay or prevent mammary cancer. The Tg.NK transgenic mouse model could be used to develop and evaluate dietary supplements and therapeutic agent combination intervention strategies to prevent breast cancer. This research may be extended to prevent or decrease environmental exposure and lifestyle-associated promotion of breast cancer.

**The Sister Study: Environmental and Genetic Risk Factors for Breast Cancer**

The Sister Study is a major NIEHS initiative to study genetic and environmental risk factors for breast cancer in a cohort of 50,000 sisters of women who have had breast cancer. These asymptomatic women will be followed over time with periodic health updates. Those who develop breast cancer during the followup period will be compared with a sample of those who remained healthy to identify factors associated with increased cancer risk. The cancer-free sisters have about twice the risk of developing breast cancer, presumably because they and their affected sister share many of the same genes and early life exposures. Breast cancer risk could be assessed in terms of exposure to endogenous hormones, exogenous hormone disruptors, growth factors, dietary components, and

environmental contaminants, such as pesticides and solvents. The Sister Study would also assess the importance of gene-environment interactions by studying polymorphisms of genes involved in metabolic activation, receptor binding, deoxyribonucleic acid (DNA) repair, or detoxification. Although the effort would target breast cancer, less common, hormonally related cancers, such as ovarian and endometrial cancer, could also be studied. Additionally, as more breast cancer-related genes and exposures are identified, the databank could be regularly re-evaluated to address this new information. This study group might also be used to evaluate other exposures important for female-predominant diseases, such as autoimmune diseases, if a large enough subset of the cohort was identified as suffering from these conditions. A companion study will assess environmental risk factors by comparing incident breast cancer cases and their cancer-free sister and will explore similarities or differences in tumor characteristics between affected sisters. The objectives of this study include defining gene-environment interactions important to breast cancer development, gene-environment interactions in ovarian and endometrial cancers, if enough cases arise in this cohort, and gene-environment interactions in female-predominant disorders, such as autoimmune disease, if enough cases are found in this cohort.

**Identifying Environmental Triggers of Breast Cancer – The Agricultural Health Study**

The Agricultural Health Study is a collaboration between NIEHS, NCI, and the U.S. Environmental Protection Agency. This study explores potential causes of cancer and other diseases among farmers and their families and among commercial pesticide applicators. The Agricultural Health Study is a prospective study of 55,000 licensed pesticide applicators and nearly 35,000 spouses of farmer applicators. Originally developed by NCI to examine cancer risks, the scope of the project was expanded with funds from NIEHS to include a multitude of other health endpoints, including those with particular relevance to women. The benefits of this study extend beyond farmers because the exposures under study (e.g., pesticides, solvents, nitrates, metals, mycotoxins, silica) are not limited to farmers, but are common to rural communities and other settings. Enrollment of the cohort has been completed, with more than 80 percent of eligible applicators in Iowa and North Carolina completing a questionnaire about their exposures and health status. Cohort members are now completing 5-year followup interviews; cancer incidence and mortality are being evaluated using cancer registries and vital records. NIEHS has identified possible links between farm exposures and some neurological health endpoints. A NIEHS-supported researcher was studying the herbicide, paraquat, which acts adversely on the dopamine system. When paraquat and the fungicide, maneb, were jointly administered to mice, the combined exposure decreased motor activity, increased dopamine turnover, and reduced other measures of dopamine effect at levels far greater than when the same chemicals were administered individually. The fact that combined exposures, such as would be found in real-world applications, can potentiate the adverse effects on the dopamine system raises important possibilities for multiple environmental risk factors being associated with Parkinson's disease development. This work is complemented by another group of federally supported researchers. They found that the organic pesticide, rotenone, produced symptoms of Parkinson's disease in laboratory animals. Women's health endpoints being examined by NIEHS include premature ovarian failure, uterine fibroids, endometriosis, systemic lupus erythematosus, and menstrual function. Other disease risks being studied are thyroid disease, diabetes, childhood growth and development, asthma and altered lung function, immunologic response, degenerative eye diseases, and neurodegenerative and neurobehavioral effects. A nested study of farming-related and other risk factors for

Parkinson's disease is being developed in collaboration with researchers from the Parkinson's Disease Institute.

**Dithiolethiones: A Promising Class of Human Anti-Cancer Drugs**

DNA adducts result from a covalent binding of carcinogenic chemicals or their metabolites and DNA. This is a critical and early step in the process of carcinogenesis. The compound oltipraz has been shown to have anti-carcinogenic effects by preventing or reducing the formation of DNA adducts. Its effects have been found to be most effective in colon and liver tissue. Oltipraz belongs to a class of compounds known as the dithiolethiones. The anticarcinogenic potential of oltipraz is compared to another compound in this class, 3H-1,2-dithiole-3-thione (D3T). Dithiolethiones are currently considered very promising chemopreventive agents because of their effectiveness in a wide variety of tumor models. Dithiolethiones were once thought to be found in vegetables such as broccoli, cauliflower, and cabbage. However, it is likely that they could also be formed *in vivo* from naturally occurring precursors found in asparagus and garlic. The researchers used a potent mammary carcinogen, dibenzo[a,l]pyrene (DBP), to promote DNA adduct formation in laboratory rats. D3T inhibited DNA adduction from 78 to 82 percent in liver, lung, and mammary tissues. Oltipraz was found to be equally effective in lung and liver tissue, but less effective in mammary tissue with only a 60 percent reduction. Other studies from this lab have shown significant reductions (up to 80 percent) cigarette smoke-induced adduct formation by oltipraz in rat lung and trachea. These results illustrate that the dithiolethiones afford strong protective effects against DBP-induced DNA damage in an animal model. The data, coupled with the low toxicity, broad specificity, and efficacy of D3T and oltipraz, support the use of these, as well as other similar compounds, in cancer chemopreventive studies in humans.

**A Potent and Selective Inhibitor of P450 1B1: Implications for Breast Cancer Treatment**

Cytochrome P450s are a class of enzymes, found primarily in the liver, responsible for metabolism of a wide variety of innate and xenobiotic chemicals. Cytochrome P450 1B1 is unique in that it is found mainly outside the liver in steroid-producing tissues, such as the ovary, testis, and adrenal gland, and in a variety of human tumors. P450 1B1 metabolically activates the hormone 17ß-estradiol (E2) to 4-hydroxy E2. This conversion has been suggested as a step in some forms of breast cancer development. The capacity of 2,4,3',5'-tetramethoxystilbene (TMS) to inhibit the activity of P450 1B1 was examined. TMS proved to be very effective in inhibiting the activity of the enzyme based on a number of different metabolic assays. It also was very selective for the 1B1 isozyme as compared to P450 1A1 and 1A2. Trapping agents, such as glutathione, N-acetylcysteine, or dithiothreitol, did not block the TMS-induced inhibition of P450 1B1. These results suggest that TMS is a potent and selective inhibitor of P450 1B1. Other studies have shown that TMS itself is not mutagenic. Therefore, it warrants further investigation as a possible preventive agent for breast cancer formation by E2 in humans. TMS is also a useful compound for characterizing the enzymatic properties of P450 1B1 because of its strong selectivity among P450 enzymes.

## *Ovarian Cancer*

**Cancer Risk Linked with Nitrate Levels in Drinking Water**

Nitrate contamination of drinking water has been documented in many areas of the United States. The source of the nitrate has been attributed to widespread use of commercial fertilizers, as well as animal and human wastes. In Iowa, the use of fertilizers, in both rural and urban settings, has resulted in 30 to 40 percent of the public water supply with nitrate concentrations greater than 5 milligrams per

liter (mg/L). The EPA limit for nitrate in drinking water is 10 mg/L, primarily to prevent methemoglobinemia in infants. However, other health risks of nitrate exposure have not been fully evaluated against this standard. Nitrates are converted to highly carcinogenic N-nitroso compounds in the digestive track. An epidemiologic study was conducted using the Iowa Women's Health Study cohort. Drinking water sources are but one of the many issues this study tracks and, with more than 40,000 women enrolled, it is an excellent resource for this type of investigation. Previous studies have found a positive association between nitrate exposure and bladder cancer. Unexpectedly, a positive association for ovarian cancer was also found. A negative association for uterine and rectal cancer was reported. All associations appear to be dose dependent. There were no associations for all other cancer types examined. Results from these studies correlate with earlier studies that show increased risk for bladder cancer as nitrate level in drinking water rises. The unexpected positive association with ovarian cancer, and the even more unexpected negative associations for uterine and rectal cancer, suggest that nitrate levels below the current EPA standard in municipal water supplies are of significant public health concern. Additional research is necessary to fully understand this issue and to make standards to protect public health.

## *Endometrial Cancer*

Endometrial cancer is the most frequently diagnosed gynecologic malignancy in the United States, but remains the least studied of the major cancers affecting women. Unlike cancers of the breast and ovary, endometrial cancer is limited primarily to women over the age of 50, and well-established risk factors suggest probable etiologic factors, most relating to estrogen. Researchers at NIEHS are using molecular genetic approaches to distinguish etiologic factors and animal models (including transgenic mice) to understand the role of physiologic and environmental factors in endometrial carcinogenesis. Endometrial cancer is being investigated in the Sister Study.

### The Tenth Report on Carcinogens

The Tenth Report on Carcinogens, prepared by the National Toxicology Program at NIEHS, lists steroidal estrogens as known human carcinogens for the first time. These are a group of related hormones that control sex and growth characteristics and are commonly used in estrogen replacement therapy to treat symptoms of menopause and in oral contraceptives. The report cites data from human epidemiology studies that show an association between estrogen replacement therapy and a consistent increase in the risk of endometrial cancer, and a less consistent increase in the risk of breast cancer. As for the other common use for steroidal estrogens, the report says the evidence suggests estrogen-containing oral contraceptives may be associated with an increased risk of breast cancer, but may protect against ovarian and endometrial cancers.

### Genotoxicity of Estrogen- and Antiestrogen-DNA Adducts

Tamoxifen, an antiestrogen used in the endocrine therapy and chemoprevention of breast cancer, induces liver cancer in rodents and is associated with endometrial cancer in women. Estrogens also are implicated in the etiology of endometrial and breast cancer. The carcinogenicity of these agents may be mediated through their genotoxic effects. The goals of this research are to establish a mechanism for the genotoxicities of tamoxifen and estrogen, and to find a safer alternative to tamoxifen. Using site-specifically modified oligodeoxynucleotides, the mutagenic and repair potential of estrogen and antiestrogen DNA adducts in mammalian cells will be determined. The three-dimensional structure of tamoxifen and estrogen adducts in DNA duplex also will be established, permitting us to understand the process of mutagenic and repair events which occur at lesion sites. Such modified oligodeoxynucleotides

also will be employed as standards in ultrasensitive 32P-postlabeling and HPLC/electrochemical detector analyses designed to quantify DNA adducts and oxidatively damaged lesions in the tissues of rodents and monkeys treated with these drugs. Taken together, this information can be used to predict genotoxicity. Translational studies have been designed to detect adducts in the endometrial DNA of patients undergoing treatment with tamoxifen or toremifene. These experiments will provide biomarkers for molecular epidemiological studies and explore the relationship between tamoxifen therapy and the development of endometrial cancer in women treated with this drug. This research should lead to a safer alternative for women undergoing breast cancer therapy and for chemoprevention.

**A Promising Anticancer Agent Derived from Vegetables**

3,3'-Diindolylmethane (DIM), a major *in vivo* product of indole-3-carbinol (I3C), is a promising anticancer agent derived from vegetables of the Brassica genus including broccoli, brussels sprouts, and cabbage. DIM has a potent cytostatic effect in cultured human Ishikawa endometrial cancer cells. A combination of northern blot and quantitative PCR analyses revealed that DIM induced the level of transforming growth factor alpha (TGF-α) transcripts by approximately fourfold within 24 hours of indole treatment. DIM also induced a fourfold increase in the activity of the estrogen response marker, alkaline phosphatase (AP). Co-treatment of cells with the estrogen receptor (ER) antagonist ICI, or with the inhibitor of PKA-mediated activation of the ER, H89, ablated the DIM induction of both TGF-α expression and AP activity. Furthermore, DIM increased the maximum stimulatory effect of estrogen on TGF-α expression. Co-treatment with the protein synthesis inhibitor, cycloheximide, abolished the inductive effects of DIM, indicating differences in the mechanistic requirements of DIM and estrogen. DIM treatment also stimulated levels of secreted TGF-α protein by less than tenfold. The ectopic addition of TGF-α inhibited the growth of Ishikawa cells, whereas incubation with a TGF-α antibody partially reversed the growth inhibitory effects of DIM. Taken together, these results extend previous findings of the ligand-independent estrogen receptor agonist activity of DIM, and uncover an essential role for the stimulation in TGF-α expression and the TGF-α-activated signal transduction pathway in the potent cytostatic effects of DIM in endometrial cancer cells.

## *Endometriosis*

**_In Utero_ PCB Exposure and Endometriosis**

Endometriosis is a relatively common disease (prevalence estimated at 5 to 10 percent) that can affect fertility, as well as other aspects of a woman's general health and well being. Animal and human data suggest that the critical exposure window for endocrine disruptors may be *in utero* because the developing fetus is extremely sensitive to endocrine hormones during reproductive development. A case-control study, nested in the National Collaborative Perinatal Project (NCPP) cohort, will extend followup through the reproductive years of the daughters of the pregnant women recruited in NCPP (1959 through 1966). During pregnancy, one or more blood samples were taken from the pregnant women and archived. The daughters will be traced and will complete a question on endometriosis and menstrual cycle characteristics. Cases are daughters with laparoscopy-confirmed endometriosis. Blood samples will be analyzed to reflect adult PCB levels that may confound the relationship between endometriosis and *in utero* PCB exposure, and will serve as a source of additional information on cumulative exposure.

**Serum TCDD Levels and Endometriosis**

Dioxin, a ubiquitous contaminant of industrial combustion processes including medical waste incineration, has been

implicated in the etiology of endometriosis in animals. A population-based, historical cohort study was conducted 20 years after the 1976 factory explosion in Seveso, Italy which resulted in the highest known population exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The relation of serum TCDD levels to fertility (time to conception and clinical infertility); ovarian function (number of ovarian follicles, presence of functional ovarian cysts, serum hormone levels); uterine health (uterine volume, endometrial thickness, and the occurrence/number of fibroids); the occurrence of benign breast disease, and the initiation/duration of lactation in the Seveso cohort are being investigated. Pre- or post-menarche exposure to TCDD is also being evaluated.

## *Uterine Fibroids*

Uterine fibroids are benign (noncancerous) tumors that are present in the muscular wall of the uterus in up to 70 percent of all women. They are the leading cause for hysterectomy in the United States. Even though they are benign, fibroids sometimes cause reproductive problems such as heavy bleeding, pelvic pressure, severe cramping, pain, infertility, and miscarriage. Little information is available about why fibroids develop or why they grow. Some evidence suggests that it may be related to a genetic problem. It is also possible that fibroids may grow in response to environmental factors, such as diet, smoking, exercise, or exposure to certain chemicals.

### NIEHS Uterine Fibroid Study

Despite the morbidity and high medical costs associated with fibroids, there has been little epidemiologic study of this condition. Indications are that African American women are at higher risk, but because this supposition is based on hysterectomy statistics, it is not known if this is a true difference or is due to differences in diagnosis and treatment. The NIEHS Uterine Fibroid Study, a cross-sectional epidemiological study of uterine leiomyomas in women ages 35 to 49, randomly selected from membership in a prepaid health plan in Washington, DC, was initiated to better define the cause of this health disparity. The prevalence of ultrasound-detected fibroids was surprisingly high, especially in the African American participants: 72 percent for African American and 50 percent for Caucasian women. Health disparity issues for uterine fibroids are reflected in the high prevalence statistics and in the fact that African American women have larger and more numerous tumors. African American women are also more likely to have surgical interventions, such as myomectomy and hysterectomy, compared to Caucasian or Hispanic women.

### Uterine Fibroid Growth Study

The Fibroid Growth Study is designed to investigate why some fibroids grow to become health problems while others do not. Funding is provided jointly by NIEHS and the National Center for Research on Minority Health and Health Disparities. Scientific direction and oversight are provided by NIEHS. The University of North Carolina Hospitals, the General Clinical Research Center, and the Integrated Laboratory Systems, Inc. are collaborators in this research. The study has four specific aims. First, fibroid growth will be evaluated over time by magnetic resonance imaging. Second, the relationship between fibroid growth and symptoms or outcomes (i.e., surgery/no surgery) will be determined. Third, identify markers that may be related to growth. Lastly, examine the hormone and lifestyle factors that may be related to fibroid growth. It is hoped that the findings from this study will help develop strategies to prevent fibroids in women at high risk for problems and develop new therapies that reduce the need for radical surgical procedures like hysterectomy.

### Environmental Estrogens and Fibroids – A Rat Model

The environmental components of this disease, such as exposures to estrogens, phthalates, and solvents, are currently under study using exposure assessment

methods in women with fibroids coupled with mechanistic studies in cell culture systems and animal models. One hypothesis, derived from mechanistic studies, is that uterine smooth muscle tumor cells closely resemble normal uterine smooth muscle cells during pregnancy, but have escaped controls that cause these cells to regress or die. Specifically, the pregnancy-like phenotype allows these cells to proliferate in response to estrogens, estrogen-like compounds, and other environmental cues. However, the neoplastic cells fail to regress or die as do normal smooth muscle cells at the time of parturition (delivery) when supraphysiological levels of prostaglandins, oxytocin, and other parturition-related hormones trigger the contractile response of the uterus during labor and remodeling of the uterus after delivery. Studies conducted using the Eker rat as an animal model for uterine leiomyoma support the research hypothesis. For example, treatment of young rats with estrogenic compounds, like diethylstilbestrol, accelerates the growth of the leiomyoma, while the tumor incidence in aged rats is significantly reduced with multiple pregnancies and deliveries. Studies investigating pregnancy and parturition as risk factors for fibroids found that full-term pregnancies, culminating in parturition, significantly decrease the risk for large leiomyomas in women.

**Environmental Estrogens and Fibroids – *In Vitro* Human and Mouse Comparison**

The Comparative Pathobiology Group has focused its research on defining the pathogenesis/carcinogenesis of disorders affecting the reproductive tract of humans and rodents, and assessing the role of environmental and endogenous factors in the induction of these disorders. Data show that transforming growth factor alpha (TGF-α) is expressed exclusively in malignant uterine smooth muscle cell tumors (leiomyosarcomas) of mice. However, in benign uterine smooth muscle cell tumors (leiomyomas) of mice and women this growth factor is not present. In mice, a positive correlation between TGF-α staining and immunoexpression of epidermal growth factor receptors and increased cell proliferation as measured by the expression of proliferating cell nuclear antigen (PCNA) in the malignant uterine leiomyosarcomas was observed. In women, we have found that IGF-I is overexpressed in unterine leiomyomas compared to normal myometrium during the proliferative phase of the menstrual cycle, and it appears that the IGF-I receptor signaling pathway is important in uterine leiomyoma growth. Studies to assess the role of Bcl-2 and Bax in modulating cell survival and death in human uterine leiomyomas have been conducted. The results show that both positive and negative regulatory proteins of programmed cell death (apoptosis) are present in human uterine leiomyomas and that altered apoptosis does not appear to play a significant role in the development of these tumors through prolonged cell survival. Human uterine leiomyoma and normal smooth muscle cell lines have been successfully immortalized by the insertion of the human telomerase gene. *In vitro* model systems for studying uterine leiomyomas are limited in that human derived leiomyoma cells grow poorly in culture and begin to senesce early. This obstacle has been overcome with the creation of an hTERT uterine leiomyoma cell line. Uterine leiomyoma tumorigenesis can be studied in a prospective manner using these immortalized cell lines.

### *Osteoporosis*

Osteoporosis is a debilitating condition characterized by fragility of the bone. It sometimes occurs in men but is generally found in postmenopausal women. Cadmium, lead and, possibly, other heavy metals found in the environment may be significant factors in developing this disease. NIEHS-supported research has shown that cadmium exposure results in increased loss of bone mineral in mice whose ovaries have been removed. The bone loss appears to occur from a direct action of cadmium on bone, not through an indirect effect on kidney reabsorption of calcium. Thus, cadmium exposure may be a significant factor contributing to

osteoporosis in older women. Continued efforts to study the basic physiology of bone metabolism, as well as the mechanisms of heavy metal toxicity in bone tissue, should provide insight into the disease mechanisms of osteoporosis. Other NIEHS-supported studies are investigating the effects of environmental lead exposures and allelic variants of the vitamin D receptor (VDR) gene on the development of osteoporosis in middle-aged women, and the health consequences of lead released into the blood stream and soft tissue due to osteoporosis. One health effect that has been identified is an increased risk for hypertension. Some of these studies are using lead as a marker to develop hormonal therapies to prevent bone reabsorption.

### *Hormonally Active Agents*

NIEHS is supporting a number of studies investigating the potential health effects of hormonally active agents (HAAs) in the environment. HAAs are a diverse group of compounds that include plasticizers, polycholorinated biphenyls, many pesticides, and dioxins. These compounds are so pervasive that studies have shown them to appear in tissues in 95 percent of the U.S. population. The concern is that, when exposure occurs very early in life, these compounds have the potential to disrupt critical endocrine pathways with potential future effects on reproductive, neurological, and immunological systems. This possibility has been verified in NIEHS rodent studies showing that early exposure to some pesticides resulted in reproductive, neurological, and immunological deficits later in life. These and other studies on the effects of early exposure to HAAs continue. Additionally, NIEHS is collaborating with the Centers for Disease Control and Prevention to assess what the actual, real-world exposures to HAAs are in a representative U.S. population. In a preliminary report, the distribution of a particular class of HAAs, the phthalate plasticizers, was assessed. It was found that although most scientific and regulatory attention has focused on two phthalates – di (2-ethylhexyl) phthalate and di-isononyl phthalate – actual human exposures indicate that three others, less common – phthalates (diethyl phthalate, dibutyl phthalate, and benzyl butyl phthalate) – account for the greater exposures in the United States. Additionally, women of reproductive age (20 to 40 years) were found to have significantly higher levels of monobutyl phthalate, a reproductive and developmental toxicant in rodents, than other age and gender groups. Results of this exposure assessment study will help guide us in selecting compounds for future study.

### *Dietary Soy and Cancer*

It is well known that mice genetically engineered to develop breast cancer will develop tumors earlier and in larger numbers when fed soy-based diets. This is a potential public health concern because soybeans are a major protein source in vegetarian diets, and many women consume soy products to reduce hot flashes and other symptoms of menopause. Increasingly, infants are also consuming large amounts of soy products in the form of soy-based infant formula and consumer products especially marketed to appeal to children. Soy has a number of components that can either mimic or compete with the hormone, estrogen. Given the biological activity of plant estrogens (phytoestrogens), the potential exists for adverse, as well as beneficial, health effects. NIEHS-supported researchers have recently identified other areas of concern in consuming large amounts of soy. They discovered that phytoestrogens in the diet increased the incidence of vulvar carcinoma in mice. Mice were given one of three natural ingredient diets or two purified diets containing predetermined levels of the predominant phytoestrogens found in soy, daidzein, and genistein. The two purified diets had similar caloric values and differed only in their protein source – derived from either soy protein or milk protein (casein). At 3 months, mice on the soybean-supplemented diet had a significantly increased incidence of vulvar carcinomas compared to mice fed a milk-derived protein source. A similar correlation was found between tumor incidence and phytoestrogen levels in the three natural

ingredient diets. In total, there was a significant correlation between the total daidzein and genistein levels in the five test diets and the incidence of vulvar carcinomas in mice.

### *Herbal Medicine*

Botanical, or herbal, formulations continue to be a major focus of NIEHS' interest in the dietary arena. One-third of the adults in the U.S. population use herbal medicines or herbal products, the majority of the users are women. The herbal industry has grown substantially over the last 10 years, and it is now a multi-billion dollar industry. Of the nearly 2,000 herbal products in use, only a few have been adequately tested for efficacy and toxicology. Since the FDA is not permitted, by law, to require pre-market testing by producers, herbal medicines are poorly standardized, and consumers are not aware of potential adverse effects, particularly those effects that might arise following long-term use. Of particular concern are developmental and reproductive effects since herbal products are used frequently by women of childbearing age. Other concerns include immunological responses, cardiovascular diseases, cancer, and interactions among the many constituents of herbal medicines or with prescribed pharmaceuticals.

### *Pregnancy*

#### Changes in Insulin-like Growth Factor-I, Osteocalcin, and Bone Turnover in Pregnant Women

Preeclampsia, a complex condition involving high blood pressure, protein in the urine, and swelling, is a common and serious problem, affecting 5 to 10 percent of all pregnant women. High blood pressure during pregnancy is a very serious complication. It puts both the mother and the fetus at risk for a number of problems. Clinical trials have suggested that calcium supplementation during pregnancy reduces the incidence of preeclampsia. Release of calcium from a pregnant woman's bones occurs during fetal development. Calcium release is a complex activity that involves bone formation and breakdown cells, growth factors, and hormones. Previous studies have shown an association between insulin-like growth factor I (IGF-I) and bone metabolism. Healthy postmenopausal women treated with IGF-I showed increased bone formation and breakdown activity as measured by biochemical markers. Osteocalcin is a protein that makes up 10 to 20 percent of the noncollagenous protein found in bone tissue. Serum osteocalcin is a marker for bone turnover. Osteocalcin is produced by bone forming cells known as osteoblasts. These investigators hypothesized that IGF-I, osteocalcin, and bone loss would be different among pregnant women with preeclampsia compared with women with normal blood pressure. In a study of 962 healthy pregnant women, 64 went on to develop preeclampsia. In women with preeclampsia, IGF-I levels were 74 percent greater in the 3rd trimester than the 1st, while normotensive women experienced only a 43 percent increase. Osteocalcin levels in preeclamptic women were twelve times higher than normotensive during the 1st trimester. Also, women with preeclamsia had little change throughout pregnancy in their osteocalcin levels, while normotensive women had a 63 percent decline in osteocalcin. Women with preeclampsia also had greater bone loss; however, this finding was not statistically significant. This study indicates that there are different relationships between IGF-I and osteocalcin concentrations during pregnancy in women who experience preeclampsia, compared with women who do not develop the condition. The findings suggest that in the 1st trimester, women who will later develop preeclampsia, there are metabolic changes associated with increasing demand for calcium mobilization as demonstrated by greater IGF-I and osteocalcin levels and loss of bone stores. The study also suggests that high levels of osteocalcin in the 1st trimester may be an early sign of the development of preeclampsia. Further studies are needed to identify the signals that are mediating the need for calcium.

#### Birth Cohorts

Studies aimed at determining the adverse effects of low-dose exposures during fetal

development are significantly complicated by the fact that many of these effects do not appear until much later in life. The best way to detect these prenatal effects in humans is through long-term epidemiologic studies that follow a child through the mother's pregnancy and into the later year's of a child's life. NIEHS is pursuing such a collaboration with the Norwegian government, which has an excellent infrastructure for this type of study, and is investigating ways to establish such a registry in this country. The Norwegian government established a registry of 100,000 pregnant women and their children in 2000. Researchers will conduct a lifetime health assessment of individuals in this registry. NIEHS plans to support the collection and storage of biological samples (e.g., blood and urine) during the mothers' pregnancy. These samples could be used later to measure maternal and fetal exposure to environmental agents such as pesticides, plasticizers, and heavy metals. Questionnaires will be administered periodically throughout the mothers' pregnancy and the babies' childhood. Study participants will also be followed through the various Norwegian national medical registries. Important health outcomes include birth defects, preterm delivery, preeclampsia, childhood development, diseases of childhood, and diseases of adulthood.

## *Neurologic Disorders*

### Heavy Metals and Neurologic Dysfunction

NIEHS has a long history in supporting research on the environmental contaminant, mercury, and its toxic effects on the nervous systems of young children, adults, and the elderly. NIEHS-supported research ranges from mechanistic studies to epidemiological studies. The knowledge gained from such studies has, and will continue, to improve our understanding of the relationship between mercury exposure and neurotoxicity, including neurodevelopmental, neurobehavioral, and neurocognitive effects, and be applicable to prevention and treatment of neurological diseases, such as autism, Parkinson's disease, and Alzheimers disease. For example, NIEHS has supported seminal studies to define human health risks associated with prenatal and early postnatal exposure to methyl mercury in fish. Subtle psychological and behavioral effects have been evaluated in young children over time. Results from these studies have important implications for assessing health risks in the U.S. population due to consumption of methyl mercury in fish.

### Taxol Induces Programmed Cell Death in Brain Neurons

Taxol is used as an anticancer drug, and its administration causes peripheral neuropathy in humans and in animal models. It has been suggested that taxol may be useful for the treatment of Alzheimers disease and multiple sclerosis. However, the toxicity of taxol for central nervous system neurons has never been determined. A NIEHS-supported study recently demonstrated that taxol induced programmed cell death and may be a useful model for studying neurodegradation characteristic of Alzheimers and Parkinson's diseases.

## *Hormonal and Reproductive Risk Factors for Development of Systemic Lupus Erythematosus*

Estrogen and prolactin may accelerate the progression of murine systemic lupus erythematosus (SLE). In humans, 85 percent of lupus patients are women, which also suggests the importance of hormonal factors in disease pathogenesis. The purpose of this study was to examine hormonal and reproductive risk factors for lupus among women participating in the Carolina Lupus Study. Breast feeding was associated with a decreased risk of developing lupus, with a statistically significant trend for number of babies breast fed and total weeks of breast feeding. There were no associations with number of pregnancies or live births. Natural menopause occurred earlier in women with subsequent development of lupus, compared with controls. There was little association between SLE and current use or duration of use of hormone replacement therapy or oral contraceptives, and no association with previous use of fertility drugs. Little evidence

was found indicating that estrogen- or prolactin-related exposures are associated with an increased risk of lupus. The reduced risk observed among women who had breast fed one or more babies should be examined in other studies. Early natural menopause, rather than decreasing risk of SLE because of reduced estrogen exposure, may be a marker of susceptibility to development of lupus.

### *The Environmental Genome Project*

NIEHS coined the phrase "environmental genomics" with the announcement of the Environmental Genome Project (EGP) in 1997. The objective of EGP is to investigate how genetic variation affects response to environmental exposures. It represents the second generation of the Human Genome Project. The project consists of three interrelated phases: 1) identifying genetic variation, 2) correlating variation with disease, and 3) determining how the variation alters function of critical metabolic pathways. The overall objective is to create animal models that mirror specific polymorphic variants of human environmental response genes found in the general population. Prevention, diagnosis, and treatment will become more individualized as differences in response to environmental or pharmaceutical interventions can be developed with specific genotypes in mind. However, one of the biggest potential pay-offs will be the ability of environmental regulatory agencies to develop more rational policies, since they will have the information necessary to devise rules that better protect sensitive individuals. Presently, genetic variation (e.g., gender differences) is not explicitly considered in estimating dose-response relationships, nor in the promulgation of exposure limits. Risk assessors now craft rules using arbitrary safety factors to protect sensitive individuals. They set the permissible exposure level to a chemical, for instance, at a tenth of that deemed acceptable for the general population. Data on the prevalence and consequence of susceptibility genes will take this sort of guess work out of risk assessment. Use of this information to reduce risk can occur by several mechanisms, including understanding gender differences, eliminating or reducing exposure, pharmacological intervention, and gene therapy.

#### Reducing Side Effects of Drugs, Drug Metabolism Variations Identified

The Environmental Genome Project was established to identify gene variations in the human genome that make some people more resistant or susceptible to diseases induced by environmental agents. Scientists have known that people express differing levels of a family of enzymes known as cytochrome P450s based on their genetic makeup. The enzymes are responsible for metabolism of a wide variety of compounds, both those made by the body and those introduced from outside the body. Approximately 55 different genes have been identified that code for the various cytochrome P450s. This large project is beginning to provide important insight into how groups within the U.S. population can differ in their ability to handle drugs and toxicants. One group of NIEHS-supported researchers identified variations in the gene for cytochrome P450-3A5 (CYP3A5). Members of the CYP3A family make up almost half of the total cytochromes found in the liver and are responsible for the metabolism of estrogens and many drugs, including HIV protease inhibitors, calcium channel blockers, cholesterol reducing agents, cancer chemotherapeutics, and transplant rejection drugs. The results indicate that the substitution of a single nucleotide, also known as a single nucleotide polymorphism, in the structure of the CYP3A5 gene disrupts the activity of the enzyme transcribed from that gene. Further genetic analyses demonstrated that only 30 percent of Caucasians and more than 50 percent of African Americans and Asians have the normal gene and produce normal levels of CYP3A5. These differences in expression are much larger than previously believed. Based on these findings, one may be able to use genetic screening to predict susceptibility to specific environmental agents.

## Initiatives

- **World Trade Center Attacks – Environmental Risks**

  New York-area NIEHS centers, in collaboration with other federal health agencies, will be monitoring area women who were pregnant at the time of the attack. A concern is that the exposures and stress experienced by these women might have an effect on their unborn child. Each child's development will be tracked for a number of years to determine if any health, learning, or behavioral problems are associated with their exposures while in the womb.

*Request for Applications (RFAs)*

- **NIEHS' Parkinson's Disease Initiative**

  Six new FY 2001 awards were made from two initiatives respectively aimed at mitochondrial function/neurodegeneration and xenobiotics, cell death, and injury mechanisms. NIEHS organized a multidisciplinary FY 2001 molecular epidemiology workshop that included pesticide chemists and toxicologists. This meeting extended the FY 2000 epidemiology meeting vision by providing new insights into designs for retrospective assessments of environmental exposures. NIEHS, the National Institute of Neurological Disorders and Stroke, the National Institute of Deafness and Other Communication Disorders, and the National Institute of Mental Health, with the counsel of several PD advocacy groups, developed a unique NIH 'fast-track', exploratory/development grant initiative to stimulate PD research. At least three new NIEHS awards will result from this initiative. A national network of NIEHS Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) will be created in FY 2002. Its collaborative consortium work will expand knowledge on the role of gene-environment interactions in PD. It will also seek to accelerate the translation of findings into the public health arena by providing the science-based foundation for intervention and prevention efforts to avoid or ameliorate the devastating effects of PD. NIEHS plans a proactive pursuit of its PD research agenda, using both innovative and targeted funding initiatives, to further expand support for research of high promise for advancing our knowledge of the etiology and pathophysiology of PD. (*Note*: Although PD is more prevalent in men, it occurs mostly in later life, thus affecting a large number of women since women constitute a majority of the elderly.) (RFA-ES-02-003)

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

  The Office of Research on Women's Health and cosponsors seek to promote interdisciplinary research in sex and gender factors through Specialized Centers of Research (SCOR). Each SCOR will promote interdisciplinary collaborations and develop a research agenda bridging basic and clinical research on sex and gender factors underlying a priority health issue. The SCOR program will complement other federally supported programs addressing women's health issues. (RFA-OD-02-002)

- **Toxicogenomics Research Consortium**

  The mission of NIEHS is to reduce the burden of environmentally associated diseases and dysfunctions by defining how environmental agents affect our health; individuals differ in their susceptibility to these agents; and how these susceptibilities change over time. Recent advances in gene expression analysis, using microarray technology, have made the assessment of effects of environmental agents on global gene expression possible. The emerging potential of this pioneering technology has clearly shown a capability for revolutionizing the way experiments are conducted and interpreted in the frontier areas of environmental health sciences research. Advancing environmental health sciences research is of enormous

importance to NIEHS and, thus, NIEHS has initiated a national program to develop and accelerate research, using microarray technology, to assess global gene expression profiles and characteristics associated with physiological mechanisms linking environmental agent exposures to environmental diseases and dysfunctions. The overall NIEHS program has as its goal a coordinated effort to define how the entire genetic complement of an organism responds to environmental agents, including chemicals, physical agents, and physiological stresses. (ES-01-002)

- **Breast Cancer and the Environment Research Centers**

  NIEHS and NCI invite applications to create a network of research centers in which multidisciplinary teams of scientists, clinicians, and breast cancer advocates work collaboratively on a unique set of scientific questions that focus on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. The research conducted will take a unique developmental approach to integrate time, susceptibility, and exposure in order to more fully appreciate the changes that occur in the mammary gland early in life that may predispose the breast to cancer. These projects will help to define specific periods of susceptibility of the breast when environmental stressors may change the molecular architecture of the gland, conferring increased risk of future cancer. The purpose of implementing a network of cooperative breast cancer centers is twofold. The first goal is to integrate scientific information on histologic, pathologic, cellular, and sub-cellular changes that occur in normal mammary gland tissue across the life span and compare this to exposure-induced changes. Discovering changes in gene and protein expression due to agents to which young girls and women may be exposed during their lifetime will be a primary goal. Experiments will be conducted cooperatively, using animal models that characterize pathways related to breast and endocrine system development during early life, puberty, pregnancy, and other time points, which may be affected by exposures to environmental stressors occurring at different windows of vulnerability. When clinical specimens are available from women at risk, they will be compared to animal models. Data from these experiments will be made available to the scientific community in order to stimulate further investigations of mechanisms of interest. A second goal is to conduct a focused and coordinated epidemiologic study of determinants of puberty in girls. Attention will be paid to understanding the shift toward earlier puberty among adolescent girls, the identification of environmental exposures in young girls, and the interplay between genetic polymorphisms and environmental exposures that may put them at risk of future breast cancer. The overall goal of this network of centers is to integrate the basic biological, toxicologic, and epidemiologic data on the development and life span of the mammary gland in a way that public health messages can be designed to educate young girls and women who are at high risk of breast cancer on the role of specific environmental stressors in breast cancer development and how to reduce exposure to those agents. This information will be useful in developing clinical and public health programs that target breast cancer prevention in young girls and women. This research program complements other programs on breast cancer and mammary gland development being conducted at the National Institutes of Health. The unique focus of this program extends that research by comparing the effects of environmental stressors, including environmental pollutants, nutritional and lifestyle factors, and other exposures on normal mammary gland development in order to more fully consider the multiple causes of breast cancer. (ES-03-001)

- **Leiomyomata Uteri: Basic Science and Translational Research**

  The National Institute of Child Health and Human Development, NIEHS, and the NIH Office of Research on Women's Health invite new and experienced investigators to submit research grant applications in basic science, environmental health science, and translational research with the goal of translating advances in our understanding of the molecular basis of leiomyomata uteri (uterine fibroids) into new therapies for prevention, treatment, and cure of this common benign gynecologic disorder. (HD-03-005)

- **Centers for Population Health and Health Disparities**

  The purpose of Centers for Population Health and Health Disparities (CPHHD) is to support interdisciplinary research leading to an understanding and reduction of health disparities in domestic populations. Applicants are invited to propose multi-level, integrated research projects that will elucidate the complex interactions of the social and physical environment, mediating behavioral factors, and biologic pathways which determine health and disease. CPHHD are expected to create an environment conducive to interdisciplinary and reciprocally beneficial collaborations among biomedical scientists, social scientists, and affected communities with the common goal of improving population health and reducing health disparities. For the purposes of this proposed Centers Program, the physical environment includes the natural environment and built structures, as well as physical, chemical, and biological agents (e.g., radiation, pesticides, infectious agents, food supply, pharmacological agents) to which individuals are exposed. The social environment includes individual-, institutional-, and community-level characteristics (e.g., socioeconomic status (SES), education, coping resources and support systems, residential factors, institutional and political forces, racial discrimination, familial and cultural factors). (ES-02-009)

- **Mechanisms of Oxidative Stress and Dietary Modulation**

  The purpose of this RFA is to stimulate and support investigator-initiated research that will provide data to enhance our understanding of the role of dietary modulators and nutritional factors in the molecular control of reactive oxygen species in initiation and progression of environmentally induced disease processes. Recent evidence has shown the importance of nutrition in delaying the aging process and in protecting against many degenerative and chronic diseases. Our growth in knowledge of reactive oxygen species, oxidative damage, and the role that nutritional antioxidants play in protection from this damage suggests that factors in our diet can be effective in preventing or retarding the disease process. In response to these findings, the National Institute of Environmental Health Sciences and the National Institute of Diabetes and Digestive and Kidney Diseases seek to stimulate research efforts aimed at enhancing our understanding of the role of nutrition and diet in modifying, positively or negatively, environmentally induced oxidative damage in the progression of disease. Results of such investigations should clarify the cellular and molecular mechanisms by which nutritional agents alter oxidative balance and thereby prevent disease. (RFA-ES-01-004)

*Project Announcements (PAs)*

- **Social and Cultural Dimensions of Health**

  Research to explore the implications of different conceptualizations and measurements of social stratification systems and processes, such as socioeconomic status (SES) and social class, age, gender, and race/ethnicity for understanding health at the individual and higher levels of

aggregation (e.g., community). Research to improve the monitoring and understanding of inequalities in health and disease among diverse groups, and the implications for monitoring of strategies used to measure basic constructs such as SES and social class, age, gender, race, and ethnicity. (PA-02-043)

- **The Role of Gene-Environmental Interactions Underlying the Health Disparity of Premature Birth**

  The National Institute of Child Health and Human Development, NIEHS, and the National Institute of Nursing Research are seeking research grant applications on the role of gene-environmental interactions underlying the health disparity of premature birth in the United States. This solicitation specifically addresses the need to better understand how adverse societal, behavioral, and environmental conditions alter gene expression and interact with diverse genetic backgrounds to increase a woman's susceptibility for premature birth in high-risk racial and ethnic groups. The solicitation encourages multidisciplinary approaches to clarify the potential role of genetics in the increased risk of premature birth in these disadvantaged populations. (PA-02-102)

*Workshops and Conferences*

- **Brainstorming Session on Breast Cancer and the Environment April 20, 2002**

  The purpose of this workshop was to gather input for a proposed NIEHS initiative on breast cancer. Congressional sources recently urged NIEHS to create multidisciplinary research centers to pursue research on mammary gland biology, carcinogenesis, and environmental influences on breast cancer. The workshop included a wide range of participants from the scientific research community and the breast cancer advocacy community. The discussion was divided into five sessions which focused on mammary gland biology and toxicogenomics, windows of susceptibility, epidemiology, model systems, and consumer involvement and advocacy.

- **Polycystic Ovary Syndrome: Basic Biology and Clinical Intervention September 17-20, 2000**

  This meeting was designed to bring together a multidisciplinary group of scientists from cellular and molecular biologists, endocrinologists, toxicologists, epidemiologists, and clinicians in order to disseminate the most up-to-date research on the etiology, mechanism, and treatment of PCOS. It was anticipated that this interdisciplinary approach would lead to fruitful discussions that would identify data gaps and needs, future research directions, and new approaches and technologies that will lead to a better understanding of this syndrome and improved intervention and prevention strategies.

- **Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk September 23-25, 2002**

  The purpose of this conference was to bring together a multidisciplinary group of research scientists (epidemiologists, clinicians, basic biologists, developmental biologists, developmental toxicologists, molecular biologists, and endocrinologists) in a joint forum to discuss the current state of emerging multidisciplinary knowledge relevant to the role of thyroid hormones in brain development and the effects of exposures to environmental agents on this system. Focus was on maternal thyroid status and neurological function of the offspring, basic studies on brain development, the role of thyroid hormones in brain development, the effects of environmental agents on thyroid hormone action during brain development, and future directions for research with emphasis on the use of genomics, genetically modified animals and imaging, and translation of basic

and toxicological research into public health benefit.

- **Gender Differences in Reproductive Biology and Toxicology Symposium November 9-11, 2000**

  This symposium was held at the Center for Toxicology, University of Arizona, Tucson, AZ. Specific aims of the symposium included: 1) to bring together a multidisciplinary group of biologists and toxicologists interested in male and female reproduction in order to facilitate their direct interactions and communications; 2) to discover and discuss gender similarities and differences in reproductive biology and toxicology at the cellular and molecular level; 3) to demonstrate how state-of-the-art technologies and animal models can be used to advance the understanding of gender differences in reproductive toxicology; and 4) to identify questions, gaps, and future directions the field should pursue. The symposium proposed to provide a unique and timely opportunity for a specialized interdisciplinary group of researchers to develop a better understanding of gender-specific aspects of responses to reproductive toxicants.

*Health Disparities*

- **Uterine Fibroid Growth Study**

  The Fibroid Growth Study is designed to investigate why some fibroids grow to become health problems while others do not. Funding is provided jointly by NIEHS and the National Center for Research on Minority Health and Health Disparities.

- **Work and Health Disparities among Rural Women**

  For more than 20 years, women in northeastern North Carolina have been organizing to address social, economic, and health issues arising from industrial work in an area with few employment opportunities. Although the impacts of racial discrimination and fast-paced, assembly-line production have been described by government inspectors, journalists, and women advocating on their own behalf, research has not quantified the occurrence of specific health outcomes or risk factors for adverse outcomes. Through a collaborative project linking investigators at Duke University, the University of North Carolina, and the Center for Women's Economic Alternatives, we propose to evaluate occupational roots of health disparities among women in a five-county region of northeastern North Carolina.

- **Social and Physical Environments and Health Disparities Project**

  Social inequalities have been linked to health disparities at the individual and population levels and are associated with income inequalities, not simply with absolute income. There is clear evidence of a strong association between socioeconomic status (SES), economic development, and cardiovascular disease (CVD), the largest contributor to all-cause mortality in the United States. The pathways linking these social and economic inequalities to health are not yet well understood. The Social and Physical Environments and Health Disparities Project is a community-based participatory research partnership between the University of Michigan School of Public Health, community-based organizations, and health care institutions in Detroit. The specific aims of the proposed project are to: 1) estimate the relationship between racial and ethnic group status, SES, and mental and physical health in a stratified, multistage probability sample (n=1000) of an adult population in Detroit, MI; and estimate the relationship between racial or ethnic group status, SES, and specific biomarkers for cardiovascular risk factors in a subset of this sample (n=200); 2) examine the relationships between neighborhood sociodemographic context (e.g., concentrated poverty), selected aspects of the physical environment (exposure to PM10 and PM2.5), and selected aspects of the social environment

(e.g., acute life events); 3) investigate independent and cumulative effects of exposure to psychosocial stressors on biological risk markers for CVD (e.g, total serum cholesterol, LDL); 4) document the strength of the association between airborne particulate matter and selected proximate risk and protective factors (e.g., elevated plasma homocysteine, F2 isoprostane) for CVD; 5) investigate potential mediating and moderating effects of behavioral and psychosocial responses to stressors (e.g., smoking), and micronutrient intake (e.g., intake of folic acid, B-6, B-12) on the relationships between selected aspects of the physical and social environments and biological markers for CVD, and self-reported CVD and depression; and 6) create a Community Outreach and Education Program to disseminate and translate knowledge gained from the study to inform new and established intervention and policy efforts in Detroit.

- **Systemic Lupus Erythematosus: The Carolina Lupus Study**

  Systemic lupus erythematosus (SLE) is an autoimmune disease that can cause severe damage to the kidneys, joints, and other tissues. Ninety percent of SLE patients are women, and compared to whites, African Americans are three to four times more likely to develop the disease. Mortality is also higher among black, compared to white, SLE patients. Reasons for the African American excess risk are not known. NIEHS and the National Center on Minority Health and Health Disparities have joined to create the Carolina Lupus Study, a population-based, case-control study in eastern North Carolina and South Carolina designed to examine hormonal and environmental influences on the etiology of SLE. This study offers the opportunity to examine hormonal, occupational, and environmental risk factors in a previously understudied population. These efforts may help illuminate etiologic pathways and develop prevention strategies for susceptible populations. The study participants are 90 percent women, and 55 percent African American. Environmental exposures under study include silica dust, solvents, heavy metals, and pesticides. The influence of genetic susceptibility to disease risk will also be assessed.

- **Uterine Fibroid Study**

  Uterine fibroids are the leading indication for hysterectomy among premenopausal women in the United States. Based on hysterectomy statistics, African American women appear to be at three- to ninefold higher risk than white women, although it is not known if this disparity reflects a true difference in incidence or prevalence of uterine fibroids or, instead, is due to differences in diagnosis and treatment. To better define the cause of this health disparity, NIEHS and ORMH have initiated a study of uterine fibroids among 35- to 49-year-old members of a large prepaid health plan in Washington, DC. After 1 year of data collection, 285 black and 123 white women have been enrolled. Data from ultrasound examinations have been completed for 226 black women and 167 white women. In this group, 73 percent of black women had uterine fibroids, compared to 48 percent of white women. These data indicate that the differences in hysterectomy rates are not just a result of diagnostic and treatment bias. There are real differences in uterine fibroid risk between blacks and whites and NIEHS hopes to help define some of the environmental triggers for uterine fibroid development.

- **Breast Cancer**

  African American women appear to be at greater risk of developing more aggressive forms of breast cancer, and are more likely to die from this disease than are white breast cancer victims. The reasons will most likely prove to be multifactorial, but environmental exposures might play a role. A recently published study, supported by NIEHS, showed that

women with higher blood levels of the organochlorine pesticide, dieldrin, had twice the risk of later breast cancer development than did women with low levels of this pesticide. Since many people of color engage in farm work, they and their families would be expected to have higher exposures to endocrine-disrupting compounds, such as dieldrin and, consequently, would be at higher risk for breast cancer development. NIEHS, in partnership with NCI, has a long-term Agricultural Health Study of farmers and pesticide applicators, as well as their spouses and children, to determine the health consequences of exposures typical in rural environments. NIEHS was particularly instrumental in ensuring that a large part of this cohort included African American families.

## NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

The mission of the National Institute of General Medical Sciences (NIGMS) is to support research and research training in the areas of basic biomedical science. NIGMS supports research on cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus. The majority of the studies supported by NIGMS do not target any particular disease or condition but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, and genetics. In addition, NIGMS supports research in drug discovery, synthetic chemistry, and pharmacology, including studies in proteomics, glycomics, pharmacogenetics, and pharmacogenomics. These studies often have broad applicability to a wide variety of diseases or organ systems, including those specific to or which disproportionately effect women.

Knowledge of normal cell structure and function is necessary in order to understand the disease process. For example, major factors in the etiology of ovarian or breast cancer involve activation of cells by hormones, in particular estrogen, and by growth factors, such as epidermal growth factor, fibroblast growth factor, and insulin-like growth factor. Similarly, an understanding of invasion and metastasis of tumor cells relies on knowledge of normal cell adhesion and cell motility.

Natural plant and animal products are a major source of bioactive agents, including those with anti-tumor activity. The clinical exploitation of such agents depends on the ability to chemically purify and synthesize them. A prime example of this is taxol, derived from the bark of the yew tree. While very promising in the treatment of ovarian and breast cancer, only limited natural supplies were available. Improved approaches for isolation, purification, and synthesis have enabled widespread clinical trials of taxol and synthetic studies of 'second generation' taxoids hold promise for improved efficacy with fewer side effects. Many other natural products are targets for synthesis and clinical testing.

Inter-individual drug responses depend on genetic variation, as well as modifying factors, such as environment, diet, age, and gender. NIGMS grants under program announcement PA-99-016, Mechanisms Underlying Individual Variations in Drug Response, supports investigations of critical candidate proteins and genes that may contribute to pharmacogenetic/pharmacogenomic variation in drug metabolism and clearance. In addition, a request for applications, Pharmacogenetic Research Network and Data Base (RFA-GM-99-004), builds on this by supporting the formation of a coordinated Pharmacogenetic Research Network and Database. NIGMS participation in programs in tissue engineering (PA-99-024), nanoscience and nanotechnology (PAR-03-045), and bioengineering (PAR-02-010) hold promise for women's health. NIGMS also provides support for interdisciplinary research training at the pre- and postdoctoral levels that supplies the personnel for biomedical research.

### Women's Health-related Research

Reduction of morbidity and mortality associated with disease relies on prevention, early diagnosis, and effective treatment of the disease. The use of these approaches

requires a basic understanding of the etiology of the disease, the predisposing factors, the cellular processes involved, and the mechanisms that promote disease progression. The National Institute of General Medical Sciences supports a broad array of fundamental research in cellular and molecular biology, chemistry, biochemistry, pharmacology, molecular biophysics, and genetics that impacts on virtually all these areas. In addition, NIGMS supports interdisciplinary research training at the predoctoral and postdoctoral levels that provides the personnel for biomedical research. NIGMS's RFA in pharmacogenetics, which addresses interindividual drug responses, depends on genetic variation, as well as modifying factors, such as environment, diet, age, and gender, can be found on the NIGMS homepage.

To illustrate the importance of basic research to women's health, an overview of the major areas of NIGMS-supported research, as they pertain to the prevention, diagnosis, and treatment of breast cancer, is given below.

Efforts on the part of NIGMS in pharmacogenetics addressing interindividual drug responses as they are influenced by genetic variation, as well as modifying factors, such as environment, diet, age, and gender, can be found on the NIGMS homepage at *http://www.nigms.nih.gov*.

## Basic Research and Women's Health

### *Estrogen Receptor Function*

Two receptors for the hormone estrogen are known to exist. The original receptor is known as ER-alpha and a second estrogen receptor, discovered in 1995 by a group at the Karolinska Institute, is designated ER-beta. The discovery of the ER-beta receptor helps explain how estrogen can exert effects on tissues, which lack the ER-alpha receptor, such as ovaries and bladder. While the functional responses of these two receptors to estrogen, estrogen analogues, and estrogen-blocking agents appears quite similar, a number of estrogen or anti-estrogen therapies are plagued by paradoxical effects. For example, the anti-estrogen tomoxifen, used to treat breast cancer, can promote the development of other types of cancers. In addition, it can lose its effectiveness in inhibiting breast cancer and even promote its growth. Dr. Scanlan, a chemist at the University of California–San Francisco whose research is supported by NIGMS, reasoned that the tissue-specific actions of estrogens, as well as anti-estrogens, may be due to the interactions of the ER-alpha and ER-beta receptors (when bound to estrogen or anti-estrogen ligand) with different gene-specific transcriptional enhancer elements. His findings provide evidence that the ER-alpha and ER-beta receptors exert different regulatory functions on the transcription of specific genes. Understanding these functions may lead to more effective therapies for osteoarthritis, breast cancer, and cardiovascular disease in women.

#### Second Generation Taxoid Antitumor Agents

The anti-estrogens Taxol and Taxotere, which are approved for use in treating breast cancer, act by a unique mechanism that involves binding to the cells microtubules, and thus interrupting the cell cycle and initiating cell death via apoptosis. While both drugs have proven clinically beneficial, their use is often accompanied by severe side effects and their efficacy may become attenuated by the development of "resistance" to these drugs by the cancer. The NIGMS-supported investigator, Dr. Iwao Ojima, developed new, highly active second-generation taxoids. These second-generation compounds improve on their parent drug in that they have outstanding oral bioavailability, have been found to be at least as active as the approved drugs when tested in human carcinoma cell lines and, most significantly, retain their activity against drug-resistant human carcinoma cells.

#### Link Between Hypertension and Female Infertility

Dr. John Oates of Vanderbuilt University has pursued work, funded in part by his NIGMS Center grant, that has lead to the recent discovery that the same receptor plays

a role in both control of blood pressure and female fertility. The EP2 receptor is one of at least four different receptors cells use to respond to the prostaglandin PGE2. Prostaglandin PGE2 is one of the hormonal signals that is known to affect blood pressure. In a study published in *Nature Medicine*, Dr. Oates and his colleagues demonstrate that knock out mice, which lack the prostaglandin EP2 receptor, present with salt-sensitive hypertension. It appears that there are apparently both dilator and constrictor receptors and that PGE2 affects the dilator EP2 receptor.

Non-steroidal anti-inflammatory drugs (NSAID) are known to block the production of prostaglandins, including PGE2, and to predispose patients to developing hypertension. Dr. Oates' findings suggest that PGE2 is an important dilator prostaglandin that acts through the EP2 receptor, and that NSAID use may increase blood pressure by blocking the production of PGE2. There is also evidence that NSAID use can lead to infertility in women, suggesting a possible role for PGE2 in infertility. Fertility studies of the EP2 knockout mice revealed reduced litter sizes due to fewer ovulated eggs and a lower frequency of fertilization, suggesting the EP2 receptor also plays a role in both ovulation and fertilization. The EP2 receptor may, therefore, be a target for new drugs designed to treat both hypertension and infertility.

## Overview of NIGMS-supported Research as it Relates to Breast Cancer

### *NIGMS-supported Research in Cell Biology*

Almost every aspect of cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus, must be investigated in order to understand the transformation of a normal cell to a cancerous one. Major factors in the etiology of breast cancer involve activation of cells by hormones, in particular estrogen, and by growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), and insulin-like growth factor (IGF). An understanding of the invasion and metastasis of tumor cells relies on knowledge of cell adhesion and cell motility. The following are examples of aspects of cell structure and function that impact on understanding cancer cell transformation and metastasis in general, and breast cancer in particular.

#### Cell Division

The cell cycle is highly regulated in normal cell growth and division. Uncontrolled cell division in cancer cells is due mainly to defects at the G1/S restriction point of the cell cycle, where DNA synthesis is initiated. Much of what has been learned about cell cycle control stems from basic genetic and biochemical studies in lower organisms, such as yeast, and the identification of highly conserved homologous mammalian genes and gene products. Continued basic cell cycle research in model systems, as well as in mammalian cells, should define the mechanistic role of tumor suppressor genes in controlling cell division, and the identification and characterization of growth-promoting genes in gene activation and amplification. Such studies should result in molecular strategies for gene therapy and inhibition of key biochemical steps in unregulated cell division.

A second critical control point in the cell cycle is the initiation of mitosis. Further knowledge of the processes required for chromosome segregation and cell division may provide targets for inhibition of cell division and prevention of abnormal chromosomal segregation leading to oncogene translocations and cancer. Microtubule proteins and molecular motors also play a role in cell motility related to tumor cell metastasis. These molecules, therefore, are targets for chemotherapeutic agents, such as taxol, vinblastine, and colchicine, that interfere with the synthesis and function of cytoskeletal proteins. As new families of cytoskeletal proteins are discovered, new opportunities will arise for targeted drug design aimed at interfering with abnormal cell growth, division, and metastasis.

### Cell Death

Controlled cell death, like controlled cell division, is a feature of normal cells. Programmed cell death, called apoptosis, occurs in development, in response to hormonal signals, and in the immune system. Cancer cells apparently have aborted cell death programs that contribute to uncontrolled cell division. A recently identified oncogene, bcl-2, inhibits apoptosis, while the p53 tumor suppressor gene may promote apoptosis. Furthermore, certain chemotherapeutic drugs appear to function by activating programmed cell death pathways. Much of what is currently known about apoptosis comes from studies in the invertebrate, *C. elegans*. Continued studies of programmed cell death in a variety of model systems should provide important new insights into mechanisms of controlled tumor cell growth and the development of new treatment strategies.

### Cell Activation

Normal cell activation ensues from the delivery of a signal to a membrane receptor and the coupling of that signal to a biochemical cascade that results in gene activation, synthesis of new proteins, and cell growth and division. Cancer cells are constitutively activated, or "turned on", by a variety of growth factors and hormones, and by expression of mutated growth control receptor genes, resulting in uncontrolled cell growth and division. Knowledge of receptor structure and function, and the specific steps in the signal transduction pathway, should provide new insights into the prevention and treatment of breast cancer.

### Cell Differentiation

Tumor cells generally are dedifferentiated; factors that promote cell differentiation also slow tumor cell growth and invasion. Basic studies on differentiation factors, such as transforming growth factor beta (TGF-ß) and retinoids of the vitamin A family in normal cell differentiation and development, will provide important information on the role of these molecules in breast cancer. Studies of TGF-ß in normal cell differentiation and development are of particular interest since TGF-ß induction by tamoxifen and retinoic acid may provide a mechanism for the prevention and treatment of breast cancer by these agents.

### Cell Adhesion

The adhesion of cells to each other, to basement membranes, and to the extracellular matrix is an important factor in tumor formation, invasion, and metastasis. A wide range of basic studies addressing mechanisms of cell adhesion are, therefore, relevant to breast cancer research. For example, overexpression of laminin receptors is associated with increased tumor invasiveness. In contrast, expression of some adhesion molecules, such as the cadherins, reduces tumor invasiveness. Several classes of glycoprotein adhesion molecules, such as p-selectin, mediate formation of intravascular tumor emboli and establishment of metastatic sites. Further knowledge of the structure and function of adhesion molecules, such as the integrins, cadherins, and selectins, as well as research on the structural and biochemical components of the cell that mediate attachment to the extracellular matrix, should provide the basis for intervention in tumor invasion and metastasis.

### Cell Motility

A second important parameter in tumor cell metastasis is cell motility. Many growth factors, such as platelet-derived growth factor (PDGF) and IGF, promote cell motility. A recently discovered tumor suppressor gene, nm23, functions by suppressing cell motility and, therefore, tumor cell metastasis. The nm23 gene product is nucleoside diphosphate kinase (NDPK), and at least one substrate for this kinase is dynamin, a newly discovered molecular motor protein involved in intracellular transport, as well as cellular motility. As the members of the cytoskeletal protein and molecular motor families grow, it is expected that new opportunities will rapidly arise for the design of drugs that target the cell motility apparatus and interfere with tumor cell invasion and metastasis.

### Intracellular Transport

One of the prognostic indicators for breast cancer is the multi-drug resistance gene (mdr). This gene encodes a transporter molecule that pumps chemicals, such as cytotoxic chemotherapeutic agents, out of the cell. The mdr gene also may be important in cancer prevention as it pumps unwanted carcinogens out of normal cells. Knowledge of the mdr gene and its encoded transporter stems, in part, from studies of cellular transport in yeast. Continuing studies on molecular motors, such as the kinesins and dynamin, also may have payoffs in understanding how drugs and carcinogens are transported in and out of cells.

## *NIGMS-supported Research in Biochemistry, Chemistry, and Pharmacology*

### Enzymology

Many enzymes are involved in the conversion and clearance of carcinogens, and in biochemical mechanisms associated with tumor cell growth and metastasis. The study of enzyme kinetics, reaction mechanisms, and substrate specificity will enable a rational approach to the design of therapeutic and preventive agents. For example, reducing enzymes are involved in the detoxification of oxidative metabolism carcinogens while other enzymes stimulate tumor growth and proliferation. The metalloproteinase enzymes, for example collagenase, promote tumor cell invasion and metastasis. DNA repair enzymes play a key role in the cell's response to carcinogens, and faulty repair may lead to gene mutations with oncogenic potential. These are just a few examples of enzyme targets for the design of inhibitors or activators that may be useful in the treatment of breast cancer. Additionally, studies are underway to identify gender-related differences in the metabolizing capacity of therapeutic drugs, particularly with respect to the P-450 enzymes.

### Chemistry and Pharmacology

Natural plant and animal products are a major source of bioactive agents with antitumor activity. The clinical exploitation of such agents depends on the ability to chemically purify and synthesize them. A prime example of this is taxol, derived from the bark of the yew tree. While very promising in the treatment of ovarian and breast cancer, only limited natural supplies were available. Improved approaches for isolation, purification, and synthesis have enabled widespread clinical trials of taxol. Many other natural products are targets for synthesis and clinical testing, and further studies on these and other agents will be needed. Such knowledge comes from basic chemical and pharmacologic research on a variety of related compounds.

## *NIGMS-supported Research on Molecular Biophysics*

### Structural Biology

In order to fully understand how biologically active molecules work, and how to interfere with or promote their function, the structure must be known at the molecular level. Research into the structure and function of receptors, growth factors, kinases, and transcription factors will greatly facilitate an understanding of the mechanisms operating in the development of breast cancer, and in strategies for treatment and prevention. Basic structural research has led to the determination of the structures of several growth factors, and receptor structure is being investigated at the molecular level. The structure of the glucocorticoid receptor recently was determined and should prove informative for an understanding of the function of the superfamily of steroid hormone receptors, including those for estrogen and progesterone. Structures of other receptor molecules, such as those for growth factors and tyrosine kinases, will be of great importance for breast cancer research. The study of molecular structure for rational targeted drug design already is underway in the search for agents active in the prevention and treatment of AIDS. A similar approach should be applicable to other clinical problems, including breast cancer.

**Imaging Techniques**

Research in molecular biophysics requires spectroscopic and crystallographic techniques. An outgrowth of these studies has been advances in magnetic resonance imaging (MRI) techniques. A newly discovered approach, called relaxographic imaging, should provide a more sensitive method for the earlier detection of breast cancer. Research on the development of photoprobes, fluorescent dyes, and other molecular tags also should yield new opportunities for the detection and treatment of cancer.

### *NIGMS-supported Research in Genetics and Molecular Biology*

The genetics of breast cancer encompasses the identification and characterization of genes that determine disease susceptibility; the regulation and expression of genes involved in transformation, growth, and metastasis of tumor cells; and genetic strategies for treatment and prevention.

**DNA Repair**

DNA breaks and repair occur in the course of normal cell growth and division. However, incorrect DNA repair can result in mutations and translocations resulting in tumor formation. Research on DNA repair genes, the functions of the proteins they encode, and on mechanisms of mutagenesis, will lead to the design of new anti-cancer drugs.

**Gene Expression**

Many oncogenes are normal cell genes that become oncogenic when they are either under- or overexpressed. Other oncogenes encode or activate transcription factors that lead to uncontrolled growth, cell division, or motility. Further research on these genes, their protein products, and the mechanisms that regulate their expression, will provide novel opportunities for gene therapy and gene replacement.

**Gene Amplification and Translocation**

Certain genes become oncogenic when amplified or translocated to a new chromosomal position subject to altered gene control. Research into mechanisms that promote abnormal gene and chromosome segregation, and gene amplification may lead to the design of cancer prevention agents.

**Gene Targeting, Replacement, and Therapy**

As genes are identified that either promote or inhibit tumor formation and metastasis, they will become targets for gene replacement or modification. Genes with clear prognostic, causative, or preventive roles, may be up- or downregulated, or replaced to prevent and treat breast cancer. Research on DNA recombination mechanisms will provide new techniques for gene therapy approaches.

### *NIGMS-supported Research in Physiology*

NIGMS supports research into mechanisms of wound repair in response to trauma and burn injury. This research encompasses studies of growth factors that are highly relevant to breast cancer research. For example, tumor invasiveness and metastasis are strongly correlated both with the density of blood vessels within a tumor and the angiogenic factors that promote both blood vessel growth and metastasis. Another aspect of wound repair involves cellular adhesion mechanisms and structure and function of the extracellular matrix. These mechanisms also regulate tumor cell interaction with the basement membrane and the propensity of cancer cells to migrate out of a local tumor site. Further studies on growth factors and adhesion mechanisms may give rise to promising chemotherapeutic interventions.

## Research Training

NIGMS extensively supports interdisciplinary research training of predoctoral and postdoctoral scientists. These training areas provide the personnel needed to attack the problem of prevention, diagnosis, and treatment of breast cancer. The Medical Scientist Training Program (MSTP) provides training of students with both a medical and scientific background. These future scientists, with both M.D. and Ph.D. degrees, will be ideally poised to address

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

## NATIONAL INSTITUTE OF MENTAL HEALTH

The epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on women's mental health. Overall, women and men do not differ in the likelihood that they will be diagnosed with a mental disorder, but they differ markedly in the prevalence and clinical course of different disorders. Starting in childhood, girls have higher rates of anxiety disorders than boys. After puberty women, have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder. Such differences are not found for other serious disorders, such as schizophrenia and bipolar disorder, but men and women with these disorders differ in important clinical aspects. For instance, women with bipolar disorder have greatly increased recurrence risk in the postpartum period. In later life, because the majority of the older population is female, women's mental health is of particular concern.

One study has provided a clear public health context for the mental disorders. This study, "The Global Burden of Disease," provided a measure of lost years of healthy life due to premature death, as well as years lived with disability. For the first time, the burden of illnesses was shifted from an almost exclusive focus on premature mortality to one that included chronic illness. The study enabled a comparison of the burden of different illnesses. Based on 1990 data, depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder were among the top ten conditions accounting for years lived with disability in women. This public health burden stems from three aspects of the epidemiology of the disorders. First, the conditions are highly prevalent. For example, in a 1-year period, an estimated 12 percent of women meet criteria for depression and approximately the same percentage meet criteria for an anxiety disorder. Second, all four of the most disabling mental disorders in women and identified in the "Global Burden of Disease" study have an early onset and a recurrent or chronic course. Third, since these disorders rise markedly in incidence in adolescence and peak in incidence in young to middle adulthood, they can adversely impact educational and occupational attainment, as well as social and interpersonal functioning. The study did not consider the impact of maternal mental illness on children in

assessing disability burden, but in other numerous studies, maternal mental illness has been associated with poorer child functioning. The best way to promote child mental health and enhance family functioning may be to reduce the burden of mental illness in women of childbearing age.

Through its research programs and related programmatic activities, the National Institute of Mental Health (NIMH) has increased scientific understanding of the effects of sex and gender* differences in mental health and mental illness. Through cross-cutting programs, such as the Women's Mental Health Research Consortium, NIMH has fostered interdisciplinary collaboration and the translation of basic findings into applications to improve diagnosis, treatment, services, and prevention. This 2001-2002 NIMH report highlights findings from areas of basic and clinical neuroscience, epidemiology and risk factors, and intervention development.

Accomplishments in these areas are grouped by five major subheadings: Developmental Aspects of Sex and Gender Differences; Depression and Anxiety Disorders; Eating Disorders; Other Serious Mental Disorders; and Health Disparities. A section on Other Program Activities describes the Women's Mental Health Program and Consortium, NIMH-sponsored meetings and research funding mechanisms relevant to women's mental health and sex and gender differences research.

## Accomplishments

### *Developmental Aspects of Sex and Gender Differences*

Many mental disorders have striking gender disparities in incidence, as shown in population epidemiology studies of U.S. adults. In fact, such disparities often have their origins earlier in the life span. Depression, anxiety, and eating disorders are three conditions for which incidence increases sharply around puberty – at the time when striking gender disparities become clear. For other conditions, such as attention deficit disorder and autism, gender disparities are manifest in prepubertal children, often from early childhood on. NIMH has initiated a program of research to study the manifestations of and risk factors for mental disorders in children, to formulate developmentally valid clinical classifications, and to assess the efficacy of treatments in pediatric samples. Much of this work is currently ongoing, and it is anticipated that gender differences in these findings will be addressed in future reports. In addition, other NIMH-funded studies are aimed at understanding how early life experiences interact with hormonal and genetically based sex differences to affect susceptibility to adverse health consequences of stress exposure, including mental disorders.

#### Basic and Clinical Neuroscience

##### Some Sex Differences in Brain Function are Due to Sex Chromosomes

Until recently, biological sex differences in health outcomes were attributed primarily to the effects of gonadal steroids on brain. A 2001 Institute of Medicine report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?*, called for more research on sex differences at the cellular level. However, existing experimental approaches were unable to differentiate sex differences, due to genetics, from hormonal effects. Recently researchers developed mice in which the gene responsible for testes development (Sry) was removed from the Y chromosome and inserted into another chromosome. This allowed for the production of hormonally determined male and female mice with either XX or XY chromosomes. Assessment of these animals revealed that the majority of reproductive and social behaviors and neurochemical measures were dependent on the presence of hormones produced by ovary or testes, but were independent of whether animals

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

expressed XX or XY chromosomes. However, a few changes were noted. The presence of a Y (i.e., male) chromosome modified the expression of the peptide vasopressin within one brain region. The expression of a catecholamine synthetic enzyme in a neural cell culture system was also affected by Y chromosome presence in a separate study. This area of research is in its infancy, but such experimental models promise to increase knowledge of how sex-linked genes contribute to sex differences in mental disorders.

### Astrocytes are Primary Targets for Hormones that Induce Developmental Sex Differences in Brain

Research has identified brain astrocytes as prime cellular targets for study of hormone-mediated sex differences in brain development and synaptic plasticity. Astrocytes are a subtype of glial cells that play important roles in brain development, neuronal synapse formation, and neurotransmission. They are also targets of gonadal hormones. In the hypothalamus, astrocytes from male rats demonstrate an early postnatal developmental differentiation and decreased functional plasticity as a result of early post-natal gonadal hormone exposure. In contrast, astrocytes in the female hypothalamus, which do not experience early hormone exposure, maintain plasticity in adulthood, and respond to cyclic changes in sex hormone levels. This hormone responsiveness is most likely important for hypothalamic regulation of reproductive hormone secretion by the pituitary.

### Identifying Developmental Brain Mechanisms Contributing to Adult Maternal Behavior

Preclinical research has provided strong evidence of the biological impact of maternal care during infancy on molecular, hormonal, and behavioral responses to stress in offspring. New preclinical data indicate that maternal care also affects the development of brain systems subserving the adult maternal responsiveness of the female offspring. Using a cross-fostering paradigm, researchers showed that maternal behavior expressed in adult female rat offspring was related to the females' early life experiences of maternal behavior. Additional findings indicate that this imprinting of maternal behavior, by early experience, is accompanied by changes in the expression of the neuropeptide oxytocin in the hypothalamus. Exposure to a responsive mother was correlated with greater oxytocin expression in female offspring and administration of an oxytocin antagonist decreased maternal responsiveness of these offspring.

### Maternal Depression in Early Development Sensitizes Children to Later Stress Exposures

Investigators have found that preschool year-old children with a history of exposure to stressful circumstances showed elevated cortisol. This effect was most pronounced if the children were also exposed to high maternal stress as infants. Maternal depression, beginning in infancy, was identified as the most potent predictor of children's cortisol response. In addition, the 4-year-old children with high cortisol levels demonstrated more symptoms of depression and anxiety when retested at the end of first grade.

### Sex Differences in Brain Circuits Regulating Emotion

Women have a higher incidence of depression and anxiety disorders than men, but are less likely than men to commit suicide. In order to investigate whether brain anatomical differences mediate these clinical behavioral differences, investigators compared brain structures involved in the modulation of mood in normal men and women. Results of one study showed that the relative volume of the orbitofrontal cortex was greater in females than in males. This brain region modulates input to the amygdala – a brain area implicated in early monitoring of and responding to threatening stimuli in the environment. In contrast to the orbitofrontal cortex, the amygdala was larger in males. Sex differences in the structure of brain regions determining

cognition and mood are functionally important as indicated by recent results of a functional imaging study. In this study, sex differences were observed in brain areas activated during performance of an emotional memory task depending on the degree of emotional arousal of the stimuli used in the task.

**Depression and Anxiety Disorders**

Depression and anxiety disorders are the most highly prevalent of the mental disorders and they affect twice as many women as men. Anxiety disorders more prevalent in females include panic disorder, generalized anxiety, posttraumatic stress disorder, and some phobias. By early adolescence, gender differences in the incidence of major depression and anxiety disorders are evident. An estimated 19 million adult Americans are affected by a depressive disorder each year, comprising 12 percent of American women and 6.6 percent of American men. Similarly, an estimated 19.1 million U.S. adults are affected by anxiety disorders each year. In addition, the depressive and anxiety disorders also affect substantial numbers of adolescents and children. Genetic and hormonal factors, as well as sex differences in stress responses and risk factor exposures, have all been implicated in gender disparities in prevalence of the disorders. Although the depressive and anxiety disorders are clinically distinct, they often co-occur and are thought to share some etiological factors. They often respond to the same classes of pharmacological treatments. Evidence points both to shared, as well as to distinctive genetic, neural, and experiential bases.

Depressive and anxiety disorders often result in significant functional impairment, decreased health-related quality of life, lost work productivity, and even hospitalization and suicide. In a landmark study of *The Global Burden of Disease*, funded by the World Bank and the World Health Organization, major depression led a list of medical conditions in accounting for years of productive life lost to functional disability in women; and this depression-related disability is projected to increase over the next two decades. There is substantial evidence that undiagnosed, untreated depression and anxiety disorders adversely affect the course of general medical conditions and may even predispose to them.

NIMH funds a wide range of basic and clinical research to enhance understanding of the depressive and anxiety disorders and their associated risk factors, and to develop effective interventions, services, and prevention strategies In order to reduce their functional impact, NIMH also seeks to translate basic and clinical findings into the more applied realm of intervention development, refinement, and improvement. Studies of women's health and of sex and gender differences are a critical component of the NIMH mission to increase understanding of brain and behavior and to, thereby, develop interventions and services that are effective in reducing the burden of mental illnesses. Below is a sample of NIMH's 2001-2002 research highlights from studies of brain mechanisms, genetics, other risk factors, and research to improve interventions relevant to gender disparities in depressive and anxiety disorders.

**Basic and Clinical Neuroscience**

**The Effects of Estrogen on Hippocampal Plasticity Mediate its Impact on Stress Responses, Learning, and Memory Formation**

The hippocampus is a critical brain region involved in learning, memory, and mood regulation; and hippocampal atrophy has been found in association with posttraumatic stress disorder and serious depression. The hippocampus is unique among brain structures in its ability to produce *de novo* neurons throughout adult life. Several NIMH-supported investigators have contributed to the recent observation that estrogen produces cyclic and reversible changes in the dendritic processes on hippocampal neurons. Structural changes are accompanied by changes in the expression of proteins

regulating synaptic activity. This anatomical and biochemical evidence of synaptic plasticity provides a potential mechanism by which estrogen may modulate mood, learning, and memory, aspects of which may be adversely impacted in depressive and anxiety disorders.

### New Mechanisms of Estrogen's Action in Brain Have Been Identified Using Genetic Strategies

Gene knockout strategies, in which a gene of interest is eliminated in an animal model, have been used to identify distinct receptors mediating estrogen's effects on expression of hypothalamic peptides oxytocin and vasopressin involved in the regulation of reproductive and affiliative behaviors. This approach has revealed that the different nuclear estrogen receptors, labeled ER alpha and ER beta, each play unique and important roles as mediators of estrogen's effects on gene transcription in brain. ER beta selectively regulates oxytocin and vasopressin in a region of the hypothalamus controlling feeding behaviors. ER alpha regulates expression of these peptides in a different hypothalamic area involved in control of maternal behaviors. Other new evidence indicates that a novel membrane receptor ER-X mediates some effects of estrogen on cell differentiation and survival. The identification of selective estrogen receptor targets in brain may lead to new estrogen therapeutic treatments for affective and cognitive disorders that lack the negative side effects associated with existing hormone treatments.

### Estrogen Regulates Mood through its Effects on Neurotransmitters

Brain serotonin and norepinephrine neurotransmitter systems are targets of commonly prescribed antidepressant and anxiolytic medications. In experimental models, estrogen- and progesterone-augmented brain serotonin and norepinephrine transmission. Data from non-human primates indicate that the mechanisms responsible for this enhancement by estrogen include increased expression of enzymes producing serotonin, decreased expression of serotonin-metabolizing enzymes, and decreased expression of receptors and signaling molecules that downregulate the serotonin system. These findings indicate the therapeutic potential of explorations of the impact of ovarian hormones on brain systems subserving mood modulation.

Selective serotonin reuptake inhibitors (SSRIs) alter serotonin signaling and neuroendocrine function. Although women constitute the majority of patients treated with SSRIs, such as fluoxetine, most animal studies of SSRIs are conducted in males only. In an attempt to correct this deficit, investigators studied the effects of long-term fluoxetine treatment in female rats. They found that fluoxetine reduced the sensitivity of brain serotonin transmitter systems (serotonin 1A receptors in the hypothalamus), altered neuroendocrine responsiveness to serotonin, and disrupted the pattern of the estrous cycle.

### Estradiol Treatment in Postmenopausal Women Attenuates Hormonal and Immune Responses

Researchers studied the ameliorating impact of estradiol replacement treatment on cytokine and hormone response to immune challenge in postmenopausal women. An endotoxin immune challenge stimulated stress hormone and cytokine release in all women, but the increase in the stress hormone ACTH in blood was attenuated by more than 50 percent in women receiving the estradiol treatment. Increases of inflammatory cytokines, induced by the immune challenge, were also significantly smaller in the estradiol-treated women. These data show that clinically significant amounts of estradiol limit cytokine and neuroendocrine responses to an inflammatory challenge in humans. The significance of these results for mental health research lies in the growing literature indicating that circulating cytokines impact brain function in areas relevant to mood and cognition.

## Epidemiology and Risks Factors

### Sex-specific Genetic Vulnerability Factors for Depressive Disorders Have Been Identified

Researchers have identified genes that are present in both males and females but are linked to susceptibility to depression only in females. The susceptibility is for recurrent, early-onset major depressive disorder (RE-MDD), a subtype of major depression in which two or more episodes occur on or before age 25. One genetic region, identified as associated with this depression in women, includes the *Creb1* gene, which encodes a neuronal-signaling protein called cAMP-responsive element-binding protein (CREB). The sex specificity of this susceptibility locus may result from reported synergistic interactions of CREB with nuclear estrogen receptors. These data suggest that there may be important sex differences in the molecular pathophysiology of some forms of major depressive disorder.

### Sex Differences in Genetic Vulnerability Factors for Phobias Vary by Phobia Type

Studies have consistently found evidence of sex differences in the incidence of irrational fears and phobias. Previous studies suggest that phobias are familial, but the relative contributions of genetics and environment in determining sex differences in occurrence of specific phobias have not been sufficiently examined. New data comparing the incidence of phobias in twins indicate equal heritability in males and females for agoraphobia, situational, and blood-injury phobias, with minimal impact of family environment on incidence. In contrast, for social phobia, twin resemblance in males was attributed primarily to genetic factors, and in females primarily to familial-environmental factors. Sex differences in genetic risk factors seen in some phobia subtypes may overlap with shared risk factors with other syndromes like major depression, where sex-specific factors have been demonstrated previously.

### A Lifetime History of Major Depression is Associated with an Early Decline in Ovarian Function

A prospective epidemiology study examined the impact of a history of major depression on an early transition to menopause. In this study, reproductive and psychiatric interviews and early follicular-phase blood specimens were obtained at study enrollment and every 6 months during 36 months of followup in a large community sample of women with and without a history of major depression, 36 to 45 years of age. Women with a history of depression had 1.2 times the rate of early perimenopause as women without the history. Women with more pronounced depressive symptoms at study enrollment had twice the risk of an earlier early perimenopause. Among the women with greater depressive symptoms, those who also reported antidepressant use had nearly three times the risk of an early perimenopausal transition than did nondepressed women. Women with a lifetime history of depression also had higher follicle-stimulating hormone and luteinizing hormone levels and lower estradiol levels at study enrollment and during the followup period.

### Lifetime History of Depression is Associated with Increased Risk for Subclinical Carotid Atherosclerosis in Middle-aged Women

Depression is associated with clinical coronary events, but the association between history of major depression and cardiovascular disease in women has received little attention. To investigate this, researchers determined the association between lifetime history of major depression, anxiety disorders, and substance abuse and subclinical carotid atherosclerosis in middle-aged women. Lifetime history of major depression was associated with arterial plaque, and substance abuse was related to changes in intime-media thickness of the carotid artery. Lifetime history of an anxiety disorder was not associated with either measure. After controlling for standard cardiovascular risk

factors, only the association between major depression and plaque was maintained. The risk of plaque was twofold in women with a lifetime history of recurrent major depressive episodes relative to women with no history of depression. These findings raise the possibility that major depressive episodes may increase risk for subclinical atherosclerosis. Prevention of recurrent episodes may also prevent further progression of atherosclerosis.

**Intervention Development**

Stable levels of gonadal steroids maintain remission of depressive symptoms in women with premenstrual dysphoric disorder (PMDD). Investigators evaluated the effects of continuous, stable levels of gonadal steroids on depressive symptoms in women with PMDD whose symptoms remitted when they were administered a gonadotropic-releasing-hormone agonist, which suppressed ovarian function. In contrast to prior findings which had found a mood destabilizing effect of a short-term add back of estradiol or progesterone in these women, new data suggest that a more prolonged exposure to continuous gonadal steroid levels is associated with a maintenance of the symptom remission induced by hypogonadism. Additionally, the data suggest that extended oral contraceptive regimens may benefit women with PMDD.

**Hormonal Alternatives to Estrogen are Under Study as Treatments of Perimenopausal Depressive Disorders**

Perimenopausal depression has been shown to respond favorably to treatment with estradiol. However, the routine use of estradiol for perimenopausal depression is controversial, due to reports from the NIH Women's Health Initiative of adverse effects of hormone replacement therapy on risk for cardiovascular disease and breast cancer. Studies are under way to test the efficacy of alternative treatments for perimenopausal depression. Preliminary evidence indicates that the adrenal androgen dehydroepiandrosterone (DHEA) significantly improves mood in perimenopausal depression. Because untreated depression has also been associated with increased risk for osteoporosis, the impact of DHEA on bone density will also be assessed. Other studies are testing the efficacy of phytoestrogens and selective estrogen receptor modulators in perimenopausal depression.

**Intervention Research**

**A Phased Approach to Treatment of Recurrent Major Depression is Effective and May be More Attractive to Women in Childbearing Years when They May Seek Alternatives to Pharmacotherapy**

Interpersonal psychotherapy (IPT) is an effective intervention which emphasizes making changes in interpersonal relationships to overcome factors that lead to or sustain depression or anxiety. A study looked at the efficacy of different combinations and sequencing of IPT and pharmacotherapy. Findings indicated that starting with IPT, and only adding medication if depressive symptoms persist, was as effective as IPT and pharmacotherapy in combination. Women with recurrent major depression who have potential to become pregnant may be more willing to seek and adhere to such treatment.

**A Relationship-based, Psychotherapeutic Intervention for Depressed Mothers and Their Toddlers Improved Outcomes for the Children at Risk for Psychopathology**

The intervention is designed to facilitate positive parent-child interactions. Children in the intervention condition had higher rates of secure attachments than those who did not receive the intervention. The intervention also prevented a decline in cognitive development seen at age 3 in the non-intervention group.

## *Eating Disorders*

Eating disorders affect eight to ten times more females than males. The incidence of the disorders rises sharply around the time of puberty when changing body shape and increased fat deposition in young females make it difficult for a majority to attain

ideals of thinness portrayed by the media. Incident cases continue to be common throughout adolescence and symptoms often continue to persist throughout young adulthood. Eating disorders are characterized by obsession with food and body image. The most common forms of eating disorders are anorexia nervosa (self starvation) and bulimia nervosa (binge eating and purging). Anorexia nervosa occurs in approximately 0.5 to 1 percent of young women. Bulimia nervosa affects 1 to 3 percent of adolescent girls and young women. In addition to evidence for social risk factors, there is also evidence of biological vulnerabilities in relation to eating disorders.

Although they are less common than depressive and anxiety disorders, eating disorders are associated with substantial disability. Weight loss and metabolic imbalances can be life threatening with mortality as high as 20 percent over 15 years of followup. Eating disorders may have long-term health consequences such as osteoporosis. NIMH is committed to funding research to help better understand these devastating disorders.

### Basic and Clinical Neuroscience

#### Alterations in Brain Serotonin May Contribute to the Pathophysiology of Eating Disorders in Women

Positron emission tomography imaging has been used to visualize serotonin 2 (5-HT2A) receptors suspected of contributing to disturbances in appetite and eating behavior in women with anorexia and bulimia. Investigators observed a reduction in serotonin binding to 5-HT2 receptors in the frontal cortex and limbic regions (hippocampus and amygdala) in women with anorexia nervosa when they are ill and after recovery. Similar changes in 5-HT2 receptor binding were seen in the frontal cortex of women with bulimia during the illness and after recovery. The finding that altered brain serotonin activity persists after recovery suggests that this may be a trait-related disturbance that contributes to the pathophysiology of eating disorders.

### Epidemiology and Risk Factors

#### Different Genes may Predispose to Restricting Anorexia and Bulimia Nervosa

Restricting anorexia nervosa is an eating disorder subtype characterized by severe limitation of food intake without the presence of binge eating or purging behavior. A recent genetic study provided evidence for a susceptibility gene on chromosome 1 for restricting anorexia nervosa in families in which at least two family members were diagnosed with the condition. However, no linkage was found when analysis was broadened to include families with just one relative diagnosed with either anorexia or bulimia. This finding suggests some specificity in genetic factors predisposing to anorexia and bulimia.

#### A Prospective Study Examined Relationships among Risk Factors for Eating Disorders

Body dissatisfaction is an established risk factor for eating disorders. A prospective study of the development of eating disorders in adolescent females found that a high body weight, perceived pressure to be thin, idealization of thinness, and lack of social support increased risk for body dissatisfaction. Other putative risk factors for eating disorders, such as early menarche, weight-related teasing, and depression, did not predict body dissatisfaction. However, the relationship between depression and risk factors for eating disorders was complex. Initial pressure to be thin, thin-ideal internalization, body dissatisfaction, dieting, and bulimic symptoms, but not body mass, did predict subsequent increases in depressive symptoms, as did increases in these risk factors over the study. The effects on risk for depression of these factors remained even after controlling for social support and emotionality. These results enhance understanding of gender-related risks for depression in adolescent girls.

**Intervention Research**

### An NIMH Clinical Trial Found Cognitive Behavioral Therapy to be Superior to Interpersonal Therapy in Reducing the Primary Behavioral Symptoms Associated with Bulimia Nervosa

Study participants who received cognitive behavioral therapy (CBT) were more likely to recover than those receiving interpersonal therapy (IPT). In addition, a higher percentage of CBT patients met community norms for eating, attitudes, and behaviors. CBT produced clinical benefits more quickly than IPT and, overall, was efficacious with a larger percentage of patients who also showed stable maintenance of their treatment gains.

### Combined Treatment for Bulimia Nervosa is More Effective than Either Pharmacotherapy or a Behavioral Intervention Alone

This controlled trial found that both vomiting and binging in bulimia nervosa were clinically improved by treatment with fluoxetine or a manual-based, self-help program, but that a combination of the two treatment approaches led to the greatest improvement. The effects of the two treatments appear to be independent and additive. This finding of effectiveness of combined treatment for bulimia nervosa may lead to development of a stepped care approach starting with the manualized self-help program and adding in pharmacotherapy.

### Dialectical Behavior Therapy is Efficacious in the Treatment of Binge Eating Disorder

A study evaluated the efficacy of dialectical behavior therapy (DBT) adapted to the treatment of binge eating disorder. The treatment, based on an affect regulation model of eating disorders, was developed to replace disordered eating behaviors with emotion regulating skills. Compared to controls, women treated with DBT showed decreased binge eating and eating pathology, and 89 percent stopped binge eating by the end of treatment. Abstinence was reduced to 56 percent by the 6-month followup.

## *Schizophrenia, Bipolar Disorder, and Other Severe Mental Illnesses*

In contrast to depressive and anxiety disorders, men and women do not differ in the prevalence of such serious mental illnesses as schizophrenia and bipolar disorder. Schizophrenia and bipolar disorder affect approximately 2 percent of the adult U.S. population. However, they are among the most serious of the mental disorders in their functional consequences. There are clinically important gender differences in clinical course of the disorders. Women with schizophrenia display more affective symptoms and generally have better functioning than men. They are older when they have their first onset of mental illness. The protective role of estrogens against psychosis in schizophrenia has been suggested from both preclinical and clinical data. Issues of childbearing complicate treatment choices; and rehabilitative services may require them to be away from their children. For women with bipolar disorder, the risk for an episode of serious or even psychotic depression is heightened postpartum suggesting that the increased risk is related to the rapidly falling levels of estrogen after delivery. Women with serious mental illnesses may be counseled to maintain psychotropic medications in order to forestall new episodes. However, drugs used to treat or protect against recurrences vary in teratogenic potential. Low risks are associated with typical neuroleptics, moderate risks with lithium, and higher risks with older anticonvulsants such as valproic acid and carbamazepine. Little is known about teratogenic risks with other newer-generation anticonvulsants and atypical antipsychotics.

Many women with serious mental illnesses also have special issues related to their role as parents, such as concerns over child custody, lack of transportation and child care needed to access mental health services, and need for counseling and other services to increase their parenting skills. For financial reasons, many receive mental health care in the public health care system. In April 2002, President Bush created the New Freedom Commission on Mental

Health. The mandate of the Commission was to address barriers that prevent all Americans from accessing needed mental health services. The Commission will release its final report in April 2003. An interim report is available at *http://www.mentalhealthcommission.gov/*. Below are highlights of 2001-2002 NIMH research relevant to women with two serious mental illnesses, bipolar disorder or manic depression and schizophrenia.

### Epidemiology and Risk Factors

#### Increased Prolactin in Women with Schizophrenia is not Solely an Effect of Antipsychotic Medications

Most antipsychotic medications have the side effect in women of elevating the hormone prolactin, and this increase has been blamed for the higher incidence of ovarian dysfunction in women with schizophrenia. A study examined the effects of different antipsychotic medications on menstrual functioning and serum prolactin levels in schizophrenic women. Researchers found significant variation in the degree to which different antipsychotics affected prolactin levels, but no difference in ovarian function. These data suggest that factors other than medication-induced increases in prolactin are responsible for the greater risk for ovarian dysfunction in women with schizophrenia.

### Intervention Development

#### Women Who Discontinue Medication for Bipolar Disorder in Pregnancy Risk Recurrence during Pregnancy and Postpartum

In a comparison of pregnant women with bipolar disorder and matched non-pregnant controls, recurrence rates in the first 40 weeks after lithium discontinuation were found to be similar for pregnant and non-pregnant women, but then sharply increased postpartum for the childbearing women. Risk was much lower during preceding treatment and less with gradual discontinuation. Among subjects who remained stable over the first 40 weeks after lithium discontinuation, postpartum recurrences were 2.9 times more frequent than recurrences in non-pregnant women during weeks 41 to 64 (70 versus 24 percent) Clinical management of bipolar disorder through pregnancy and postpartum requires assessment of maternal and fetal risks and benefits.

#### Premenopausal Women may be More Responsive to Newer Antipsychotic Medications than Either Men or Postmenopausal Women

Reanalysis of data from a large clinical trial of olanzapine, compared with haloperidol, was performed to test for sex differences in therapeutic response. Results indicated that the effective dose of olanzapine for decreasing schizophrenia symptoms, measured by a Brief Psychiatric Rating Scale, was lower for women than men and that treatment response with slightly larger in women. Relative effectiveness of haloperidol in women was less clear and depended on the chronicity of disorder. These data support other findings suggesting that estrogen may decrease the severity of schizophrenia symptoms in women. Future studies will further test this hypothesis and examine whether this sex difference in response to olanzapine is due to differences in the brain action or metabolism of the antipsychotic medication.

### Services Research

#### A Study of Women with Severe Mental Illnesses, Who are also Mothers, has Identified a Number of Unmet Service Needs Related to the Parenting Role

This study examined the parenting needs of severely mentally ill women in the public health sector. Aside from sharing in common a condition of poverty, women were diverse in terms of their educational levels, number of children, number of fathers for their children, and family living arrangements. These women faced many significant stresses: living alone with their children, significant child behavior problems, and financial worries. Still, the majority of women endorsed the significance of motherhood in their lives. Analysis of findings focusing on women caring for teenaged children, found that youth depression was related both to

maternal mental health symptoms and to parenting style. Youth anxiety and self efficacy were related both to maternal symptoms and to community functioning. Inattention to parenting issues by health care providers may have adverse consequences for women and their children.

## *Mental Health and Health Disparities*

A landmark 2001 Surgeon General's report entitled *Culture, Race, and Ethnicity* highlighted disparities in mental health services for racial and ethnic minorities in the United States. Barriers to access include stigmatization of mental illness among different cultural groups and limited financial resources. Partly as a response to these and other access disparities, President Bush convened The New Freedom Commission on Mental Health in 2002. A subcommittee of that commission was formed to consider research needs in relation to ethnic minorities in the United States and to make policy recommendations. The Subcommittee on Cultural Competence of that Commission recently issued a report calling for more research on the role of culture and social context in mental health and on the provision of culturally appropriate care as such care relates to better mental health outcomes. Below are highlights of 2001-2002 NIMH-funded research addressing health disparities in samples of ethnic and minority women.

### Epidemiology and Risk Factors

#### Cultural Differences Modify Gender Differences in Suicide Risk

In the United States, a study of rates of major depression and suicide, compared by gender and ethnic group, yield unexpected variation. The comparison included five ethnic groups: whites, blacks, Mexican Americans, Cuban-Americans, and Puerto Ricans. Lower than expected suicide rates (given their rates of depression) were found in Mexican Americans and Puerto Ricans of both genders and in Cuban American and black females. Standardized measures suggest that two factors, familism and fatalism, may protect against suicide risk in depression among the Hispanic samples. Familism, an emphasis on close relationships with extended kinship, may offer protection against stress. Fatalism, the expectation of adversity, may be an adaptive stance in the setting of chronic stress. The findings of cultural and gender differences have implications for the development of preventive interventions.

#### Black and Hispanic Women Report High Levels of Depressive Symptoms and Reduced Health-related Quality of Life in Late Pregnancy

Maternal depression during pregnancy and postpartum has been associated with poorer child behavioral outcomes. However, few studies have addressed health disparities in mental health in relation to pregnancy. One study assessed mental health and functional outcomes in a sample of low-income black and Hispanic women with uncomplicated pregnancies. Women reported low levels of social support and high frequency of adverse life events in the last year. Half of the sample reported elevated levels of depressive symptoms, which in turn were strongly correlated with lower health-related functioning. Depressive symptoms were also associated with a lower sense of vitality and physical well being.

#### Women Who Received Welfare in Early Adulthood Report More Psychological and Physical Health Problems in Later Life

In a study of black mothers from a poor neighborhood, those who received welfare during the child-rearing stage of life reported more social isolation, health problems, and depressed mood 20 to 30 years later. Regular church attendance was protective for later physical and psychological health. A second study, using data from the National Longitudinal Survey of Youth and the National Survey of Families and Households, found that single mothers who received Aid for Dependent Children (AFDC) and single mothers who were jobless or working for low wages but did not receive AFDC reported similarly high levels of depression and hopelessness. The findings lend support to the conclusion that mental health symptoms stem primarily from financial hardship rather than from the stigma attached to welfare.

#### History of Abuse and Other HIV-related Risk Factors is Related to Seropositive Status

Risk factors for HIV/AIDS were assessed in a community sample of black, white, and Hispanic women. Regardless of race and ethnicity, HIV-positive women had more sexual partners, more sexually transmitted diseases, and more severe histories of abuse than did HIV-negative women. Trauma history was a general risk factor for women, irrespective of race and ethnicity. Limited material resources, exposure to violence, and high-risk sexual behaviors were the strongest predictors of HIV risk.

### Intervention Research

#### *A Phase III Behavioral Intervention* Reduced Incidence of High-risk Behaviors and Sexually Transmitted Diseases

Sexually transmitted diseases are a risk factor for HIV infection. In an assessment of the effectiveness of a preventive intervention, 935 inner city women were randomly assigned to one of three conditions: a small group, 6-session communally oriented HIV prevention intervention; a yoked general health promotion intervention control; or a standard care control. Both interventions involved the interactive use of videotapes by live group leaders. The HIV-prevention intervention, in particular, resulted in significant positive effects on self-reported and behaviorally assessed safer-sex behavior. Women in the HIV prevention group showed reduced point prevalence of medically tested sexually transmitted diseases at followup in some comparisons.

### Services Research

#### Three Quarters of Females in Juvenile Detention were Found to have Mental Illness, Suggesting Significant Unmet Service Needs

Among juvenile detainees in Cook County, Illinois, 10 percent were female, 88 percent were black, 17 percent Hispanic, and 5.6 percent non-Hispanic white. About half of the detained teens were abused or addicted to drugs, and more than 40 percent had disruptive behavior disorders: oppositional defiant disorder and conduct disorder. Even when conduct disorder (common in this population) was excluded, nearly 60 percent of males and more than two-thirds of females met diagnostic criteria for, and also were functionally impaired by, one or more mental or substance use disorders. Overall, disorders were more prevalent among older youth and females, more than 20 percent of whom had a major depressive disorder. The only categories for which boys showed higher rates than girls were a manic episode, psychotic disorders, any substance abuse disorder, and marijuana use disorder. In a departure from the overall pattern, older girls had lower rates of oppositional defiant disorder than younger girls. The extent of mental disorders and functional disability in this population suggests an unmet need for treatment and services.

#### A Study of Poor, Predominantly Hispanic and Black Women Living with HIV/AIDS Revealed High Levels of Both Sexual and Physical Trauma Before the Age of 16

Both types of early trauma were correlated with later trauma, and all forms of trauma were significantly associated with current perceived health. Two scales measuring perceived internal versus external locus of control were independent predictors of perceived health. Findings underscore the importance of addressing trauma and perceptions of control over one's physical health in the provision of health services to HIV-positive women.

## Initiatives

- **The *Women's Mental Health Program* is Located Organizationally within the Office for Special Populations, Office of the NIMH Director**

  The women's mental health position was established to ensure coordination of NIMH-funded research on women's mental health and on sex and gender differences. Other functions include serving as an organizational focal point for women's mental health science communication, and liaison with the NIH Office of Research on Women's

Health and other governmental and non-governmental organizations interested in women's issues. A paper entitled "The NIMH Women's Mental Health Program: Establishing the Public Health Context for Women's Mental Health" summarizes the goals of the program. The paper can be accessed at *http://www.nimh.nih.gov/wmhc/bleharten.pdf*. The Office for Special Populations also has program positions dedicated to minority research training, health disparities, and rural mental health. The office coordinates NIMH activities that serve to fulfill the Congressional mandate for tracking the inclusion of women and minorities in clinical research.

- **The *Women's Mental Health Consortium* Serves as the Focal Point for Coordination of NIMH Scientific Activities Related to Women's Health and Sex and Gender Differences Research**

  Members of the consortium include representatives from all four extramural research and research review divisions: the Division of Neuroscience and Basic Behavioral Science; the Division of Mental Disorders, Behavioral Research and AIDS; the Division of Services and Intervention Research; the Division of Extramural Activities; and the NIMH Intramural Research Program. Other components represented in consortium membership include the following offices: Communications and Public Liaison, Science Policy and Program Planning, Constituency Relations and Public Liaison, and the Executive Office. Consortium members work across disciplinary boundaries to plan workshops and conferences and to prepare and review science reports and program announcements related to women's mental health. The NIMH Women's Mental Health Consortium (*http://www.nimh.nih.gov/wmhc/index.cfm*.) maintains a website which provides information on upcoming women's mental health events, bibliographies of scientific reports, major reviews of gender differences research, NIMH meeting summaries, and links to NIMH women's mental health reports. The site lists consortium members throughout NIMH and their areas of expertise. The site links to other Federal women's health sites and to a variety of public information literature on mental health topics prepared by the NIMH Office of Communications and Public Liaison.

*Meetings and Reports*

- **Wye River Summit on Women and Depression October 2000**

  The interdisciplinary conference, cosponsored with the American Psychological Association, focused on risk factors, interventions, and services for women with depression. A conference report was published in 2002. Full text of the report may be accessed at *http://www.apa.org/pi/wpo/women&depression.pdf*

- **The NIMH Conference on Perinatal Mood Disorders July 2002**

  Four panels in this interdisciplinary conference addressed research needs in areas ranging from epidemiology, clinical research, and risk factors to basic neuroscience, interventions development, and services research. The meeting, cosponsored with the Office of Research on Women's Health, covered bipolar and unipolar mood disorders and psychotic and non-psychotic mood disorders. A meeting summary is available at *http://www.nimh.nih.gov/wmhc/index.cfm*.

- **NIMH Strategic Plan for Mood Disorders Research**

  This plan was developed over a 2-year period, based on a series of meetings and teleconferences. The plan includes discussion of research needs for women with mood disorders. A full report of the strategic plan was published in 2002 and may be accessed at *http://www.nimh.nih.gov/strategic/stplan_mooddisorders.cfm.*

- **The Development of Research Priorities for the Treatment of Anorexia Nervosa: Overcoming Existing Barriers**
  **September 2002**

  The goals of the meeting were to review known treatments, address research difficulties, and provide recommendations to improve intervention, development, and implementation.

- **Women's Mental Health Roundtable: Prevention and Treatment of Depression in Pregnancy and the Postpartum Period**
  **January 2001**

  This 1-day meeting surveyed intervention research in the area and developed recommendations for other research. A meeting report is available at *http://www.nimh.nih.gov/wmhc/matdepsum.cfm*

- **Depression in Men and Women: What's the Difference?**
  **March 2001**

  As part of the Smithsonian Resident Associates program, the 1-day panel, cosponsored with the Society for Women's Health Research, focused on understanding sex differences in depression and their clinical treatment implications. A meeting summary is available at *http://www.nimh.nih.gov/research/differencesummary.cfm*

- **National Rural Women's Health Conference: Linking Mental, Behavioral, and Physical Health: Quality-of-Life Issues, Outcomes, and Strategies for Health Promotion**
  **September 2002**

  This conference was organized by Penn State. The meeting goals were to improve health-related quality of life for women of all ages who reside in rural communities. Funding for the meeting was provided by an NIMH grant. (R 13 MH 66413)

*Program Announcements (PAs)*

- **Women's Mental Health and Gender Differences Research**

  PA under revision in 2003. *http://grants.nih.gov/grants/guide/pa-files/PA-00-074.htm* (PA –00-074)

- **Mental Health Research in Eating Disorders**

  *http://grants.nih.gov/grants/guide/pa-files/PA-96-064.html*

- **Exploratory/Development Grants for Intervention Research**

  *http://grants.nih.gov/grants/guide/pa-files/PA-99-134.html*

- **Supplements to Promote Re-entry into Biomedical and Behavioral Research Careers**

  *http://grants.nih.gov/grants/guide/pa-files/PA-01-081.html*

*Request for Applications (RFAs)*

- **Exploratory/Developmental Translational Grants for Borderline Personality Disorder**

  *http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-03-001.html*

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

  *http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-02-002.html*

- **Building Interdisciplinary Careers in Women's Health**

  *http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-02-001.html*

- **The Influence of Gender on HIV Risk**

  *http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-01-002.html*

## NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease – a burden borne by every age group, by every segment of society, by people all over the world. To achieve this goal, NINDS supports research on the causes, diagnosis, treatment, and prevention of neurological and neuromuscular disorders.

Most neurological diseases and disorders affect men and women equally; however, there are several nervous system disorders that are more prevalent in, or are of special interest to, women. These include multiple sclerosis, pain (especially headache), and stroke. Also of interest are the effects of antiepileptic drugs on the fetus, and the role of hormonal cycles in seizure activity. Investigators are looking at the role of female hormones in pain and stroke, and are conducting studies to see if estrogen and progesterone protect neurons in degenerative disorders, such as Alzheimers or Parkinson's disease.

- *Multiple sclerosis* (*MS*) is an autoimmune disease that is characterized by inflammation and scarring of the thick sheath, called myelin, that encases the nerve fibers, resulting in a slowing or disruption of electrical impulses. It is one of the most common neurological disorders of young adults, and as in a number of autoimmune diseases, is overrepresented in women. There are 300,000 to 350,000 MS patients in the United States, with an estimated 200 new cases diagnosed each week. As published in *Multiple Sclerosis*, a 1998 survey by the Center for Health Policy Research and Education at Duke University, the cost of medical care, including patient rehabilitation and loss of productivity, is estimated to represent an economic burden in excess of $6 billion annually to the United States.

- *Stroke* is the third leading cause of death in the United States, and a major cause of disability in both women and men. According to current estimates, Americans suffer about 700,000 strokes each year. About one-third of stroke victims die and another third face permanent disability. 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. Survivors are vulnerable to the acute effects of stroke and the long-term problems of permanent disability. The risk of stroke doubles each decade after age 50, and it is estimated that by the year 2050 there will be more than 70 million women over 50 years of age.

- *Migraine headaches* affect 16 to 18 million Americans, of whom nearly two-thirds are women. It is estimated that as many as 17 to 20 percent of all women will suffer moderate to severe migraines during their lifetime. Migraine accounts for an estimated 30 million days of lost productivity at a cost of almost $12 billion annually. Current research is aimed at discovering the etiology of migraine and fostering new treatments.

### Accomplishments

#### *Estrogen Replacement Does Not Protect against Recurrent Stroke*

Results of a clinical trial evaluating the impact of hormone replacement treatment on recurring stroke in menopausal women were announced in October, 2001. The Women's Estrogen for Stroke Trial (WEST), supported by NINDS, is the first randomized, controlled clinical trial of estrogen therapy for secondary prevention of cerebrovascular disease. Investigators found that estrogen hormone replacement therapy does not reduce the risk of stroke or death in postmenopausal women who have already had a stroke or transient ischemic attack. (Published in the October 25, 2001 issue of *New England Journal of Medicine.*)

### *Estrogen Wires the Brain*

According to NINDS-supported investigators, estrogen appears to encourage neurons to hook up with their neighboring neurons in the part of the adult rat brain called the hippocampus, known primarily as a site for memory and learning. This finding may ultimately help explain these functions in humans, and it could clarify the role of estrogen in some kinds of epilepsy. (Published in the March 13, 2001 issue of *Proceedings of the National Academy of Sciences.*)

### *The Brain's Dopamine Neurons May Require Estrogen*

Men are more likely to develop Parkinson's disease (PD) than premenopausal women, but the reasons for this gender disparity are not fully understood. Sex hormones, such as estrogen, could be one factor since the likelihood of developing Parkinson's disease increases for women after menopause. In addition, postmenopausal women with PD improve with estrogen replacement therapy. These observations suggest that estrogen might influence the survival of the dopamine-containing neurons that degenerate in PD.

Through studies in nonhuman primates, researchers have now discovered a link between estrogen and the number of dopamine neurons in the brain. Ten days after removing the ovaries, the major source of estrogen in females, investigators counted the number of dopamine neurons in the vulnerable brain region. Compared to animals that received estrogen replacement therapy, the number of dopamine neurons in estrogen-deficient female animals was reduced by 40 percent. Estrogen replacement therapy rescued these neurons if it was given within the first 10 days after estrogen deficiency.

The connection between estrogen and the survival of dopamine neurons in the brain brings scientists much closer to understanding the gender and age disparities in the rate of PD in the population. Further research into the effects of sex hormones on neuronal survival should benefit PD therapies for both men and women. (Published in the December 1, 2000 issue of *Journal of Neuroscience* 20:8604-8609.)

#### Ovarian Hormones Alter Pain Perception

In a study from the same laboratory, the effects of ovarian hormones on pain perception were explored. Self-reported pain and responses to painful heat stimuli were assessed in three groups of adults; postmenopausal women on hormone replacement therapy and those not on hormone replacements, and men. The women on hormone replacement therapy showed lower pain thresholds and tolerances than the other two groups, suggesting that estrogen plays a role in pain perception. (Published in the May 2001 issue of *Pain* 92[1-2]:229-34.)

#### Animal Models for Chronic Pain

Estrogen replacement therapy alleviates the vaginal hyperalgesia (excessive sensitivity to pain) which is sometimes associated with loss of ovarian function through aging or removal of ovaries. An NINDS-supported researcher has developed an animal model to help determine the mechanisms by which estrogen alleviates pelvic pain. Ovariectomy in rats evokes vaginal hyperalgesia that can be alleviated by estrogen replacement. The model may lead to development of better treatment therapy for chronic pelvic pain. (Published in the February 2002 issue of *Maturitas* 26;41[2]:157-65.)

#### Anti-seizure Drugs and Birth Defects

A finding, supported by NINDS, showed that anti-seizure drugs taken by pregnant mothers, rather than epilepsy seizures themselves, were the cause of a higher-than-normal rates of birth defects in their babies. It has long been recognized that anti-seizure drugs contribute to the higher birth defect rate among epileptic mothers; however, seizure activity was believed to be a major contributor. The new study found that when pregnant women stopped taking anti-seizure drugs, they were no more likely than other women to have children with birth defects. This finding emphasizes that additional research is needed to find more and safer drug choices for pregnant epileptic women. (Published in the April 12, 2001 issue of the *New England Journal of Medicine.*)

**Experiments Offer Major Clue to Repairing Diseased Nerves**

In a mouse model, NINDS-supported investigators have discovered that the protein, tumor necrosis factor-alpha (TNF-α), plays a central role in how nerves and the brain repair themselves. This was a surprise, since the TNF-α protein is usually associated with inflammation, and has been considered detrimental rather than beneficial. Mice engineered to have the TNF-α gene "knocked out" did not show myelin regrowth that was seen in control mice. This finding has relevance to the pathology of multiple sclerosis, a disease more prevalent in women. (Published in the November 2001 issue of *Nature Neuroscience.*)

**Venom Component Fights Multiple Sclerosis-like Disease in Rats**

A compound extracted from the venom of sea anemones fights multiple sclerosis-like damage in rats. If the same is true in humans, the venomous substance, called ShK, could form the basis for a new class of drugs for MS. Additionally, it may be effective in other T cell-mediated autoimmune diseases, such as type 1 diabetes mellitus and rheumatoid arthritis. (Published in the November 20, 2001 issue of *Proceedings of the National Academy of Sciences*, vol. 98, #24.)

**Key Gene Identified for Multiple Sclerosis Progression**

An NINDS grantee has identified a gene in the brains of people with MS that may hold the key to understanding why some patients develop a more progressive form of the disease. Large-scale sequencing of cDNA libraries from plaques dissected from brains of MS patients indicate an abundance of transcripts for osteopontin, a protein known to play a role in the inflammatory response. (Published in the November 23, 2001 issue of *Science*, vol. 294, p. 173.)

**The Brain Produces New Cells in Multiple Sclerosis**

The brain produces new cells to repair the damage from MS for years after symptoms of the disorder appear, according to this study. However, in most cases the cells are unable to complete the repairs. These findings suggest that an unknown factor limits the repair process and may lead to new ways of treating this disorder.

In patients with MS, brain inflammation in random patches, or lesions, leads to destruction of myelin – the fatty covering that insulates nerve cell fibers called axons in the brain and spinal cord – and aids in transmission of signals to other neurons. This inflammation causes the myelin to deteriorate and leads to symptoms of MS. Previous studies have shown that some brain lesions are repaired during the early years of MS; however, many other lesions are not repaired.

One of the central questions in MS research is how to promote myelin repair. Many researchers have concentrated on increasing the number of myelin-producing cells, called oligodendrocytes, through stem cell transplantation or other means. However, this study suggests that problems with the axons, or with the tissue that surrounds them, may prevent remyelination. Many of the axons that were not remyelinated looked abnormal, whereas remyelinated axons appeared healthy. This suggests that therapies which prevent axon degeneration or help oligodendrocytes complete the repair process in other ways may be necessary. More research is needed to identify drugs that may be useful for this purpose. While the study shows that the brain's attempts to repair itself decrease over time, new cells were produced even in patients who had had MS for as long as 15 years, implying that there is a long window of opportunity for treatment. (Published in the January 17, 2002 issue of the *New England Journal of Medicine*, vol. 346, No.3, p. 165.)

## Ongoing Research

### *Multiple Sclerosis Research*

MS is about twice as common in women than in men. NINDS maintains an extensive portfolio of MS research projects, several of which are looking specifically at gender issues, such as pregnancy and the immunoregulatory role of female hormones in MS, and gender-specific differential gene expression.

Scientists are looking into the body's autoimmune system, infectious agents, and genetics as culprits in MS. Studies into these areas strengthen the theory that MS is the result of a number of factors, rather than a single gene or other agent. Studies use a technique called magnetic resonance imaging (MRI) to visualize the evolution of MS lesions in the white matter of the brain.

### *Prediction Markers for Disease Course in Multiple Sclerosis*

NINDS intramural investigators, collaborating with staff at the National Human Genome Research Institute, are using microarray analysis to develop markers for disease activity in MS. The NINDS group is following MS patients, both clinically and by using MRI, correlating these with biomarkers in order to predict disease course.

### *Blocking Nerve Damage in Multiple Sclerosis*

NINDS supports investigators who are looking at chemokine receptors – areas on cells that detect these chemicals – in order to find a way to block the cells' attraction to chemokines. It is thought that by disrupting the cell-chemokine interaction, the damaging inflammation within the brain and spinal cord can be prevented.

### *Gender Differences in Stroke*

In animal studies, it is clear that females have better outcomes after stroke than males, and that ischemic events (a blockage of blood flow to the brain that occurs during a clot-caused stroke) can be altered by estrogen priming of the cerebral vasculature and of the brain. However, specific neuroprotective mechanisms are unknown and potentially include both vascular and neuronal actions. This study will examine any inherent sex-linked injury protection mechanisms that may salvage brain tissue after an ischemic event.

NINDS currently supports a trial that is comparing the efficacy of two procedures that unblock a clogged carotid artery in the neck, a significant risk factor for stroke: carotid endarterectomy and carotid stenting. One facet of the trial will examine gender differences in these procedures. Previous research has shown that women may not benefit from carotid endarterectomy as much as men do.

Another ongoing trial studying the epidemiology of the "stroke belt" will document gender differences.

### *Gender Differences in Cardiac Arrest and CPR*

Despite four decades of research concerning cardiac arrest and CPR, clinical outcome remains poor. Although women have less sudden cardiac death than men, survival differences and neurologic and neuropsychologic evaluations between men and women after cardiac arrest have not been closely examined. Estrogen has historically been considered to be protective in coronary heart disease, but it is not clear if the steroid is also an important neuroprotectant in either women or men. More critically, the comparative vulnerability of females and males to brain tissue injury once cardiac arrest and CPR is ongoing remains unknown. Preliminary findings suggest that brains of females are better protected from cardiac arrest than males, and that estrogen may be involved with this neuroprotection. The goal of an ongoing project is to determine if there are inherent sex-linked neural injury mechanisms in experimental cardiac arrest and CPR, and if the principal biologically active estrogen in mammals plays a key role in salvaging brain tissue after cardiac arrest and CPR.

### *Women with Epilepsy Face Special Problems*

A significant proportion of women with epilepsy experience increased seizure frequency during phases of the menstrual cycle in which estrogen is elevated. Using an animal model of epilepsy in female rats, NINDS-supported investigators are exploring whether estrogen may facilitate seizure activity by altering the structure of neuronal connections in the hippocampus, an area that has been previously implicated in epilepsy. Another grant is studying how sex hormones differentially affect the development of brain areas that play a role in the spread of seizure activity. Finally, NINDS is currently funding a clinical trial to assess the safety of hormone replacement therapy for menopausal women, and another trial testing the efficacy of adjunctive progesterone in treating epilepsy.

### *Women, Migraine, and Other Pain*

Migraine headaches affect 16 to 18 million Americans, of whom nearly two-thirds are women. It is estimated that as many as 17 to 20 percent of all women will suffer moderate to severe migraines during their lifetime.

NINDS supports a large headache program-project grant, as well as numerous other investigator-initiated grants, that are looking at headache causes, and drug and non-drug treatments. Also, grantees supported by NINDS are looking at uterine and gynecological pain, and at gender, hormones, and menstrual cycle effects on pain and analgesia.

### *Inclusion of Women in Clinical Trials*

NINDS stroke clinical trials have appropriate numbers of women enrolled enabling subgroup analysis in order to detect significant gender differences.

## Initiatives

*Request for Applications (RFAs)*

- **Hyperaccelerated Award Mechanism in Immunomodulation**

  Cosponsored by NINDS, NIAID, NIA, NIAMS, and NIDDK.
  RFA AI 01-001
  (10/24/2000)

- **Sex-based Differences in the Immune Response**

  Cosponsored by NINDS, NIAID, NIAMS, ORWH, and the Multiple Sclerosis Society.
  RFA AI-01-005
  (2/12/01)

*Program Announcements (PAs)*

- **Identifying Functional Links between the Immune System and Brain Function, Including Behavior**

  Cosponsored by NINDS, NIMH, NIDA, and NIAMS.
  PA-02-045
  (1/16/02)

*Workshops*

- **Multiple Sclerosis: Current Status and Strategies for the Future**
  **April 2001**

  NINDS staff participated in this Institute of Medicine workshop.

- **Multiple Sclerosis and Chemokines: Prospects for Therapeutic and Prophylactic Intervention**
  **July 9-10, 2001**

  Cosponsored by NINDS, the Cleveland Clinic Foundation, Berlex, ChemoCentryx, Merck, Schering Plough, and Serono, the workshop was held in Chevy Chase, Maryland to articulated the current state of the art and provide future directions. It is hypothesized that chemokines and their receptors are involved in the

pathogenesis of multiple sclerosis, and that chemokine receptor blockade might be a feasible, near-term strategy for modulating disease course. However, there are substantial challenges: MS is a complex, poorly understood disease and the chemokine field is elaborate and complicated. Experts from both fields, MS and chemokines, attended. The synopsis of this meeting was published in the November 2001 issue of *Trends in Immunology*, Vol. 22, No. 11.

- **Astrocyte Function in Health and Disease September 25, 2002**

  This workshop was held in Rockville, Maryland. Astrocytes are the most abundant cell in the nervous system, and despite current research, our knowledge is surprisingly limited. Over the past decade, research findings have revealed that astrocytes exhibit a wide variety of biological activities, and probably play a role in several neurological disorders, including MS. The goal of this workshop was to bring together leaders in the field of astrocytes biology to discuss current research findings, assess the state of knowledge regarding astrocytes function in the healthy and injured or diseased states, and set a research agenda for the study of astrocytes biology.

## National Institute of Nursing Research

The National Institute of Nursing Research (NINR) supports clinical and basic research to establish a scientific basis for the care of individuals across the life span – from management of patients during illness and recovery to the reduction of risks for disease and disability and the promotion of healthy lifestyles, promoting quality of life in those who suffer from chronic illness, and care for individuals at the end of life. This research may also include families within a community context. NINR's research extends to problems encountered by patients, families, and care givers, and emphasizes the special needs of at-risk and underserved populations, with an emphasis on health disparities. The research mission of NINR is available at *http://www.nih.gov/ninr/research/diversity/mission.html*

Studies focusing on women's health constitute a large component of the funded research at NINR and are central to the mission of NINR's extramural research activities. NINR-supported researchers are conducting a variety of studies related to the leading causes of morbidity and mortality among women. Findings from these studies are providing direction for improving the health and well being of American women.

Significant areas of research focus on promoting health among women across the life span, identifying and addressing the needs of women with chronic illnesses, exploring issues related to pregnancy and postpartum, and examining gender and sex differences in health status and outcomes. In the area of health promotion, several investigators are examining the role of exercise in improving the health and well being of women, from midlife to the elderly. Other investigators are exploring ways to prevent falls in elderly women. NINR researchers are identifying and addressing the unique needs of women living with chronic illness and are designing interventions that will assist these women to live more productive and healthier lifestyles, despite their chronic conditions. These studies are investigating such chronic disease issues as delays in seeking care for cardiovascular disease, symptom management for women with breast cancer, the health promotion needs of women with chronic illnesses, and prevention of osteoporosis.

Research on pregnancy and related issues is addressing a number of important areas, including interventions targeting high-risk pregnant women, postpartum stress and immunity, and support for mothers of premature infants. In addition, NINR supports research on women experiencing menopause. Several NINR researchers are examining aspects related to sex/gender differences in health status and health outcomes.

For example, studies examining the mechanism of cardioprotective benefits of estrogen, the effects of estrogen in moderating pre- and post-ischemic platelet function, and sex differences in inflammatory pain and irritable bowel syndrome.

These diverse studies on women's health also illustrate NINR's long-standing commitment to research on health disparities and minority health. A large number of studies are devoted to addressing the needs of racial/ethnic minority women, which highlights the importance of examining psychosocial and cultural variables that influence health-seeking behaviors and health outcomes of these populations. Findings from these studies will add to the growing body of literature related to reducing the excess burden of illness borne by racial and ethnic minority women.

## Accomplishments

### *Health Promotion in Women across the Lifespan*

Insufficient exercise is one of the leading factors leading to premature morbidity and mortality in the United States. Therefore, exercise and physical activity have been a major component of NINR-funded health promotion research. Studies have focused on how to get women to exercise, as well as how to keep them exercising. Another goal of the research in this area has been to target vulnerable populations of women, such as minorities, low income, and the elderly.

One researcher has examined the psychosocial and environmental influences on physical activity and psychophysiological health outcomes in women to identify the factors that need to be incorporated into intervention programs focused on increasing physical activity and improving health outcomes in women. These findings were published in the *Journal of Nursing Scholarship* in 2002. Other findings from this study, published in *Nursing Clinics of North America* in 2002, described the significant regional differences between women living in the north and those in the south, indicating that awareness of the relationship between community, neighborhood, and physical activity can be useful for designing fitness programs that are sensitive to environmental differences in women's lives.

Another related study tested the efficacy of a 48-week home-based walking intervention on low-income midlife African American women. Findings published in *Women's Health* in 2002 reflected the influence of a culture of poverty and the importance of environmental safety and community support. The findings will be used to inform the development of community-based exercise interventions and policies that are culturally and socially sensitive to the needs of low-income, urban African American women.

Other recently funded investigators are testing exercise interventions in older women. One researcher is testing the hypothesis that cognitive behavioral therapy (CBT) will improve exercise behavior and physical outcomes among older, community-dwelling women. The intervention group is being taught to modify their negative interpretations of exercise in order to address the problem of compliance with exercise behaviors in older adults. Another investigator is testing the efficacy of a community-based diet and exercise intervention on older rural women. Few community-based interventions target both behaviors. Positive changes in these behaviors can modify midlife and older women's risk for disability and premature death.

Another related study is testing the efficacy of a fall prevention program for high-risk elderly women. The aims of the study are to determine the effects of the fall prevention program on postural competence, functional performance, mood, health-related quality of life, and fear of falling and fall-related injuries; health service utilization and costs; and identify demographic, clinical, personal, functional, and postural competence variables that predict long-term exercise adherence. This study has been co-funded by ORWH for fiscal years 2000 to present.

### *Managing Chronic Illness in Women*

Cardiovascular disease (CVD) continues to be the leading cause of mortality for women in the United States, with myocardial infarction (MI) being the leading cause of death. After an acute MI, women have a 16 percent mortality rate, compared with 11 percent for men. There is a growing consensus among clinicians and researchers that women with MI experience different symptoms than men. Research investigating delay in seeking treatment associated with MI consistently reports women delay seeking treatment because they do not recognize symptoms of MI since their symptoms differ from expectations. NINR supports a cadre of researchers examining the symptoms unique to women that often result in a delay in seeking treatment for MI. One NINR-funded investigator is conducting two complementary studies delineating prodromal and acute symptoms of MI in white, African American, and Hispanic women. Results of these studies will help to fully describe prodromal and acute symptomatology in women with heart disease and MI. This information will facilitate the development of educational materials tailored to women of color and should lead to earlier diagnosis and treatment.

Another investigator is conducting a descriptive study to identify and describe women's decision trajectories for seeking medical care. Findings from this study will be used to design an intervention to enhance women's decisionmaking self efficacy and, thus, decreasing delay in obtaining medical care for the symptoms of acute MI. A third investigator in this area is determining whether a one-to-one education and counseling intervention, delivered specifically to patients with documented ischemic heart disease, will: 1) reduce pre-hospital delay, 2) increase 911 use, and 3) increase aspirin use in those patients who experience acute MI symptoms. If effective, this intervention could result in significant improvement in morbidity and mortality of women with heart disease.

HIV/AIDS is another chronic illness that is having a major impact on women. Epidemiological data reveal a rapid increase in the incidence of AIDS among adolescents. One NINR-funded researcher is evaluating a school-based, HIV prevention program aimed at reducing sexual risk behaviors in inner-city pregnant and parenting teens, predominantly of Latino and African American backgrounds. Recently published findings in *Research in Nursing and Health* indicate that programs must address more of the realities of the lives of the young women, and include their male relationship partners, to be successful. Another investigator is developing an intervention to target the high prevalence of STDs and HIV for girls in the juvenile justice system. Knowledge, attitudes, and behaviors, along with biological markers of sexual activity, are being assessed during and after the intervention. This study provides a unique opportunity to implement and evaluate a community-based STD/HIV preventive intervention in an understudied, vulnerable population.

Another study targeting prevention of HIV/AIDS in a vulnerable population is Project SEPA, a culturally specific HIV/AIDS prevention intervention. The goal of this intervention is to increase HIV-prevention behaviors for inner-city Mexican and Puerto Rican women. Culturally relevant issues of unequal power, such as Machismo/Marianismo, are specifically addressed in this study. Findings will assist in the development of interventions to reduce the AIDS pandemic in women of color. Additionally, NINR is funding research testing the effectiveness of a peer counseling intervention to support rural women in managing HIV/AIDS and achieving positive outcomes. HIV-infected women residing in rural areas are at risk for poor adaptational outcomes because they are isolated from supportive services due to geographic distance and limited transportation.

As previously cited, NINR-funded investigators are testing exercise interventions as a means of health promotion. Other research is testing the effectiveness of exercise as a means of coping with chronic illness. Nearly 6 million Americans are living with fibromyalgia (FM), a debilitating chronic pain syndrome affecting mostly women. Other symptoms associated with this

disease include disrupted sleep, fatigue, decreased cognition, visceral and other pain syndromes, neurological symptoms, post-exertion muscle pain, and exercise intolerance. Researchers are testing the effects of exercise training in women with FM, whose growth hormones profiles have been experimentally manipulated with low-dose pyridostigimine bromide, on quality of life, cognition, pain, and associated FM symptoms.

Another area in which an NINR-funded investigator is examining ways to manage chronic illnesses is a longitudinal followup study of vulnerable rural and urban populations with multiple sclerosis. Findings from the initial study, published in *JOGNN* in 2002, indicate that disability and concern for children are independent predictors of depressive symptoms, and social support can partially mediate the effect of concern for children on depressive symptoms. Therefore, appropriate support should be identified and provided by nurses caring for mothers with disabilities, such as MS, to decrease the depressive symptoms related to the concern they have for their children. In addition to followup on the MS patients, the investigator is also validating the explanatory model in a new sample of persons with post-polio syndrome. The findings from this new study will expand knowledge of health promotion and quality of life among persons with chronic neurodegenerative conditions.

In the area of mental health for women, NINR funds a series of interrelated studies addressing a range of topics from depression to eating disorders. Depression constitutes a major public health problem and is one of the ten most costly illnesses in the United States, comparable to the cost of treating arthritis and coronary heart disease. It is the most common mental illness experienced by women whose rate is twice that of men. Poverty and stress among low-income single mothers place them at an increased risk for poor mental health and depressive symptoms. One researcher is testing the effects of a cognitive-behavioral intervention designed to reduce negative thoughts, chronic stress, and depressive symptoms among low-income single mothers. Another investigator is investigating the relationship between abuse, prenatal health, and postpartum depression. NINR is also funding the development of mental health interventions for couples who have miscarried.

The eating disorders of anorexia nervosa (AN) and bulimia nervosa (BN) are life-threatening problems that affect millions of American females each year. While a number of psychotherapeutic approaches to treatment have been developed, their effectiveness remains low. Part of the limited effectiveness is due to a lack of attention devoted to underlying causes. NINR is funding research testing the effectiveness of a cognitive behavioral social identity intervention program to foster development of new and separate self cognitions, and promoting recovery from AN and BN. Findings from this research will contribute to the development of an evidence-based psychiatric nursing treatment to promote recovery of health in women with an eating disorder. Preliminary work for this study was supported by a Shannon Award from ORWH in FY 2000.

The diagnosis of breast cancer and its treatment constitute a major source of psychological, emotional, and physical distress. Another study, in which the preliminary work was supported by a Shannon Award from ORWH in FY 1999, is examining the immunological, psychosocial, and clinical symptom outcomes of an 8-week integrated support program for patients newly diagnosed with breast cancer. This investigator is testing whether the support intervention, designed to combat stress and to provide social support and exercise training, has differential effects on patients with persistently low versus high baseline natural killer cell activity. In a related area, another researcher is examining the effectiveness of the antidepressant venlafaxine in treating the hot flashes experienced by many women following breast cancer. A third study, currently funded by an ORWH Shannon Award in 2001, is testing an individualized representational intervention to improve symptom management and quality of life in older women with breast cancer.

In the United States, more than 2 million women are living with lymphedema. The impact of untreated lymphedema affects quality of life, interpersonal relationships, functional abilities, occupational roles, and self esteem among women surviving breast cancer. In another study related to quality of life, a researcher is describing the measurement, incidence, and management of lymphedema among women diagnosed with the condition and treated for breast cancer and followed for over 30 months. Findings from this research will provide important information on self-care issues, quality of life, and the impact of lymphedema in women diagnosed with breast cancer. Other ongoing breast cancer research, supported by NINR, is focused on screening in Korean American women and treatment and prevention of long-term, treatment-related side effects.

The increasingly common use of adjuvant chemotherapy for breast cancer has led to a rise in long-term, treatment-related side effects, including osteoporosis, early menopause, increased risk for cardiovascular disease, and declines in quality of life. Osteoporosis is a major public health problem and a common finding in breast cancer survivors. One innovative study is testing the effects of home-based exercise and raloxifene in postmenopausal breast cancer survivors. Results of this study will contribute to knowledge about reducing the morbidity, mortality, and health care costs of common, long-term complications that confront breast cancer survivors. Another investigator is testing whether strength and weight training exercises enhance the effectiveness of risedronate, calcium, and vitamin D in improving bone mineral density, thereby preventing osteoporosis in postmenopausal breast cancer survivors.

In a related study focusing on postmenopausal women, an NINR-supported investigator is evaluating the effect of dual energy x-ray absorptiometry (DXA) screening on osteoporosis-preventing behaviors (OPB). The hypothesis is that the DXA screening will increase knowledge and influence OPBs (increased calcium intake, weight-bearing exercise, smoking cessation, alcohol intake moderation, hormonal replacement therapy, and non-hormonal drug therapy) through potentially mediating health beliefs. Another investigator is focusing on the prevention of osteoporosis, earlier in life, by focusing on the bone quality of pubertal females by increasing dietary calcium intake. This study began following children at the age of 9 and will continue through the age of 18.5. It is the first intervention study to evaluate the effects of optimal calcium intake on bone health throughout the period of highest bone mass and bone quality accrual.

Diabetes is another chronic illness that impacts the health of women in the United States, and black women suffer disproportionately from type 2 diabetes and related complications. Poor diabetes control, substandard diabetes care, and lack of diabetes education and self-management skills have been linked to the poor outcomes for this population. An NINR researcher is testing the effectiveness of a culturally sensitive education program designed to improve glycemic control and to empower women with the knowledge and skills needed to assume self management. Findings from this study may be helpful in identifying a model of diabetes care that will improve diabetes outcomes and contribute to decreasing the personal and public health burden of the disease.

ORWH has also provided a Shannon Award, is FY 2002, to support an investigator examining the prevalence of risk factors for coronary heart disease in women with a history of gestational diabetes mellitus (GDM) compared to women without a history of GDM. These researchers are also evaluating women's perceptions of their future risk of developing both coronary heart disease and diabetes, and whether perception of risk is related to actual risk. Findings from this study may be helpful in informing future interventions directed toward risk reduction in women with a history of GDM.

NINR researchers are also developing and testing biobehavioral approaches to managing urinary incontinence (UI).

UI affects approximately 13 million Americans with a higher prevalence rate in women. For example, although pelvic floor muscle (PFM) exercise is frequently recommended for treating UI, there is no conclusive evidence that PFM exercise is more effective with or without biofeedback. One investigator is comparing the efficacy of PFM exercises augmented with biofeedback to PFM exercises without biofeedback in women. The results will help design the most effective interventions to treat this condition. Another related study is testing a followup relapse prevention intervention in a population of homebound elderly 4-years post-treatment. The investigator is also conducting a descriptive study to identify predictors of relapse in UI. This study represents a unique opportunity to gain knowledge about long-term behavioral change and continence outcomes.

Vaginal birth has been associated with the development of UI in women, and UI increases with increasing parity. An NINR-funded investigator is studying the effects of pelvic muscle exercises on incontinence in pregnant women. The exercise program includes standardized instruction in pelvic muscle exercise tailored to the woman's individual ability, with muscle identification exercises preceding strength-building efforts. Preliminary findings, published in *The Journal of Nurse Midwifery*, highlight the importance of developing childbirth management protocols that will protect the pelvic floor during childbirth and support the choice of spontaneous pushing birth as a safe alternative to directed pushing childbirth.

### *Pregnancy, Postpartum, and Menopause*

A significant portion of NINR's research on pregnancy is devoted to identifying and ameliorating risk factors for pregnancy complications or adverse outcomes. Preeclampsia, the sudden onset of high blood pressure along with proteinuria during pregnancy, is a serious complication affecting nearly one in every 20 pregnancies. It is the main cause of maternal death worldwide, and affects women of all races and socioeconomic groups. Unfortunately, no definitive preventive treatment is currently available for this ominous disease. Scientists now believe that preeclampsia is a disease of the endothelium, due in part to oxidative stress. As such, regular exercise has emerged as a potential preventive measure. This contrasts to daily, low-dose aspirin or calcium supplements which have failed to demonstrate a significant effect and may have adverse effects. One NINR-funded investigator is determining if moderate-intensity exercise during pregnancy will reduce the incidence of preeclampsia, and assessing the process (involving oxidative stress and antioxidant process) hypothesized to explain the effect of exercise on preeclampsia.

Additionally, women who experience preeclampsia in more than one pregnancy are at an increased risk for developing cardiovascular disease in later life. Given the similarities in cardiovascular disease and preeclampsia, another investigator is examining the effects of a moderate-intensity exercise intervention on markers of metabolic syndrome in sedentary pregnancy women. Researchers will also explore the usual health behaviors, self efficacy, and differences in health behaviors adopted during pregnancy. This study will add to a program of research directed at health-promoting lifestyle behaviors in women who are at risk for pregnancy complications.

Abuse is also a risk factor associated with low birthweight, increased prenatal hospitalizations, and psychosocial distress. Approximately 7 to 34 percent of pregnant women are abused during pregnancy. An NINR investigator is testing a nursing intervention designed to increase women's opportunities to disclose abuse during pregnancy, decrease hospitalizations, and reduce psychosocial stress and severity of abuse in an ethnically diverse sample of urban and rural women. Findings from this study may be helpful in shaping future practice to improve both maternal and infant outcomes in women who are at high-risk for abuse.

Another risk factor for adverse pregnancy outcomes is smoking. Low-income women, in particular, are the most likely group to smoke during pregnancy. Smoking cessation

programs have been beneficial for some populations; however, more studies are needed targeting pregnant women. NINR investigators are comparing the effectiveness of an established smoking cessation program for pregnant women and a nurse-delivered telephone social-support intervention among low-income pregnant women attending WIC clinics. A secondary aim is to determine the prevalence of relapse among women who quit, related factors and characteristics associated with smoking cessation.

Low birthweight is a leading cause of infant mortality in the United States, and Hispanics have a pronounced increase in the preterm birth rate associated with length of stay in the United States. Few studies have examined the biological factors related to low birthweight in this population. An investigator, funded by NINR, is testing a biobehavioral model of causal pathways initiated by stress, cervical changes, and depression that may alter endocrine and immune factors leading to an inflammatory response, cervical changes and, ultimately, low birthweight and preterm birth in Hispanics. Findings from this study may be helpful in understanding ethnic disparities in low birthweight, as well as the pathways involved in preterm birth. This study was funded in response to the NINR program announcement "Low Birth Weight in Minority Populations" (PA99-045).

Premature and low-birthweight infants are at risk for a number of developmental problems; rural African American premature infants are at higher risk for these problems when compared to other premature infants. There are a number of factors related to this health discrepancy, including poverty, barriers to service usage, the mother's emotional distress from the infant's birth and hospitalization, and resultant parenting styles that may be less facilitative of infant development. In another study focused on a vulnerable population, researchers are examining the effectiveness of a culturally congruent intervention providing support to rural African American mothers of premature infants. The intervention focuses on enhancing psychological well being, mother-child relationship, child development, and longer use of developmental surveillance services.

In addition to the previously mentioned projects on postpartum depression, NINR funds research in other areas related to post-partum maternal health, such as the effects of lactation and the management of weight gain. Studies indicate that lactation may offer a maternal health-protecting effect. However, since all women do not lactate, research is needed to understand the regulation of neuroendocrine and immunological responses to naturalistic stress. NINR researchers are investigating the relationships among lactational state and stress, hormones, immune function, and symptoms of infection. Findings will enhance our understanding about whether a lactational stress exists in humans, and whether lactation offers any immunological or health benefit to the mother.

Obesity constitutes one of the most prevalent health conditions in the United States, reaching epidemic proportions in recent years. The prevalence of obesity is higher among women, and even higher for some ethnic minority women. Childbearing is a critical time for weight gain and obesity development. NINR researchers are conducting a prospective longitudinal design to measure weight, nutrition, and psychosocial variables during the first year after childbirth among low-income African American, Hispanic, and white women. Study findings will be used to formulate a postpartial weight management intervention for these populations.

Another important area related to reproductive health is menopause. One NINR researcher is describing the bio-psycho-social-cultural health environment of multiethnic groups of midlife women and the patterns of change over time in biological, psychosocial, and ethnic and cultural factors. Findings from this study will assist in understanding the relative contributions of women's physiologic, cultural, and psychological environments to their experiences of menopause, an area of research where little is known.

NINR is also a participant in funding the Study of Women's Health Across the

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

### *Sex and Gender Differences*

In the area of sex and gender differences, NINR is supporting both clinical and basic research in the areas of pain and cardiovascular disease (CVD). The focus of NINR's research on gender differences in pain began with an RFA published in 1997 by NIDCR, "Sex and Gender-related Differences in Pain and Analgesic Response." NINR funded two highly productive and still ongoing projects from this RFA.

Clinical studies indicate that women are more likely than men to experience a variety of chronic, recurrent visceral pain syndromes, such as irritable bowel syndrome (IBS). However, in contrast to well-characterized sex differences in animal models, experimental evidence to support gender differences in human pain perception remains inconclusive and mechanisms remain poorly understood. NINR researchers are using PET imaging of the brain, together with measurement of perceptual, autonomic, and neuroendocrine responses to noxious rectosigmoid stimulation, to test whether women exhibit differences in responses to potentially harmful sensations arising from the pelvic organs. The participants in this study are healthy control subjects and IBS patients. Findings published in *AJP-Gastrointestinal and Liver Physiology* and *Psychosomatic Medicine* in 2001 demonstrated stronger increases in cerebral blood flow in males compared to females in response to similar stimuli.

Many inflammatory diseases not only have a female preponderance, but are also associated with greater severity of pain and inflammation in females. The other study, funded in response to the RFA, is examining the basis for sex differences in inflammation and accompanying pain-like behavior. The investigator is testing whether sex differences in inflammation and pain are due to differences in the sex steroids in male and female rats. Findings from this study may help enhance our understanding of sex differences in pain, and in particular inflammatory pain. This investigator is also researching sex differences in pain modula-tion by opioid analgesics in humans. In the initial phase of this study, the investigator demonstrated that kappa (k)-partial agonist opioids produce significantly greater analgesia in females than in males. In the second phase of the study, the investigator is identifying the mechanism of the anti-analgesic action of the k-partial agonists; determining optimal doses for the specific k-partial agonist in other clinical settings; and exploring gender and ethnic differences in analgesic responses.

Several NINR investigators are examining topics related to gender differences in cardiovascular disease. CHD is the leading cause of death in women, and the incidence of CHD increases sharply following menopause. Data suggest that higher estrogen levels may protect women from developing CHD, and may protect women who already have CHD. However, the cardioprotective benefits of estrogen alone may be countered by the addition of progesterone, which is typically included in hormone replacement therapy (HRT). The mechanisms responsible for estrogen's cardioprotective benefits have not been fully identified. Recent studies have shown that estrogen appears to improve

vascular endothelial function. This study is testing the acute effects of estrogen and estrogen plus progesterone interventions on systemic vascular resistance, at rest and during stress. This research will help clarify how HRT may alter risk in CHD through hemodynamic effects that are hypothesized to be secondary to alterations in endothelial function.

Chronic stable angina pectoris, the chest pain associated with reversible myocardial ischemia, has detrimental effects on health-related quality of life, particularly in women. The limited research on gender differences in chronic stable angina suggests that angina may be experienced differently in women and that women report greater functional disability related to angina symptoms. Another NINR-funded research has conducted a descriptive study to examine gender differences in characteristics of chronic stable angina and to explore relationships among these pain characteristics and perceived limitation in performing physical activities in patients with coronary artery disease (CAD). Results of the study, recently published in *Pain,* suggest that men and women with chronic stable angina had more similarities than differences in chest pain characteristics. No significant gender differences were demonstrated in total sensory or affective intensity scores, the present pain intensity index, or the number of pain words chosen. However, women were significantly more likely to describe their chronic angina as 'hot-burning' and 'tender' and to have greater intensity of pain for these two descriptors. Despite the similarities in pain characteristics, women reported greater physical limitation related to anginal pain. This is one of the first studies that has assessed chronic anginal pain using a reliable and valid generic pain instrument, and findings indicate that more research is needed to better understand the nature of gender differences in functional limitation secondary to anginal pain and the physiologic, cognitive-perceptual, and psychosocial mechanisms that lead to angina-related functional disability.

Platelet activation in the cerebrovasculature has been implicated as a mediator of tissue injury following stroke or other ischemic events. Data suggest that premenopausal women are at lower risk than men for cardiovascular diseases, including stroke and transient ischemic attacks, conceivably due to the effects of estrogenic hormones on platelet biology or vascular function. Although many women take hormone replacement therapy, controversy surrounds the risks versus the benefits of estrogen therapy. This NINR investigator is studying the effects of elevated estrogen on platelet biology to determine if the hormone moderates alterations in pre- and post-ischemic platelet function or microvascular vasodilator capacity. Study results will help clarify the contribution of exogenous estrogen therapy in ischemic brain injury, both mechanistically and according to dosage, and contribute to our understanding of the controversy surrounding the safety and efficacy of estrogen replacement regimens.

## Initiatives

*Request for Applications (RFAs)*

- **Informal Caregiving Research for Chronic Conditions**

  This request for applications, published by NINR, solicited applications for research to advance the science in informal caregiving in the home for care recipients with chronic illness, disability, or functional impairment requiring partial or full dependency on others. (RFA: NR02-001)

*Program Announcements (PAs)*

- **Chronic Fatigue Syndrome**

  NINR is a cosponsor of this announcement which solicits applications to support research on the pathophysiology and treatment of chronic fatigue syndrome (CFS) in diverse groups across the life cycle. Epidemiological data is limited and requires further investigation. Studies suggest that CFS occurs 3 to 4 times more frequently among women than men. (PA02-034)

- **Informal Caregiving Research for Chronic Conditions**

  This program announcement, published by NINR, solicits research to advance the science in informal caregiving by focusing on care givers of individuals with chronic illness, disability, or functional impairment requiring partial or full dependancy on others. Surveys have shown that the majority of care givers are women. (PA02-155)

- **The Role of Gene-Environmental Interactions Underlying the Health Disparity of Premature Births**

  NINR is a cosponsor of this announcement that seeks applications on the role of gene-environmental interactions underlying the health disparity of premature births in the United States. This announcement seeks to better understand how adverse societal, behavioral, and environmental conditions alter gene expression and interact with diverse genetic backgrounds to increase women's susceptibility for premature birth in high-risk racial and ethnic groups. (PA02-102)

*Workshop*

- **Chronic Pelvic Pain: Pathogenic Mechanisms, Treatment, Innovations, and Research Implications**
  **April 8-9, 2002**

  NINR cosponsored this workshop to bring together a broad spectrum of experts, including clinicians and basic and translational scientists, to define a multidisciplinary framework for developing a research agenda in chronic pelvic pain in women.

*Activities Related to Health Disparities*

- NINR continues to develop and implement initiatives related to its "Strategic Plan on Reducing Health Disparities." The overall focus of this plan is to provide leadership in emphasizing the inclusion of cultural and ethnic considerations throughout the areas of scientific inquiry within NINR's domain. The three components of the NINR strategic plan on health disparities include: 1) research, 2) infrastructure, and 3) outreach. A detailed discussion of this plan is located on NINR's website at *http://www.nih.gov/ninr/research/diversity/mission.html*

## NATIONAL INSTITUTE ON AGING

The National Institute on Aging (NIA) leads a national scientific effort to understand the mechanisms of aging and to extend the healthy, active years of life to all Americans. Many of the advances in knowledge about the biological, behavioral, and social changes that occur with aging have saved lives and prevented disabilities by contributing to improvements in public health and health care. Numerous findings have challenged stereotypes about the inevitability of decline in old age, generating effective strategies that can maintain or even enhance both physical and cognitive abilities in old age. Other discoveries have provided exciting insights into the secrets of aging and longevity. These successes have the potential to benefit all generations and all women.

As baby boomers reach retirement age and medical breakthroughs, as well as more healthy lifestyles, continue to contribute to increasing life expectancy, the numbers of older American women, in particular, are projected to increase. "At her 120th birthday party, a journalist hesitantly told Mme. Calmet, "well, I guess I'll see you next year." Instantly, she shot back, "I don't see why not. You look to be in pretty good health to me!" Mme. Calmet lived longer than any other human in recorded history (NIA, 2002). Exceptional longevity is a wonder and a challenge to understand. Recent data from the census bureau statistics show that the numbers of those aged 65 and older have increased approximately 7 percent and now number 34 million, comprising about 13 percent of the general population. Projections for the middle of the century place those over age 65 at around 20 percent of the population.

Women make up a majority of the older population. In 1994, elderly women outnumbered elderly men 3 to 2 and numbered nearly 2 million. The combined factors of men generally being older than their spouses and higher life expectancy for women than men, contribute to the proportion of women living alone, the earlier institutionalization of women than men, disproportionately high level of poverty, and a need for special support (Bureau of the Census, 1996, 65+ in the United States). The death of a husband often marks the point of acute economic reversals for the surviving wife.

NIA supports a diverse portfolio of research on older women's health addressing health and wellness, basic biology of aging, neuroscience and neuropsychology of aging, diseases and conditions of older adults, and behavioral and social problems of older women. Thus, not only are the common age-related diseases under study (e.g., Alzheimers disease, Parkinson's disease, stroke, atherosclerosis, osteoarthritis, diabetes, cancer), but the determinants of healthy aging are also being defined. NIA research includes several long-term research projects that are in progress. The projects focus on physical disability, decline in function of older women, hormone therapy and menopause, hip fractures, osteoporosis and age-related muscle loss, memory, dementia and Alzheimers disease, care giver burden, and cancer in older-aged women. The following narrative describes one long-term intramural research program: Women's Health and Aging Study (WHAS) and selected highlights (Part II) of NIA studies on women's health during FY 2001 and 2002.

## Women's Health and Aging Study

Women make up a majority of the older population and report higher rates of physical disability, spend more years in the disabled state, make up a substantially larger proportion of the nursing home population, and have a greater need for formal and informal care than men. A number of important hypotheses related to disability and loss of independence in older women are being addressed by WHAS. It is a prospective study of a sample of 1,000 older, community-dwelling women with moderate to severe disability. Its unique aspect is the examination of women with disease and disability. The purpose is to understand the diseases and physiologic impairments underlying the disability, and then prospectively evaluate the course of disability and how the underlying conditions, such as health habits, psychological and social factors, and cognitive functioning, affect that course. Recent research from WHAS is described below.

### *Improved Strength and Functional Outcomes in Older Women Using Angiotensin-converting Enzyme Inhibitors*

As life expectancy continues to increase, it has become important to understand factors that contribute to physical functioning, independence, and quality of life in persons reaching advanced old age. Although some disability in the older population is a result of catastrophic events, such as stroke and hip fracture, a large proportion of disability results from progressive decline in multiple physiologic systems that lead to gradual progression of functional limitations and onset of disability. Loss of muscle mass and muscle strength plays an important role in this progressive decline; interventions targeted at preserving muscle structure and function could have a major impact on reducing age-related decrements in physical functioning. Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve physical function in patients with congestive heart failure, but these improvements have been attributed to beneficial effects of these drugs on the cardiovascular system. However, these drugs could also have a direct effect on skeletal muscle, as they influence the renin-angiotensin system, which has been associated with mechanical, metabolic, and biochemical changes in muscle. This study used data from WHAS, a longitudinal epidemiological study of the causes and course of disability in the one-third most disabled women living in the

community. Women with hypertension were stratified into four groups according to type and duration of antihypertensive treatment over 3 years: continuous use of ACE inhibitors (n=61); intermittent use of ACE inhibitors (n=133); use of other drugs (n=301); and no drug use (n=146).

**Advance**

Knee extension strength and gait speed declined very slightly over 3 years in continuous users of ACE inhibitors and declined significantly more in the other antihypertensive treatment groups. These analyses were adjusted for many potential confounders of the relationship of antihypertensive drug use with strength and gait speed, including age, race, baseline systolic blood pressure, body mass index, diabetes, ischemic heart disease, and stroke.

**Implications**

ACE inhibitor use may slow the decline in muscle strength that is seen in aging and plays an important role in loss of functional abilities.

## Highlights

The Assistant to the Director for Special Populations is responsible for providing the Director, NIA and senior staff with advice and guidance on matters relating to health research related to women and minorities and their enhanced participation in aging research; and serves as the NIA focal point for establishing NIA-wide goals for women and minority group member research and training programs and for the coordination and development of these programs. The Assistant to the Director for Special Populations works in coordination and collaboration with NIA intramural and extramural programs, as well as the Work Group on Minority Aging. The Work Group is comprised of senior staff from each of the NIA research programs, plus representation from the Office of Planning, Analysis, and Evaluation and the Office of Communications and Public Liaison.

## Accomplishments

### *Women Caring for Family Members with Dementia Can Benefit from an Exercise Program*

It is now recognized that caregiving burdens can result in a variety of negative health outcomes. Researchers have shown that individuals who exercise can benefit in terms of lower stress-induced high blood pressure and improvement in self-reported quality of sleep. Yet, no previous studies have specifically examined the impact of sustained physical activity on older care givers. This study is the first to examine the role that a regular moderate-intensity exercise program plays in the enhancement of health and quality of life for women caring for loved ones with dementia.

**Advance**

This study explores the use of an in-home, telephone-based counseling program delivered by a trained health educator. This 1-year study involved a sample of 100 women, age 49 to 82 years, who were sedentary, free of cardiovascular disease, and caring for a relative with dementia. Participants received either a home-based, telephone-supervised, moderate-intensity exercise training or nutrition education program. Exercise consisted of brisk walking for four 30- to 40-minute sessions per week. Compared with the nutrition education group, exercise participants showed clinically significant improvements in physical activity levels, stress-induced blood pressure reactions, and sleep quality. The nutrition group reported significant improvements in percentages of total calories from fats and saturated fats relative to exercisers. Significant reductions were also observed among nutrition participants in daily servings of fats, oils, sweets, and high-fat snacks. Both groups reported significant improvements in psychological distress, including depressive symptoms and self-rated stress.

**Implications**

Understanding how best to tailor programs to the needs and preferences of different populations remains a critical public health challenge. This research demonstrates that properly tailored health promotion programs can improve the health and functioning of older women family care givers.

### *Estrogen May Attenuate the Age-associated Systolic Blood Pressure Rise in Postmenopausal Women*

Although systolic blood pressure (SBP) is generally higher in men than women until middle age, this gender difference disappears after menopause, due to an accelerated rise in SBP in older women. Although the reason for this accelerated rise in SBP is unclear, the loss of endogenous estrogen production that accompanies menopause may be responsible.

**Advance**

Both cross-sectional and longitudinal data from the Baltimore Longitudinal Study of Aging (BLSA) suggest that estrogen replacement therapy (ERT) in healthy postmenopausal women attenuates their age-associated increase in systolic blood pressure. In the first study, 77 postmenopausal BLSA women, aged 67 + 11 years who were receiving ERT, had lower SBP, as well as lower diastolic BP when compared to 57 women of similar age, who were not receiving ERT.

To confirm these cross-sectional findings, investigators compared longitudinal blood pressure changes in 77 BLSA women, who remained on ERT for a mean of 5.2 years, to those of 149 similar women, who did not take estrogen. Although baseline characteristics, such as age, education, physical activity habits, body fatness, smoking status, and cholesterol levels, were similar in the two groups, the rise in SBP was less pronounced in the women receiving ERT. Furthermore, this beneficial effect of ERT was more prominent in women who began ERT at older ages, and in more obese women. Statistical analyses showed that the rise in SBP per decade in a 55-year old woman on ERT was 7.6 mm Hg, compared to 18.7 mm Hg in a non-user. Diastolic BP, however, did not significantly change, over time, in either group.

**Implications**

These studies suggest that ERT may attenuate the brisk rise in SBP that occurs with age in healthy postmenopausal women. Because the age-associated rise in SBP is an important risk factor for future coronary events and stroke, these data further suggest that long-term ERT may reduce cardiovascular risk in this large subset of the population. Definitive determination of whether estrogen exerts a protective effect will require analysis of clinical trials, such as the ongoing Women's Health and Aging Study.

### *Low-dose Estrogen Reduces Bone Breakdown in Older Women*

Estrogens have been shown to diminish bone loss (osteoporosis) in women. However, many older women are reluctant to take estrogens for prevention of osteoporosis because of side effects. These include breast tenderness, bloating, fluid retention, headache, and vaginal bleeding. Many older women and their doctors also have concerns about uncertainty regarding estrogen's effects on risks for age-related conditions, such as breast cancer and coronary heart disease. Since the risk of adverse effects of a treatment is usually related to the dose taken, the lowest dose needed to produce a desired effect (in this case, preventing osteoporosis) is preferred. Thus, it is important to determine if lower doses of estrogens than are currently used provide satisfactory protection against bone loss in women.

**Advance**

More than 100 black, Hispanic, and white women over the age of 65 participated in a study of three different doses of estrogen (17 estradiol) therapy. The highest of these doses, is the amount most commonly used today in estrogen replacement therapy, and the lowest dose was one-fourth of this amount. The participants were studied for

6 months: 3 months on treatment and 3 months off. The low dose markedly reduced bone breakdown as measured by several serum markers. This reduction was similar to that produced by the highest estrogen dose. Breast tenderness, bleeding, and thickening of the lining of the uterus (an indicator of potential adverse uterine effects), were significantly less frequent with the lowest dose. In fact, low-dose therapy resulted in no more side effects than placebo.

**Implications**

This study indicates that low-dose estrogen therapy may be an effective, safer, and more tolerable intervention for osteoporosis prevention in older women, compared to the commonly prescribed higher-dose therapy. With fewer undesirable side effects, low-dose therapy could not only provide an alternative for older women currently taking estrogens, but could also provide an acceptable treatment for those who would otherwise decline to take estrogens or discontinue treatment because of adverse side effects. Long-term studies are needed to determine whether the effects on bone metabolism seen with low doses estrogens will translate into increases in bone density and decreased incidence of fractures.

## *Cardiovascular Disease, Interleukin-6, and Risk of Mortality in Older Women*

The presence and severity of chronic disease conditions may explain the association between elevated circulating markers of inflammation and the risk of mortality. Systemic chronic inflammation has been found to be related to all-cause mortality risk in older persons, but the underlying mechanisms are not fully understood. Interleukin-6 (IL-6) is a marker of inflammation, and was measured in women enrolled in the Women's Health and Aging Study, a prospective study of the causes and course of disability among moderately to severely disabled older women living in the community. Findings confirm that serum IL-6 level is helpful in identifying a subgroup of older women with cardiovascular disease who are at high-risk of death over 3 years. Although IL-6 was not specifically related to cardiovascular mortality, these results suggest that the relation with mortality is not explained simply by the presence and severity of other existing diseases and that systemic inflammation, as measured by serum IL-6, may be related to poorer clinical outcomes in women with cardiovascular disease.

## *Newly Understood Action of Sex Hormones Points the Way to New Treatment for Osteoporosis*

One cause of osteoporosis (loss of bone) in women is loss of estrogen production at menopause and a consequent imbalance between bone-building and -destroying cells. When estrogen is lost at menopause, bone-destroying cells live longer, and bone-building cells show a shortened life span. Estrogen acts on multiple tissues and by several pathways. New research identifies a rapidly acting pathway for both estrogens and androgens, and shows that this pathway functions to extend the life of bone-building cells in culture. This work could lead to new treatments for low bone density and osteoporosis using specially modified estrogen-like drugs that have selective positive action on bone-building cells without the unwanted side effects of estrogen. Since estrogen affects multiple tissues, the possibility of activating specific pathways for selected estrogen effects in these tissues also holds broad potential for improvement of health and treatment of disease in both men and women.

## *Importance of Local Estrogen Biosynthesis in Improved Cardiovascular Function*

Estrogen appears to protect women from atherosclerosis during their reproductive years, while loss of estrogen after menopause appears to increase their risk. Androgens are thought to confer an increased risk of atherosclerosis and are associated with increased lipid-associated risk factors, particularly in several animal models on high cholesterol diets. Recent studies in mice show cardioprotective effects for

testosterone, however. Cardiovascular tissue appears to be able to convert testosterone to estrogen, so testosterone may, in fact, play a protective role against cardiovascular disease. In this study, testosterone attenuated early atherogenesis in castrated mice, most likely through conversion to estrogen in walls of blood vessels. Local estrogen production, whether in cardiac, bone, or brain tissue, may provide sufficient protection directly at the sites where needed, and thus avoid the need for systemic estrogen treatments, which may create an increased risk for adverse health events, such as breast cancer.

### *Raloxifene Does Not Affect Cognitive Function in Postmenopausal Women*

Estrogen replacement therapy (ERT) is used to treat menopausal symptoms and reduce the risk of osteoporosis and heart disease. ERT may also have a beneficial effect on cognition, but increases the risk of breast or uterine cancer in some women. Raloxifene is a selective estrogen receptor modulator (SERM) used for the prevention and treatment of osteoporosis that is not associated with an increased risk of breast or uterine cancer. Raloxifene had not been tested for either positive or negative effects on cognitive function. Results from the Multiple Outcomes of Raloxifene Evaluation trial indicated no significant differences between the treatment groups and controls in performance on cognitive tests or the development of dementia after 3 years, although there was a slightly lower risk of cognitive decline in verbal memory and attention with raloxifene treatment. Women who choose raloxifene treatment for osteoporosis can be reassured that it does not have negative effects on cognitive function.

### *Positive Emotions in Early Life Linked to Longevity*

Findings from the Nun Study indicate that positive emotional content in early life autobiographies was strongly associated with longevity six decades later. Nuns who expressed more positive emotions in their autobiographies lived significantly longer than nuns expressing fewer positive emotions. Finding such a strong association between written positive emotional expression and longevity indicates a need for research that sheds light on the underlying mechanisms responsible for and associated with this relationship.

## Study of Women's Health Across the Nation

Study of Women's Health Across the Nation (SWAN) is an ongoing cohort relevant to examining potential longitudinal changes with aging. Funded initially in September 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center (CC), an advisory panel, and a repository of blood, urine and DNA specimens. The study is supported by NIA (GCG and BSR), the National Institute of Nursing Research, and the NIH Office of Research on Women's Health. Ancillary studies are supported by NNA/NIA, NIMH, NHLBI, and the National Center for Complementary and Alternative Medicine.

The specific aims of SWAN are to elucidate the menopausal transition in a cohort of socially and culturally diverse women and: 1) to describe the symptoms, hormonal changes, and bleeding patterns of the menopausal transition; 2) to relate these patterns to changes in the amount of fat and lean, markers for osteoporosis, heart disease, and diabetes; 3) to relate personality and behaviors, including lifestyle behaviors and use of menopausal hormone therapy, to age at onset, symptoms, and physical changes of the menopause transition; 4) to differentiate what are menopause-related changes and what are age-related changes; and finally, 5) to describe cultural and ethnic differences among women with respect to their midlife aging and the menopausal transition. SWAN is a prospective, multicenter,

multiethnic, multidisciplinary study of the natural history of the menopausal transition in African American, Caucasian, Chinese, Hispanic, and Japanese women who were premenopausal, not taking hormones and between 42 to 52 years of age at the time of enrollment. The overall study design includes a cross-sectional study and a longitudinal cohort study using common protocols at the seven sites. Two additional sources of data, the monthly menstrual cycle calendars and the annual 28-day daily urine specimen and diary data collection, are critical in more precisely characterizing the menopause. A variety of methods were used to recruit a sample of multiethnic women. A total of 202,985 households or telephone numbers were screened for women eligible to participate in the SWAN Cross-sectional Study, of whom, 16,065 women were found to be eligible and have completed the interview. Of these, 6,521 women were cohort-eligible and invited to participate in the SWAN Longitudinal Study; a total of 3,306 women entered the Longitudinal Study.

In the longitudinal phase, a cohort of premenopausal women from the cross-sectional phase were enrolled beginning in January of 1996. The fifth annual follow-up visit was completed at the end of 2002; the sixth follow-up visit is nearing the half-way mark. A SWAN Symposium (February 14, 2002, Bethesda, Maryland) was organized by a number of SWAN investigators. The aims of the symposium were to update NIA on the current status and findings of the study and to introduce the plans, objectives, and rationale for a 5-year renewal application which was proposed to be submitted in FY 2002 to continue follow-up of the cohort. A central goal of the symposium was to solicit opportunities for input and collaboration by staff throughout NIA and from representatives of other NIH institutes and offices (who were in attendance). SWAN investigators have been productive and a sample of research outcomes follows.

### *Racial and Ethnic Differences in DHEA Levels during the Menopause Transition*

There is widespread belief that DHEAS may play a role in preventing diseases of aging because: 1) it is an abundant circulating steroid and potentially an important androgen and estrogen precursor, and 2) more than 80 percent of its secretion declines between the ages of 20 and 70 years opposite to the increasing risk of the chronic diseases of aging and in association with the development of atherosclerosis, insulin resistance, and even cardiovascular mortality. Because DHEAS replacement studies have reported some beneficial, but inconsistent (especially inconsistent with respect to gender), effects related to immune function, mood, and other outcomes, the role of DHEAS in the aging process remains an intriguing biological question. Data from SWAN indicate significant ethnic and racial differences with the highest levels among Chinese and Japanese women, and lowest levels among African American and Hispanic women (even after adjustment for confounders, such as BMI). Importantly, circulating DHEAS levels did not decline at a steady rate during the menopausal transition, and in fact, actually increased transiently (especially during the transition to late perimenopause) in some women. Changes in circulating testosterone, and to a lesser extent, estradiol, were correlated to changes in DHEAS. These data are important in understanding the endocrinology of the menopause transition, defining the relationship of adrenal steroid production during declining ovarian function, and determining a rationale regarding supplementation with DHEAS or other androgens for older women.

### *Ethnic Group Differences in Bone Density May Explain Differences in Risk of Fracture*

Bone mineral density (BMD) and fracture rates vary among women of differing ethnicities. Most reports suggest that BMD is highest in African Americans,

lowest in Asians, and intermediate in Caucasians; yet Asians have lower fracture rates than Caucasians. To assess the contributions of anthropometric and lifestyle characteristics to ethnic differences in BMD, lumbar spine and femoral neck BMD was assessed by dual-energy x-ray absorptiometry in over 2,200 premenopausal or early perimenopausal women (mean age, 46.2 years) participating in SWAN. Before adjustment for covariates, lumbar spine and femoral neck BMDs were highest in African American women, next highest in Caucasian women, and lowest in Chinese and Japanese women. Unadjusted lumbar spine and femoral neck BMDs were 7 to 12 percent and 14 to 24 percent higher, respectively, in African American women than in Caucasians, Japanese, or Chinese women. After adjustment, lumbar spine and femoral neck BMD remained highest in African American women, and there were no significant differences between the remaining groups. When BMD was assessed in a subset of women weighing less than 70 kg, lumbar spine BMD became similar in African American, Chinese, and Japanese women, and was lowest in Caucasian women. Femoral neck BMD was highest in African Americans and similar in Chinese, Japanese, and Caucasians. It was concluded that among women of comparable weights, there are no differences in lumbar spine BMD among African American, Chinese, and Japanese women, all of whom have higher BMDs than Caucasians. These findings may explain why Caucasian women have higher fracture rates than African Americans and Asians.

### *Joint Pain in African American Women is More Likely to be Associated with Radiographic Osteoarthritis of the Knee Compared to Caucasian Women*

Radiographic osteoarthritis of the knee (OAK) has been the standard case definition of OAK in epidemiologic studies; however, symptomatic OAK, typically defined by self-reported knee pain, is the most common presenting symptom of the clinical problem. In most studies, while there is an association between radiographic changes of OAK and self-reported pain, there are a considerable number of persons with discordance of these findings. Clinically, it is well recognized that individuals may have radiographic evidence of OAK without pain symptoms, and that there are those who report having knee joint pain, but do not have radiographic evidence of OAK. An analysis was conducted of a combined data set from pre- and perimenopausal participants of SWAN and of the Michigan Bone Health Study to determine how correlates related to pain and radiographic outcomes of OAK differ between African American and Caucasian women. Similar to other studies, previous knee injury was associated with knee pain in both African American and Caucasian women. Although the odds of having radiographic OAK increased with BMI >32 kg/m2 in both groups, knee pain was related to BMI only in Caucasian women. Because joint pain in African American women was more likely to be associated with radiographic OAK compared to Caucasian women, there may be differences between these populations in both how pain is experienced in the OAK process. Resolution of the incongruency between radiographic evidence and report of pain will become important as treatment options for OA expand, because efficacious treatment will require an understanding of the full scope of characteristics determining joint structure changes and the experience of pain.

In brief summary, millions of American women are leading healthier lives based, in part, on discoveries from aging research. NIA is working with ORWH and other components of NIH to ensure an overall strategy to advance women's health research that will result in improved health and healthy longevity for all women.

## Initiative

- **Building Interdisciplinary Research Careers in Women's Health**

  This initiative is cofunded with the Office of Research on Women's Health and seeks to support research career development of junior faculty members, to be known as Interdisciplinary Women's Health Research Scholars, who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, clinical, and/or health services research relevant to women's health. The goal of this initiative is to promote the performance of research and transfer of findings that are relevant to women's health, including sex and gender similarities or differences in biology, health, or disease. (RFA-OD-02)

# NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports research on the biomedical and behavioral causes and consequences of alcohol use, abuse, and alcoholism, and on new and improved ways to prevent and treat these significant public health problems. Alcohol abusers, alcoholics, and their families – an estimated 98 million Americans – are the primary potential beneficiaries of this research. Society as a whole will also benefit from reductions in the high social, economic, and human costs of alcohol abuse and alcoholism to our society. These costs are estimated to be $185 billion and in excess of 100,000 deaths annually.

Of the 13.8 million alcohol-abusing or alcohol-dependent individuals in the United States, over one-third (approximately four million) are women. Women drink less alcohol and have fewer alcohol-related problems and dependence symptoms than men. However, among the heaviest drinkers, women equal or surpass men in the number of problems that result from their drinking. Further, the proportions of young men and women who begin drinking at age 13 are similar, and young people who begin drinking at this age are four times more likely to develop alcohol dependence sometime during their lifetimes than young people who begin drinking at age 21.

Our most comprehensive knowledge about alcohol use, abuse, and dependence among women comes from the 1992 NIAAA National Longitudinal Alcohol Epidemiologic Survey (NLAES). This survey collected data on alcohol consumption and alcohol problems and related disorders in a nationally representative sample of 42,862 adults 18 years of age and over. According to the NLAES findings, women are less likely to be drinkers than men (34 vs. 56 percent) and are more likely to be abstainers than men (45 vs. 22 percent). Women also were found to have started drinking about 1½ years later than men, on average. The findings, both with regard to the percentage of women who drink and the percentage who abstain, are consistent with the findings from epidemiological studies over the past 30 years. A recent NIAAA-supported study, in fact, has found that this pattern of drinking is not only consistent across time, but across countries and cultures worldwide.

## Accomplishments

### *Psychosocial Determinants of Drinking in Women*

**Sexual Harassment, Gender, and Drinking**

Findings from a study on the role psychological distress plays in mediating the relationships between harassing and abusive interpersonal experiences in the workplace and alcohol use and misuse suggest that distress engendered by workplace harassment and abuse contributes to increased alcohol use and misuse. This longitudinal study population included 1,098 female and 940 male employees at a Midwestern university. Results from the study indicated that generalized workplace abuse (GWA) is predictive of psychological distress (depression, anxiety, and hostility) in women and that sexual harassment (SH)

is predictive of psychological distress in men and women. Furthermore, depression, anxiety, and hostility were positively correlated with nearly all alcohol outcomes, including higher frequency and quantity of drinking, heavy episodic drinking, and drinking to intoxication. When distress variables were included in the analysis, chronic generalized workplace abuse and the onset of sexual harassment remained significantly predictive of quantity of drinking, although the strength of the associations was diminished.

In another analysis of data from this study, investigators evaluated the relationship between active coping efforts to counter sexual harassment (SH) and generalized workplace abuse (GWA), and the positive relationship between SH/GWA and alcohol use and abuse. Their results showed that active coping had no significant impact on the ability to end harassing or abusive experiences. Moreover, the use of problem-focused coping strategies that were unsuccessful was predictive of some drinking outcomes for both women and men.

**Gender Differences in Alcohol Use among American Indians**

A comprehensive prevention study, based on active surveillance in four American Indian communities, found differential patterns of drinking. Some Indian adults are very heavy drinkers who drink daily, and most drinkers are binge drinkers who typically exhibit a modal pattern of abstinence. Although some non-Indian segments of the U.S. population engage in similar binging patterns, this pattern of infrequent drinking on any given day among Indians exerts disproportionate morbidity and mortality, including higher rates of FAS and ARBD than occurs in the general population. While Indian men drink more frequently and in larger quantities than women, the highest prevalence and heaviest drinking occurs among both women and men less than 30 years of age; and the overall consumption of alcohol decreases during mid-life years. These findings suggest that more research is needed to investigate social and psychological factors that influence drinking patterns in order to develop targeted prevention interventions to reduce alcohol-related problems among American Indians.

**Comparison of Alcohol Consumption by Lesbian and Heterosexual Women**

Research examining the relationship between sexual assault and alcohol abuse in heterosexual and lesbian women has found some differences in drinking levels between these groups. In a study involving 63 lesbian and 57 demographically matched heterosexual women, investigators found that while the majority of women in both groups were current drinkers, a greater percentage of lesbians than heterosexual women were 12-month abstainers. Although no lesbians reported being lifetime abstainers, a number of heterosexual women did. In addition, significantly more lesbians than heterosexual women reported being in recovery. Lesbians were also more likely to meet the study definition for childhood sexual abuse (CSA). CSA was associated with lifetime alcohol abuse for both the lesbian and the heterosexual women. The results of this study should be interpreted cautiously since the sample sizes are relatively small.

**Drinking and Comorbid Eating Disorders**

Eating disorders affect approximately 10 percent of women between the ages of 15 to 30 years of age and often co-occur with psychiatric disorders, including alcohol abuse and dependence. Findings from a longitudinal study of over 3,000 non-treatment-seeking college students showed that women with bulimia nervosa reported significantly more severe alcohol-related problems than non-eating disordered women. The study found that eating disordered women do not drink more frequently or in greater quantity than non-eating disordered women. However, alcohol-related negative consequences, including interpersonal, academic and feelings of alcohol dependency, were reported by bulimic women up to twice the rate of non-eating

disordered women. These findings suggest that prevention interventions offering coping skills for high-risk circumstances may benefit women with eating disorders.

## *Biobehavioral Correlates of Alcoholism in Women*

### Genetic Risk Factors for Alcoholism

Although alcoholism and other psychiatric disorders are substantially inherited in both men and women, rates of several psychiatric disorders differ between men and women. Men are more likely to develop alcohol dependence. Women are more likely to experience anxiety and depression. The NIAAA Laboratory of Neurogenetics has recently provided evidence for a sex effect of a specific vulnerability gene which helps explain some of these differences. The gene is COMT, a key enzyme in the metabolism of catecholamine neurotransmitters, including dopamine (involved in reward, movement, and cognition) and norepinephrine (involved in anxiety). Val158Met is a common functional polymorphism of COMT which has been linked to alcoholism and other behaviors. The Met158 allele, which is associated with better cognitive function, is also associated with a higher stress and pain response. Recently, researchers have found that this same Met158 variant leads to higher levels of anxiety in women from two populations, but not men. These results emphasize the need to study women in order to define gender-specific and -influenced factors in the etiology of alcoholism and other psychiatric disorders.

### Cerebral Structural and Metabolic Correlates of Aggressive or Addictive Behavior

Research is ongoing to determine neuroanatomical and neurochemical correlates of addictive and aggressive and impulsive behavior in human subjects. The principal focus of these studies is the measurement and correlation of regional cerebral glucose metabolic activity, using positron emission tomography (PET); brain volumes using magnetic resonance imaging (MRI); cerebrospinal fluid metabolites; and measures of impulsive and aggressive behavior and excessive alcohol consumption. Prior research in this area has demonstrated that alcoholics show greater brain degeneration over time than non-alcoholics, and that women appear to be more affected than men. In addition, female and male alcoholics have smaller intracranial volumes than controls. Since intracranial volume is a function of growth and not affected by the brain degeneration normally seen with aging, this finding suggests that alcoholics may have mildly reduced brain sizes, even before they begin drinking heavily. In more recent research, investigators have begun using functional magnetic resonance imaging to examine brain activity related to motivation. These studies have shown that men and women develop identical patterns of brain activation while anticipating working for a monetary reward. In contrast, both male and female alcoholics show a blunted activation in the brain regions activated by reward in non-alcoholics. These studies provide an illustration of how addictive substances take over the brain's normal reward circuits, making them less responsive to normal motivation.

## *Violence and Other Social Consequences of Alcohol Misuse*

### Ethnicity, Alcohol, and Partner Violence

The effect of alcohol use on interpersonal relationships within families is substantial. Many of these effects are negative and vary with race, ethnicity, and SES characteristics of the family. This study evaluated the hypothesis that past-year alcohol-related problems and drug use, by either or both male and female partners, was associated with severe male-to-female inter-partner violence (MFIPV) by analyzing data from a national household sample of couples (both married and unmarried). Results support previous findings that problems with alcohol and other drugs are associated with increased MFIPV and increases their generalizability. Both male and female partner alcohol use problems independently predicted MFIPV; female (but not male) drug use also predicted MFIPV.

Female compared to male alcohol and other substance use problems were each stronger predictors of MFIPV. For both sexes, prediction was much stronger for severe compared to moderate MFIPV.

**Effect of Alcoholism Treatment on the Incidence of Domestic Violence**

In a study of male alcoholics treated in AA/12-step oriented treatments, the prevalence of male-to-female overall violence was 56 percent in the year before treatment, four times the prevalence of 14 percent in a comparison community-based sample. At 1-year post-treatment, the prevalence of overall male-to-female violence was 15 percent, nearly identical to the comparison sample, whereas its prevalence was 32 percent among relapsed patients.

**Impact of Spousal Aggression on Women's Drinking Patterns**

This study explores drinking patterns over the transition to marriage to assess whether changes in drinking patterns are influenced by husband-to wife physical aggression. Over 500 couples, who were recruited after applying for their marriage licenses, are participating in a longitudinal study of marriage and alcohol. Couples have completed questionnaires at the time of marriage and at their first anniversary. Longitudinal analyses indicated that wives who experienced physical aggression from their husbands during the first year of marriage reported increased stress, lower levels of marital satisfaction, and were more likely to report separation from husbands due to marital problems. In addition, experiences of partner physical aggression prior to marriage was associated with a higher frequency of heavy drinking episodes among wives. Results suggest that experiences of husband-to-wife aggression have negative consequences for women's psychological well being and marital functioning.

**The Role of Alcohol Use on Women's Victimization**

A study using event-level data found that incidents involving *mutual* substance use were more likely to result in rape, take place outside the home, and involve perpetrators who were less well-known to the victim compared to incidents where the perpetrator was the only one drinking or where neither person was using substances. Findings suggest that women from a representative sample, who meet standard criteria for alcohol abuse or dependence, report similar types of victimization experiences as do women in substance abuse treatment, and that a history of childhood sexual abuse contributes to less stable and poorer-quality intimate relationships, characterized by physical and sexual aggression in later life.

**Alcohol Use and Interpersonal Violence**

A comprehensive pilot study testing an intervention to reduce abusive behavior in adolescent-dating relationships conducted measures among 400 13- to 17-year olds. The study found that female adolescents who use alcohol are over three times more likely to be victimized than are their peers who abstain from alcohol use.

**Alcohol, Aggression, and Women**

Recent evidence suggests serotonin function confers vulnerability to the aggression-increasing effects of alcohol among women. This is inferred by comparing the effects of manipulating plasma levels of alcohol and the precursor of serotonin, L-tryptophan (and ultimately serotonin levels in the central nervous system), on aggression in female subjects. In these studies, subjects are given the opportunity to aggress toward a fictitious person who ostensibly presents an aversive stimulus to the subject. The effects of alcohol and amino-acid drink mixtures, which either increase or decrease plasma L-tryptophan levels, are compared at different time points in two groups of women at two different phases of the menstrual

cycle associated with differential serotonin function. The two groups differ in the severity of menstrual-related symptoms experienced at various points in the menstrual cycle. Results suggest tryptophan depletion increased aggression in women, whereas tryptophan augmentation decreases aggression. Acute alcohol administration produced differential alcohol-induced aggression which depends on menstrual cycle phase. Work on this project demonstrates a causal relationship between brain serotonin function and aggression in women. It identifies women who are susceptible to alcohol-heightened aggression, and reveals a biological mechanism for this susceptibility.

### Alcohol's Affect on Women's Job Quality and Earnings

Understanding the relationship between alcohol problems and labor market outcomes is a key for understanding the impact of alcohol problems and economic well being. Research, using a nationally representative sample of young women, showed that higher levels of drinking are strongly associated with lower wages and benefit levels. The negative effect of alcohol use on compensation and job quality appears to work through years of schooling and other forms of human capital development. Interestingly, the effect of heavy drinking on job outcomes is more strongly negative than that for alcoholism. This may result from reporting issues that hamper researchers' ability to identify alcoholics in surveys, or from a selection process by which female alcoholics, who manage to remain in the labor force, are high achieving relative to their peers who have dropped out.

## *Impact of Alcohol Use and Misuse on Women's Physiology*

### Chronic Brain Effects in Alcoholic Women

Up until recently, very little was known about brain structural and functional changes in alcoholic women. However, cognitive and neuroimaging studies are beginning to focus on brain changes resulting from chronic alcohol consumption in women and compare them to those previously found in men. For example, neuropsychological deficits in men are most notable on tests of executive and visuospatial ability and functions of gait and balance, even after 1 month of sobriety. In a recent study of alcoholic women who were sober on average for 3.6 months, functions most severely affected were visuospatial and verbal and nonverbal working memory processes, as well as gait and balance. Areas of relative sparing in the women were executive functions, declarative memory, and upper limb strength and speed. Furthermore, total amount of lifetime alcohol consumption was a predictor of severity of cognitive impairment, suggesting a dose effect of alcohol abuse in women that is not seen in men. Thus, while some areas of cognitive dysfunction overlap with those of men, there are some differences between men and women in the pattern of neuropsychological deficits associated with chronic alcoholism.

Working memory and visuospatial deficits that are detectable in alcoholic women suggest a disruption in connections of the neural circuitry involving particular areas of the brain, the prefrontal and superior parietal regions. However, unlike men, structural brain changes are not consistently identified in women using techniques aimed at measuring brain macrostructure. A recent study using diffusion tensor imaging (DTI) identified abnormality of the microstructure of cerebral white matter in alcoholic compared to control women not detectable with conventional magnetic resonance imaging (MRI). Whereas gross measures of corpus callosum are similar in the alcoholic and control women, DTI revealed alcohol-induced disruption of white matter integrity. The white matter abnormalities are related to lifetime alcohol consumption and correlated with a test of visual search in the women. Furthermore, there are gender-related differences on the DTI measures in different areas of the corpus callosum.

**Alcohol, Estrogen Replacement Therapy, and Cognition in Menopausal Women**

Research on the positive cognitive effects of estrogen replacement therapy (ERT) in postmenopausal women has produced mixed results, possibly due to confounding factors, including alcohol consumption. Since many postmenopausal women drink alcohol, recent studies have investigated the possible interactive relationship between moderate alcohol use and ERT on cognitive and psychosocial functioning in postmenopausal women. So far, results suggest that ERT and alcohol have an interactive effect on several domains of cognitive and psychosocial functioning, but this relationship is complex. For example, when considered alone, ERT does not differentially benefit concentration and attention. However, when alcohol consumption is taken into account, light drinking (one to three drinks per month) ERT nonusers have better attention and concentration than their ERT-using peers. For visual learning and visual-spatial processing, the relationship between moderate levels of alcohol consumption and HT becomes more complex. For example, the combination of ERT plus Progestin may be more beneficial to visual-spatial processing than ERT alone, but only at light-drinking levels (one to four drinks per month). As alcohol consumption level continues to increase beyond moderate weekly (one to four drinks per week), the beneficial effect of progestin on visual-spatial processes disappears. More research is needed to identify key factors that play a specific mediating role in the complex multidimensional relationship between alcohol consumption, ERT, and cognition.

**Moderate Alcohol Consumption and Estradiol Levels in Postmenopausal Women**

This research evaluated two mechanisms as possible contributors to the increase in postmenopausal estradiol levels associated with moderate alcohol consumption: alcohol stimulating the production of adrenal steroids (thereby increasing the availability of precursor androgens) and alcohol increasing aromatization of precursor testosterone to estradiol (E2). The authors reported estimated aromatization and adrenal stimulation as independent contributors to postmenopausal estradiol levels. The results indicated that among black women who drink alcohol there was a trend towards lower E2 levels, no difference in the aromatization estimate, and a significant increase in the adrenal stimulation estimation, raising the question of a potential role of polymorphisms in metabolism of alcohol and estradiol.

**Alcohol Consumption and the Risk of Hypertension**

In a prospective study of the association of moderate intake of alcohol (wine, beer, liquor) and the risk of developing hypertension in women, light drinkers (those who consumed 0.25 to 0.50 drinks per day) showed a modest decrease in risk (RR=0.86) compared with non-drinkers; more regular heavy drinkers (those who consumed >2 drinks per day) showed an increase in risk (RR=1.31). A sample of nearly 71,000 women, between 25 and 42 years of age (from the prospective cohort Nurses' Health Study II), were followed for 8 years, during which time 5.9 percent of the women reported incidents of hypertension. After adjustment for confounding factors, including body mass index, the authors found that the association between alcohol consumption and the risk of hypertension in this population follows a J-shaped curve. These findings were similar for beer, wine, and liquor. For all alcohol types, the risk of developing hypertension tended to increase with drinking more than one drink per day. Episodic drinking (>10.5 drinks over 3 or fewer days per week) was not associated with increased relative risk, although regular intake of >1.5 drinks per day was associated with an increased risk of hypertension in these women.

**Gender Differences in Alcohol-induced Effects on the Neuroendocrine System**

Investigators supported by NIAAA are actively investigating the effects of alcohol use on the hypothalamic-pituitary-adrenal (HPA) axis in relation to stress and immunity. Alcohol exposure profoundly alters many

biochemical functions in the body carried out by the neuroendocrine system. This system is composed of the nervous and endocrine/hormonal systems, which helps ensure communication among various regions of the body. The neuroendocrine system is controlled by the HPA axis, a region within the brain responsive to stress, whether internally imposed or externally generated. Brain cells in the HPA axis produce minute amounts of peptide hormones that mobilize host defenses, such as the familiar 'fight or flight response' or the changes that occur in response to immune 'stressors', such as infections. The investigators have recently shown that the HPA is activated to a greater degree in rats exposed to alcohol prenatally, as evidenced by increased secretion of corticotrophin releasing factor (CRF) in response to various stimuli. This prenatal influence is significantly greater in male compared to female animals. These researchers conclude that alterations in HPA axis activity in adult offspring of alcohol-exposed dams may be related to changes in the hypothalamic responsiveness to nitric oxide.

**Increased Susceptibility of Women to Alcoholic Liver Disease**

Alcoholic liver disease (ALD) is a major cause of mortality and morbidity in this country. Although men account for a higher number of liver cirrhosis cases, women are more susceptible than men to ALD. Women develop this disease more rapidly than men and with lesser amounts of alcohol intake. Using a rat model of ALD, NIAAA-supported researchers are investigating the underlying mechanisms of increased susceptibility of women to ALD. In this study, alcohol-induced liver injury was more severe in female rats than in male rats. Female rats had higher levels of plasma endotoxin, and higher levels of certain markers of oxidative stress (i.e., lipid peroxidation products, iron) in the liver. In addition, female rats had more early markers of inflammation. These results suggest that greater increases in plasma endotoxin levels and oxidative stress and associated increased inflammatory mediators may be responsible for increased susceptibility of women to alcohol-induced liver injury.

## *Drinking during Pregnancy*

**Maternal Alcohol Use during Pregnancy**

Studying the long-range developmental consequences for children exposed to alcohol prenatally continues in two prospective longitudinal studies. These studies continue to uncover deleterious outcomes in the areas of cognitive and social functioning among individuals exposed to alcohol prenatally. Recent research has revealed evidence of neurological deficits in learning and memory skills, as measured by the Wide Range Assessment of Memory and Learning, at 10 years of age in children prenatally exposed to alcohol.

Given the potential adverse consequences of maternal alcohol consumption during pregnancy, the feasibility of and approach to screening pregnant women for alcohol use is an important issue. One study, examining the feasibility of screening women attending general obstetrics clinics for current and previous alcohol drinking behaviors and problems, found that over 90 percent of women attending the clinics agreed to fill out a self-administered questionnaire while they waited for their medical appointments. Consistent with other studies, the researchers identified approximately 15 percent of the participating women as having drunk some alcohol during their pregnancy. While most drank at very low levels, about 25 percent of those who consumed some alcohol were identified as higher-risk drinkers (drinking greater than one drink per week and/or any binge drinking during pregnancy). An indirect measure reflecting outcomes from drinking alcohol identified additional higher risk women, some of whom were not identified by the questions addressing quantity and frequency of drinking. The investigators, therefore, recommend the use of both direct and indirect ascertainment of alcohol use during pregnancy. They concluded that alcohol screening in obstetrics clinics is feasible and acceptable to women.

**Maternal Report of Prenatal Alcohol during the Antenatal Period Predicts Offspring Outcome More Accurately than Retrospective Reporting**

Alcohol drinking during pregnancy is linked to fetal alcohol spectrum disorders (FASD), a constellation of cognitive and neurobehavioral deficits that result in life-long problems for the affected offspring. Research has shown that maternal self report of alcohol use is correlated to infant outcomes. However, evidence that women underreport the amount of alcohol consumed when they are interviewed in the prenatal clinic suggests that poor infant outcome may be associated with heavier prenatal exposure. To help resolve this issue, the validity of antenatal and retrospective reports of pregnancy drinking, in relation to infant neurobehavioral outcomes, were directly compared for the first time. As expected, women reported higher levels of alcohol when interviewed at 13-months postpartum compared to clinic reporting. However, only the antenatal reporting predicted poorer cognitive performance on four infant neurobehavioral measures that are known to be affected by alcohol. This finding demonstrates the importance of asking about alcohol use while the woman is pregnant in order to minimize the risk of failing to detect adverse alcohol effects in the infant, and also suggests that threshold values for alcohol-related deficits derived from prenatal reports are reasonably accurate.

**Drinking Patterns among Mothers At-risk for Having Children with Fetal Alcohol Syndrome**

In a comprehensive prevention study of four American Indian communities, women who were current drinkers were found to have periods of abstinence of up to 28 days compared to 25 days for men. However, when engaged in binge drinking, women consumed on average more than five drinks per occasion (compared to seven to nine for men). A large proportion of the community felt that alcohol should not be served to pregnant women, and that hours of operation for bar and package outlets should be limited.

A second arm of this study is examining the prevalence of FAS and assessing the characteristics of children with FAS and their mothers in the Western Cape Province of South Africa. Preliminary results show that mothers of children with FAS initiated drinking at an earlier age and reported higher rates of heavy drinking in their extended family when compared to controls.

**Effect of Brief Intervention on Alcohol Use among Pregnant Women**

Progress on a recent study of pregnant women receiving prenatal services in 12 Women, Infants and Children (WIC) clinics demonstrated decreased alcohol consumption among women who received brief interventions when compared to women who received screening only or the WIC standard of care. Seventy-seven percent of women who received brief interventions reported no drinking during pregnancy compared to 50 percent who received screening only. Findings indicate that brief intervention can result in significant decrease in the consumption of alcohol during pregnancy.

**Effect of Brief Intervention on Postnatal Drinking Behavior**

A preliminary analysis of a current study of women receiving prenatal services in private OB-GYN clinics in Wisconsin, and who engaged in binge drinking during pregnancy, showed that women who received brief intervention demonstrated less alcohol use post-delivery than women in the control group. Results suggest the need for continued, long-term postpartum followup of reduced alcohol consumption among women binge drinkers.

## *Treatment of Women with Alcohol Use Disorders*

**Screening and Treatment for Homeless Women**

Understanding alcohol screening and the use of alcohol treatment and other medical care services among vulnerable women is

crucial for designing and evaluating public policies aimed at expanding access to services. Results of an ongoing study of homeless women living in the Los Angeles area showed that women with a history of alcohol use were more likely to report being screened for alcohol problems than those without a comparable history. High rates of screening among alcohol-abusing and -dependent women stem from the fact that these women are more likely to have had contact with the health care delivery system through a recent hospitalization.

## Initiatives

### Psychosocial Determinants of Drinking in Women

- **Rape and Risk of Heavy Drinking among Women**

  A new NIAAA study will use a mail survey of approximately 1,000 respondents from three distinct rape victim populations (college students, community residents, and mental health agency clients) to assess the role of social reactions in the victim's adjustment to the rape experience. The study will evaluate how sexual assault experiences may engender negative social reactions in members of the victim's social network, and investigate whether these negative reactions are associated with maladaptive victim responses. Such maladaptive responses could lead to more psychological symptoms and drinking problems among victims who have positive expectancies involving alcohol's self-medication function. A followup study of the most recent victims will investigate how reactions to disclosure of their experiences, any intervening sexual assaults, alcohol expectancies, coping, and other attributions affect PTSD symptom severity and subsequent drinking problems.

- **Changes in Alcohol Consumption among Lesbian Women Over Time**

  A newly funded study involves the re-interview of 450 lesbians recruited in an earlier study to examine changes in drinking patterns over the 3 years between the initial and followup interviews. The project will develop models of risk and protective factors associated with heavy drinking and drinking-related problems in the lesbian population across age and racial and ethnic groups.

- **Influence of Work Role on Women Managers' Alcohol Use**

  A longitudinal study of 1,244 men and women in a large manufacturing organization found that managerial women reported substantially higher levels of alcohol consumption and problems than nonmanagerial women, male managers, and male nonmanagers. Future research will include examination of the influence of specific work stressors and types of coping responses on changes in alcohol use and problems among a larger sample of women managers (Moore, Grunberg & Greenberg, 2001).

### Violence and Other Social Consequences of Alcohol Misuse

- **Preventing Domestic Violence**

  Domestic violence is a problem of major proportions in the United States. Federal Bureau of Investigation statistics indicate that 30 percent of all the women murdered in the United States are killed by their spouse or significant other. Perpetrators with the highest chronic alcohol consumption were the most likely to be violent. To date, there are no studies that have specifically examined the effectiveness of pharmacological interventions to decrease aggression in perpetrators of domestic violence. Since serotonin reuptake inhibitors (SSRI) have been shown to decrease aggression in other patient populations, NIAAA is currently conducting a protocol to examine the effectiveness of SSRIs in reducing aggression in perpetrators of domestic violence. In this protocol, perpetrators of domestic violence are randomized according to a

double-blind design to receive either the SSRI, fluoxetine, or placebo. All participants receive psychotherapy while being carefully monitored in the NIAAA outpatient clinic for 3 months. Drug efficacy will be established using validated rating scales and provocative aggression-inducing scenarios.

- **The Role of Alcohol and Gender in Domestic Violence**

  Until recently, relatively little has been known about domestic violence among alcoholics except through cross-sectional studies which do not permit tests of a sequential causal relationship between active alcoholism and domestic violence. During the past decade, a few longitudinal studies have been completed or initiated on domestic violence in alcoholics and drug abusers. One of the most important of these to NIAAA is a study of domestic violence among 88 male alcoholics who, with their spouses, sought treatment for evidence-based behavioral marital therapy. Results of this study showed high levels of domestic violence versus a community control group at the inception of treatment, and significant decreases in domestic violence post-treatment, especially among remitted alcoholics. This natural history study currently is being replicated in a sample of alcoholic women from the same community. The women's study will provide a more comprehensive and balanced picture on the role of gender in alcohol-related domestic violence.

- **Alcohol-related Violence Program Announcement**

  NIAAA is developing a new program announcement on alcohol-related violence, including violence against women (e.g., date rape, domestic violence, and child abuse from women, as well as men).

### Alcohol and HIV/AIDS

- **Alcohol-related HIV/AIDS Request for Applications**

  NIAAA has published a Request for Applications (RFA) which will initiate a program of research on the role of alcohol in HIV/AIDS among women. The number of women with HIV infection and AIDS has been increasing steadily worldwide. According to the World Health Organization, approximately 16 million women are living with HIV/AIDS worldwide, accounting for 46 percent of the 32.4 million adults living with HIV/AIDS. As HIV/AIDS research becomes more focused, there is growing evidence that alcohol consumption may play an important role in sexual transmission, susceptibility to infection, and progression of HIV disease among women. In addition, alcohol use, abuse, and dependence among women may have a significant impact on pregnancy and birth outcomes, adherence to medications and provider advice, and the occurrence and course of comorbid conditions, such as hepatitis C and tuberculosis. Research supported by this RFA will seek to identify and characterize the role of alcohol, drinking behaviors, and drinking environments in the transmission, progression, and treatment of HIV/AIDS among women. It is anticipated that results of this research will inform a wide range of medical and behavioral interventions aimed at reducing the global burden of HIV/AIDS

### Drinking during Pregnancy

- **Preventing Fetal Alcohol Syndrome Program Announcement**

  NIAAA is issuing a Program Announcement which continues and expands its program of research that develops and/or tests interventions that have the potential for preventing fetal alcohol syndrome among human populations, and thereby reducing its incidence and prevalence.

Estimates of FAS prevalence vary widely among groups, depending also on the method of ascertainment. A recent review of the literature sets the overall prevalence rate as between .5 and 2.0 per 1,000 births in U.S. populations, but some communities show much higher rates (e.g., as high as 9.8 per 1,000 live births). It is generally agreed that FAS, ARBD, and ARND are completely preventable birth defects and neurodevelopmental abnormalities. According to the Institute of Medicine report on FAS (1996), there are two viable approaches to its prevention: women should stop drinking alcohol at all phases of pregnancy; or, alternatively, women who drink alcohol should not become pregnant unless and until they can control their drinking. Thus, women who are at-risk for alcohol consumption while pregnant may be targeted for universal, selected or indicated prevention interventions. Girls and women with FAS, who constitute a subpopulation at high-risk of ultimately giving birth to alcohol-impaired children, may also become the target of prevention or treatment research under this PA.

- **Fetal Alcohol Spectrum Disorders Request for Applications**

  NIAAA has published an RFA to support one or more consortia to conduct collaborative research on fetal alcohol spectrum disorders (FASD). The purpose of this initiative is to inform and develop effective interventions and treatment approaches for FASD through a highly integrated multidisciplinary research approach involving basic, behavioral, and clinical investigators, and projects. Furthermore, the objective is to integrate existing resources within the alcohol research community, and also create new resources that are crucial to the success of the research questions to be addressed. This initiative will also provide opportunities for collaboration between scientists in the alcohol field and prominent investigators from other research areas, resulting in the application of new ideas and technology to the study of alcohol-related fetal injury.

### Treatment of Women with Alcohol Use Disorders

- **Gender Differences in Drinking Patterns and Health Service Use**

  An ongoing study examines how and why gender differences in drinking patterns affect the use of health services. This study, conducted in a large managed care organization, examines the role of alcohol in gender-based differences in attitudes, health behaviors, functional status, and stated willingness to use services, including substance abuse treatment. The results of this study will facilitate the development of gender-specific screening and interventions to reduce the adverse consequences of alcohol-related health problems.

- **Patterns of Alcohol Treatment Services Utilization among Lesbian Women**

  Research is underway to investigate the treatment utilization patterns exhibited by lesbian women. A wide array of previous clinical and epidemiologic investigations have suggested that self-reported homosexual orientation could be interpreted as either a risk factor for alcohol abuse, a predictor for subsequent utilization of treatment services, or both. This new award will illuminate the extent to which sexual orientation could be used as a latent or explicit predictor variable in subsequent health services research studies, and to establish a foundation for subsequent testing of programmatic interventions targeted toward lesbian women. The investigative team will have access to one of the nation's largest HMO claims databases to conduct two studies. The first will be a collaborative cross-sectional study comparing drinking patterns and substance abuse treatment utilization

patterns among self-reported lesbian and bisexual women versus matched heterosexual women utilizing both a randomized survey and linkages with automated records within the HMO. The second study will use qualitative methods to explore relationships between drinking status, lesbian and female bisexual culture, predictive value of stress and "distress" factors in this population, and the degree to which alcohol serves as a precursor for other health risk behaviors exercised by lesbian and bisexual women.

## National Institute on Deafness and Other Communication Disorders

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms, as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. NIDCD also conducts and supports research and research training related to disease prevention and health promotion.

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 NIDCD disproportionately affect women. Examples of significant research programs have been selected for inclusion in this report. Highlights of the latest research advances and plans for the future in these areas follow.

### Accomplishments

#### *Cytomegalovirus*

Cytomegalovirus (CMV) is the leading cause of nonhereditary deafness. CMV is also recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital CMV infection may account for as many as 40,000 new cases of sensorineural hearing loss (SNHL) per year. NIDCD-sponsored scientists continue to make significant progress to fully characterize the effects of CMV on sensorineural hearing loss (SNHL), as well as the mechanisms and epidemiology of CMV maternal transmission. Recent results demonstrate a highly significant effect of CMV infection on the development of late onset SNHL.

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.

#### *Age-related Hearing Loss*

Presbycusis, hearing loss associated with aging, affects men and women differently. It has long been known that women enter their 6th to 7th decades with better hearing sensitivity than men, but women, paradoxically, are also known to have a greater rate of loss of hearing sensitivity than men over the ensuing decades. This paradox appears to be due to dysfunction of the stria vascularis, a structure on the lateral wall of the cochlea that is the energy source for cochlear function.

NIDCD investigators have examined the rate of change of hearing over 15 years in the Framingham Heart Study cohort. The only significant biomedical variable associated with excessive hearing loss

was number of pregnancies. They have also compared rate of hearing loss with rate of change in otoacoustic emissions in the Framingham Offspring group (the children of the original cohort). Results support the theory that strial degeneration, not sensory hair cell loss, is the key factor in aging of the inner ear. They have previously reported the high inheritance of signs of strial hearing loss in families (cohort and offspring) for both men and women, but at a much greater rate in the women.

Putting these three associations together, one might conclude that atrophy of the stria vascularis is a common cause of auditory aging, and that strial atrophy is an inherited trait that is more prevalent in women than in men, and further, that women's multiple pregnancies is a risk factor for greater decline in hearing with age. Because the stria is biologically a simpler system than the sensory auditory hair cell system, there is a great potential for biologic remediation. Research will continue to determine if there are ways of providing more "energy" to the system to help overcome the disadvantage imposed by strial dysfunction.

### *Taste Perception*

There are genetic and pathological variations in taste quality perception that affects the intensity of bitter foods and the preference for sweet and fat foods, which are important mediators of proper nutrition, cardiovascular disease, and cancer. Oral phantoms (sensations in the absence of stimulation) and oral pain (burning mouth syndrome) often accompany pathologies associated with the taste cranial nerves. Burning mouth syndrome occurs predominantly in postmenopausal women. NIDCD-funded research is exploring the dysfunctional relationships between the taste system and oral (trigeminal) pain systems in women with burning mouth syndrome, and will provide new insights into oral pain assessment and treatment.

### *Olfactory Loss in Multiple Sclerosis*

Multiple sclerosis is the most common neurological disability in the young adult and is characterized by a progressive demyelination of axons in the central nervous system. A greater proportion of women than men with multiple sclerosis show olfactory loss, and the loss is more profound in women. Olfactory loss has significant adverse dietary and nutrition consequences that impact on overall health status. NIDCD-funded research will define the nature of the olfactory dysfunction present in multiple sclerosis in women, and will determine the relationship between the degree of olfactory deficit, cognitive function, and pathological alterations within specific central nervous system structures.

### *Gestational Diabetes and Altered Taste Sensitivity*

Gestational diabetes is a common complication of pregnancy that requires special attention to diet to insure proper maternal and child health. NIDCD-funded research has shown that gestational diabetes can adversely affect nutrition by increasing the preference for and intake of sweet-tasting foods. Altered sweet sensitivity appears to be related to the blood levels of certain hormones and metabolites, and to a change in glucose tolerance that often accompanies pregnancy. The long-term goals of these studies are to better understand the various mechanisms underlying gestational diabetes, to isolate risk factors, and to develop better preventive and therapeutic dietary interventions.

### *Assessment and Treatment of Voice Disorders*

Voice disorders effect millions of Americans, influencing their quality of lives and impairing their ability to communicate effectively and to function in our society. A number of voice disorders appear to effect women more frequently than men. NIDCD currently supports a number of projects focused on normal and disordered voice processes. Of note are the studies examining behavioral vocal hyperfunction. Vocal hyperfunction is not organic in origin, but rather a result of a habitual pattern of overuse, misuse, or possibly abuse of the vocal mechanism. A currently funded project is examining the vocal performance of teachers, a

profession predominantly comprised of women. Research in the area of voice with representation of women, should enhance our knowledge of this human ability and maximize laryngeal health and prevention of injury. Efforts to study voice restoration would minimize disabling effects and function and enhance quality of life.

### Initiatives

If funds allow, NIDCD has a planned initiative on CMV-related hearing loss.

## National Institute on Drug Abuse

The National Institute on Drug Abuse (NIDA) supports over 85 percent of the world's research on the health aspects of drug abuse and addiction. NIDA-supported science addresses the most fundamental and essential questions about drug abuse, ranging from the molecule to managed care, and from DNA to community outreach research. Within this science, there is a major NIDA effort to investigate issues specific to women and to study sex and gender differences. Leadership for this effort is provided by NIDA's Women & Gender Research Coordinator and Deputy Coordinator, along with NIDA's Women & Gender Research Group, which has representation from all of NIDA's program branches, offices, and centers. The major goal of this effort is to infuse the study of sex and gender differences and issues specific to females in all areas of drug abuse research, and to disseminate research findings in this area.

As recently as a decade ago, NIDA supported virtually no gender-based research and very little research on women. Most of the research on women was from a pregnancy perspective and, in particular, the concern over the possible adverse effects on infants prenatally exposed to drugs and how to best treat drug-abusing pregnant women, topics that continue to be of great importance to NIDA today. In the early 1990s, however, NIDA began to have growing concerns about the lack of knowledge of other issues specific to women and whether there are important, but unidentified, differences between males and females throughout the various aspects of drug abuse. To assess these issues and to identify research gaps, in 1994 NIDA held a conference, "Drug Addiction Research and the Health of Women." From that conference, three broad areas of gender-based drug abuse research needs were apparent: the need to study females of all ages, not just those of child-bearing age; the need to address issues specific to females in all areas of drug abuse research; and the need to study sex and gender differences in all areas of drug abuse research.

Since that meeting, NIDA has been actively engaged in a number of efforts to fill these research gaps and the drug abuse research field has responded, as evidenced by a growing number of NIDA-supported research grants in this area. Today, NIDA supports gender-based research in all of its major program areas. From basic research on the biological underpinnings and consequences of drug abuse, to field research on etiology and consequences of drug abuse, to research on prevention and treatment, evidence for the importance and fruitfulness of taking a gender-based research approach and analyzing data separately for males and females is growing. NIDA-supported research is repeatedly showing that gender matters in drug abuse.

The research findings summarized below, published in 2001 or 2002, are representative of NIDA's research on women and gender differences. These research findings fall into five major research areas: Biological Mechanisms and Consequences, Nicotine, Adolescents, Treatment and Services, and HIV/AIDS. These findings strongly suggest that the identification and understanding of sex and gender differences can improve our understanding of the nature and etiology of drug abuse and have implications for tailoring prevention and treatment interventions to maximize outcomes for both males and females.

## Accomplishments

### *Biological Mechanisms and Consequences*

NIDA-supported research over the past several years has shown that the biological underpinnings and consequences of drug abuse are not always identical for males and females. Animal studies, for example, have reported for several drugs of abuse that females typically learn to self-administer drugs sooner and take in larger amounts than males; that a larger percentage of females than males acquire self-administration and that females exhibit stronger motivation to self administer and exhibit a greater tendency to relapse following drug cessation. Other animal work has shown that estrogen plays a role in the interaction of drugs of abuse and neurotransmitter systems. Sex differences have been reported in both animal and human pharmacokinetic studies, as well as studies of biological and behavioral adverse of effects of abused drugs. And, both human and animal studies have clearly shown that the menstrual/estrous cycle is a determinant of drug action, both pharmacokinetic and behavioral. NIDA-supported published research over the last 2 years has built on this growing body of knowledge. Animal studies have further elucidated the role of estrogen and the estrus cycle in cocaine self administration and have shown sex differences in drug sensitivity and vulnerability, as well as effectiveness of potential pharmacologic and behavioral treatments. Human studies have reported sex differences in cocaine craving and cerebral perfusion abnormalities. And menstrual cycle studies have shown that phase of the cycle is a determinant of cocaine craving and that estrogen may play a neuroprotective role in response to stimulant-induced brain injury.

#### Animal Research

##### Gender is a Stronger Determinant of Drug Self administration than Saccharin-preference Phenotype

Prior research has shown that rats with a high preference for sweet-tasting solutions acquire self administration of amphetamine, ethanol, and morphine more rapidly than rats with a low preference. University of Minnesota researchers sought to extend this observation to cocaine and heroin and to compare males and females. Using rats selectively bred for high saccharin (HiS) or low saccharin (LoS) preference, they found that female, but not male, HiS rats acquired cocaine self administration more rapidly than LoS rats, and a higher percentage of females of both phenotypes met the acquisition criterion, and did so more rapidly, than males. Acquisition of heroin self administration was more rapid in females than males, but was not affected by saccharin phenotype. These findings suggest that gender is a stronger determinant of self administration than saccharin-preference phenotype.

##### The Role of Estrogen and Phase of the Estrous Cycle on Cocaine Self Administration

Two studies by these same University of Minnesota researchers report that regulation of cocaine self administration is modulated by sex and by phase in the estrous cycle. The first study employed a two-lever drug self-administration procedure consisting of two active drug levers, one producing an increase in the dose delivered with each press and the other producing a decrease. The relationship between interdose interval and preceding dose size was used as a measure of regulation, i.e., the extent to which animals titrate cocaine intake to achieve a constant level. These researchers found that once responding stabilized, cocaine self administration was less regulated in female rats compared with males, with the greatest variability in the spacing of individual infusions observed when females were in the estrus phase (when estrogen levels are high but decreasing). Further, when females were in the estrus phase, the highest dose of cocaine was selected almost exclusively, whereas males and females in other phases of the estrus cycle did not prefer the largest dose. In order to assess the role that estrogen might play in this sex difference, in the second study, the researchers compared acquisition of cocaine self administration in female rats

for whom estrogen was blocked, either chemically by tamoxifen or surgically by ovariectomy, with female rats, for whom estrogen was not blocked. Acquisition was markedly reduced by ovariectomy and restored by estrogen replacement. These studies indicate that estrogen plays a role in the acquisition of cocaine self administration among females and also in sex differences seen in the acquisition of cocaine self-administration. Understanding the factors that affect cocaine self-administration in the female rat may yield valuable strategies for cocaine abuse prevention in women.

### Maternal Separation Produces Sex-specific Changes in Sensitivity to Chronic Morphine in Neonatal Rats

Researchers at Emory University report that early postnatal stress, produced by repeated separation from the dam, resulted in sex-related alteration in sensitivity to morphine's antinociceptive (pain-relieving) effects. Specifically, male but not female offspring were less sensitive than non-stressed controls to morphine's antinociceptive effects, and the development of tolerance was enhanced in males, but not females. In both males and females, maternal separation was associated with an increase in the severity of withdrawal from chronic morphine, suggesting the development of a greater degree of dependence. These sex-based findings tentatively suggest that the impact of maternal separation on the opioid system is less in female than in male offspring. Whether maternal separation affects subsequent rewarding properties of morphine, and perhaps differentially in males and females, is yet to be determined.

### Sexual Experience Activates Neurons in the Nucleus Accumbens and Cross Sensitizes Female Hamsters to the Behavioral Effects of Amphetamine

Dopamine transmission in the nucleus accumbens can be activated by drugs of abuse, stress, and motivated behaviors (e.g., sexual activity), and repeated exposure to these stimuli or events can sensitize this dopamine response. Purdue University researchers found that sexual activity elevated c-Fos induction (a measure of neuronal activity) in the core of the nucleus accumbens, but not the shell where drugs of abuse have most often been observed to activate neurons. Nevertheless, prior sexual activity made female hamsters more sensitive to the locomotor effects of amphetamine, indicating that that sexual experience can cross-sensitize neuronal responses to amphetamine. This finding raises the question of whether prior sexual activity can serve to sensitize or enhance amphetamine self administration.

### Baclofen Reduces Cocaine Self Administration More in Female Than in Male Rats

Researchers at the University of Minnesota report that the GABA agonist, baclofen, reduces acquisition of cocaine self administration in male and female rats. Specifically, baclofen reduced the percentage of both male and female rats that acquired cocaine self administration. The effect was much more dramatic in female rats, with only 15.4 percent of females vs. 77.7 percent of male rats meeting the acquisition criterion during baclofen pretreatment compared to 100 percent in both male and female rats who did not receive baclofen pretreatment. Female rats that did not meet the acquisition criterion with baclofen treatment acquired self administration within a few days after treatment termination.

### Ketaconazole Suppresses Food-restriction Increases in Heroin Self Administration in Female but Not Male Rats

Augmentation of drug self administration by food restriction is well established, and given that food restriction produces an increase in the stress hormone corticosterone, it has been hypothesized that food deprivation is a stressor and thus acts as other stressors to elevate drug self administration. Researchers at the University of Minnesota recently sought to determine whether ketaconazole, a corticosterone synthesis blocker, would suppress the increase in heroin self administration produced by food restriction. In both male and female rats, heroin self administration

was increased approximately twofold by food restriction. Ketaconazole suppressed the food-restriction increase in heroin self administration in females, but not in males. This outcome lends support to the hypothesis that stress mediates the effects of food restriction on increased drug self administration, but clearly indicates that sex is a modulator of this effect. These findings also suggest that sex may be an important variable to be examined in the development for medications to treat opiate abuse.

### Wheel Running Decreases Cocaine Self Administration Significantly in Female Rats Only

These same University of Minnesota researchers examined wheel running as a nondrug alternative reinforcer form of treatment for cocaine self administration. After steady rates of cocaine self administration in both males and females were established, when concurrent access to the running wheel was provided, females exhibited a 70.6 percent reduction in cocaine infusions, whereas in males, infusions decreased only 21.9 percent. Infusions increased to baseline levels when wheel access was terminated in both females and males. These results indicate that the voluntary wheel-running model in rats, and possibly voluntary exercise in humans, might be used as a substitutable natural reward to reduce drug abuse, especially in women.

## Human Studies

### Non-treatment Seeking Women Who Use Cocaine Have Higher Cocaine Craving Scores and Greater Depressive Symptomatology than Men

In a pilot study investigating 21 non-treatment seekers with cocaine dependence, researchers at Harvard University found that following at least 12 hours of abstinence, female subjects self reported higher total craving scores than male subjects on a craving questionnaire. Importantly, they scored substantially higher on responsivity to drug-conditioned stimuli items, expressed a higher desire to use cocaine within the last 24 hours, and a lower desire not to use cocaine in the last 24 hours. Further, females showed greater depressive symptomatology and severity of family and social problems than their male counterparts. These results suggest that gender may influence different aspects of cocaine craving, and they add to a growing body of data suggesting that symptomatology and course of cocaine dependence are not identical in men and women.

### Gender-specific Cerebral Perfusion Abnormalities in Abstinent Cocaine Abusers

Cocaine has been implicated in a variety of neuropsychiatric complications, including cerebral infarcts, depression, and neuropsychological abnormalities. Researchers at UCLA evaluated regional cerebral blood flow (rCBF) abnormalities both in cocaine abusers who were abstinent for at least 4 months and in healthy controls without a history of drug use. Compared to controls, abstinent cocaine abusers exhibited increased rCBF in the frontal white matter and in the globus pallidus, and decreased rCBF in the putamen and the temporal cortex. Female, but not male, cocaine abusers showed significantly reduced relative rCBF in the parietal gray matter and increased relative rCBF in the frontal and temporo-parietal white matter, whereas male, but not female, cocaine abusers showed significantly increased rCBF in the thalamus. These data demonstrate that there are regional cerebral perfusion abnormalities in abstinent cocaine users, and importantly that some of the abnormalities are gender specific.

### Phase of Menstrual Cycle is a Determinant of Cocaine Craving and Subjective Response to Smoked Cocaine

In a study by researchers at the New York State Psychiatric Institute and Columbia University, 11 female research volunteers, who were currently using cocaine were allowed to smoke up to six doses of cocaine, in both the luteal phase which follows ovulation (levels of the hormone progesterone are at their highest) and the follicular phase which precedes ovulation (levels of estrogen are at their highest). The number of cocaine doses administered did not

vary between phases; however, following cocaine administration, heart rate and several positive ratings ("good drug effect," "high," "stimulated") were increased more during the follicular phase. Under placebo conditions, resting heart rate, reports of dysphoria, and cocaine craving were greater during the luteal phase. Following cocaine administration, luteal phase dysphoric ratings were dose-dependently improved. Cocaine craving was greater during the luteal phase than during the follicular after 3mg and 25 mg cocaine, but after 12 mg cocaine, craving was higher in the follicular phase. Cocaine-produced ratings of mood states, positive drug effects, and drug quality ratings were generally greater during the follicular phase. The differential subjective effects of cocaine in the luteal and follicular phases, as well as the cocaine-produced amelioration of mild luteal phase dysphoria observed in this study, warrant investigation of the mechanisms underlying these effects, as well as an exploration of treatment implications of these findings.

#### Cocaine-induced Cerebral Vasoconstriction Differs as a Function of Gender and Menstrual Cycle Phase

Prior research has shown that chronic cocaine-abusing women experience fewer cerebral perfusion defects and less neuronal injury than men with comparable drug use histories. In a group of occasional cocaine users, researchers at Harvard University found that cocaine had no significant effect on cerebral blood flow during the follicular phase of a women's menstrual cycle. In the luteal phase, however, cocaine reduced blood flow by about 10 percent, which was not significantly different from the 20 percent decrease in cerebral blood flow observed in men. The insignificant effect of cocaine on women's brain blood volume prior to ovulation may be attributable to the protective effects of estrogen, which improves blood vessel elasticity and may counter the vasoconstrictive effects of cocaine.

#### A Possible Neuroprotective Role of Estrogen in Response to the Methamphetamine-induced Brain Injury

In an investigation of regional cerebral blood flow (rCBF) and cognitive function in abstinent methamphetamine users, researchers at the Brookhaven National Laboratory evaluated 20 methamphetamine-dependent participants who had been abstinent for an average of 8 months, and 20 age- and gender-matched controls without a history of substance abuse. Methamphetamine users performed within normal ranges on standard neuropsychological testing, although they were slower on working memory tasks. Both male and female methamphetamine users showed similar disrupted rCBF in several brain areas, although in several brain areas, male methamphetamine users exhibited a decreased relative rCBF, whereas female users exhibited an increase. These gender differences suggest a possible neuroprotective role of estrogen in response to the methamphetamine-induced brain injury.

### *Nicotine*

The prevalence of smoking has decreased for both men and women over recent decades. Unfortunately, however, the rates have declined much more slowly for women than men, and nicotine dependence rates are higher among women than men, although women smoke fewer cigarettes per day than men. Women are less successful than men at quitting smoking, have higher relapse rates after quitting and have a poorer response to nicotine replacement therapies than men, thus pointing to the need for gender-based research on nicotine addiction. Indeed, NIDA-support research, from basic laboratory studies with animals and humans to clinical studies of smoking cessation, is increasingly demonstrating that gender plays a powerful role in the nature of nicotine dependence, its etiology, its effects, and how to treat it. Over the past 2 years, NIDA-supported published research, described below, utilizing animal models has reported important sex differences

in nicotine self-administration and in the patterns of CNS defects due to fetal vs. adolescent nicotine exposure. Field studies have uncovered sex differences in rates of nicotine dependence and in the predictors of smoking, and laboratory-based human studies have described sex differences associated with abstinence and in the role that sensory cues play in nicotine dependence, findings that may have implications for prevention and treatment. And clinical research has provided evidence for the efficacy new treatments for smoking cessation, especially in women.

**Sex Differences in Nicotine Self-administration in Rats**

University of Pittsburgh researchers compared acquisition of nicotine self administration in male and female rats. They found that nicotine self administration acquisition, at the lowest dose tested, was faster and more stable in female than in male rats. Females also made more bar presses to receive nicotine infusions and they displayed a shorter latency before self-administering the first nicotine infusion in a session than males. These results suggest that the motivation to obtain nicotine may be higher in females than males.

**Gender-distinct Patterns of CNS Defects Following Adolescent Nicotine Exposure in Rats**

Researchers at Duke University examined the effects of nicotine on the serotonin neurotransmitter system in both pregnant and adolescent rats using doses that replicate the plasma nicotine levels found in smokers. They found that vulnerability to nicotine's alteration of serotonin neurotransmitter systems extends from fetal life through adolescence. Following adolescent nicotine exposure, although both females and males displayed serotonergic abnormalities, the patterns of effects were gender-selective in various brain regions. This line of research is especially important given recent work showing that many adolescent smokers exhibit signs of nicotine dependence in a matter of days to weeks after initiation of occasional tobacco use, often well before the development of daily smoking. Importantly, for teenage girls, the median latency to report symptoms of dependence has been shown to be within 21 days of occasional smoking, whereas for boys, the median latency has been shown to be 6 1/2 months. Thus, it will be extremely useful for future research to examine whether gender-selective effects on neurochemical systems, as seen in this study, also correspond to differential early onset of nicotine dependence in males and females.

**Nicotine Dependence Rates Higher among Women**

Using data from subjects who were last-month smokers from the National Household Survey on Drug Abuse from 1991-1993, researchers at Columbia University found that nicotine dependence rates are higher among females than males, Whites than minorities and the lowest among older adults. Dependence rates increase sharply and significantly when the quantity smoked increases from less than one cigarette a day to one to five cigarettes a day, or from one to five cigarettes a day to half a pack a day. Thereafter, the increased risk is minimal. The higher rate of dependence among women results from a greater number of dependence symptoms at the same quantity smoked, i.e., women become dependent smoking fewer cigarettes per day than men. There is also an increase in the gender gap in the rate of dependence as quantity smoked increases. These findings suggest that different thresholds of quantity and duration of smoking should be used in assessing different groups for risk for nicotine dependence.

**In a Laboratory Setting, Women Report Greater Desire to Smoke Than Men following Both Abstinence and Ad Libitum Smoking**

Researchers at the University of Minnesota examined the effects of short-term abstinence from smoking on psychophysiological activity and mood changes at both rest and in response to acute behavioral challenges.

Thirty habitual smokers (15 men and 15 women) participated in two laboratory sessions conducted on two separate days following 18 to 21 hours of abstinence from smoking or following ad libitum smoking. Abstinence produced significant withdrawal in all participants, and women reported being less calm and less in control than men on both days. Participants showed greater systolic blood pressure responses to the behavioral challenges in the abstinence condition than in the control condition, and showed worse performance on the behavioral tasks following abstinence. Both men and women showed increased desire to smoke following the behavioral challenges. Both men and women reported stronger desire to smoke in the abstinence condition than in the ad libitum condition, and women reported a greater desire to smoke in both conditions than men. This greater desire to smoke reported by women is of special interest given that the men and women had similar levels of nicotine addiction and similar smoking histories. This finding could have implications for the design of gender-sensitive smoking cessation procedures.

**Olfactory/Taste Cues Associated with Smoking Play a Greater Role in Women's Smoking Behavior Than in Men's**

Aside from its delivery of nicotine, cigarette smoking behavior may also be reinforced by stimuli associated with smoking. University of Pittsburgh researchers examined the effects of smoking sensory cues (sight and smell/taste) on smoking behavior by having smokers wear opaque goggles to block visual cues and/or swimmers' noseclips to block olfactory/taste stimuli during smoking. When both visual and olfactory/taste cues were blocked, both men and women exhibited decreased liking and satisfaction from smoking, but only women decreased smoking. When only visual cues were blocked, there were no effects on the subjective effects of smoking nor on the amount smoked in either men or women. When olfactory/taste cues were blocked, however, both men and women reported decreased subjective liking and satisfaction from smoking, and this effect was stronger in women. Importantly, following the blockade of olfactory/taste cues, only women decreased their smoking. Thus, both the subjective pleasure and reinforcing effects of smoking are influenced by olfactory/taste stimuli, but not visual stimuli, particularly in women. These observations suggest that nicotine stimuli associated with smoking are more reinforcing in women than in men, and also suggest that interventions to help smokers quit may benefit from a greater focus on eliminating stimuli associated with smoking, particularly olfactory/taste stimuli, and that this approach could be particularly beneficial for females who tend to have less success in quitting.

**Sex Differences in Adolescent Smoking Trajectories**

Researchers at Rutgers University investigated developmental trajectory groups for cigarette smoking in 374 males and females who were interviewed five times from age 12 until age 31. Girls were more likely than boys to begin smoking, and they began smoking daily earlier than boys (15.7 vs. 17.4 years of age). For females, but not males, having a friend or parent who smoked was significantly related to smoking. Also for females, but not males, lower parental socioeconomic status was associated with both smoking and heavy smoking. Further, the occasional/maturing out group was made up of more females than males. These findings have implications for the development of gender-sensitive prevention efforts. Future research should examine transitions and turning points from adolescence to adulthood, as well as other factors that may affect cessation and escalation differently for females and males.

**Dealing with Daily Hassles: Smoking and African American Adolescent Girls**

University of Michigan researchers examined cigarette use and its relationship to daily life hassles in an urban sample of 105 African American adolescent girls. Girls who had ever smoked had a significantly greater number of daily life hassles in

contrast to girls who had never smoked. Academic and family stressors were related to smoking, but peer and personal safety stressors were not. Age of smoking initiation was negatively related to the number of hassles, indicating that girls who started to smoke at a younger age reported more hassles. These findings that daily hassles are correlates of African American adolescent girls' smoking, as well as the age at which they begin smoking, may be useful in the design of ethnic- and gender-related smoking prevention programs for African American girls.

**Girls May Progress Through the Stages of Smoking Earlier than Boys**

Researchers at RAND investigated the relationship between emotional distress and tobacco use in 2,961 adolescents from 30 schools in California. The participants were assessed longitudinally in grade 10, grade 12, and in young adulthood. Previous research has provided support for the distress-to-use (i.e., self-medication) hypothesis, and one might expect girls, who tend to have higher rates of emotional distress, to exhibit a somewhat stronger relationship between distress and smoking than boys. Although girls did have consistently higher emotional distress scores than boys, the relationship between emotional distress in the 10th grade and smoking in the 12th grade was stronger for boys. A possible explanation for this unexpected result may be related to the timing of this measurement in relation to the stages of smoking. In the current sample, more girls than boys had tried cigarettes than boys by grade 10, and the proportion of occasional or regular smokers was significantly higher among girls than boys in grades 10 and 12. This difference, however, was not evident in young adulthood, at which point smoking rates appeared to even out for the two genders, thus suggesting that girls may progress through the stages of smoking earlier in their development than boys. If the impact of distress on smoking is strongest at a particular stage, for example, during the transition from experimentation to regular use, then this effect would occur earlier for many girls.

**Cognitive-behavioral Therapy to Reduce Weight Concerns Improves Smoking Cessation Outcome in Weight-concerned Women**

Smokers concerned about weight gain are less likely to want to quit, report greater withdrawal if they do quit, are more likely to drop out of treatment, have poorer overall abstinence outcome, and are more likely to be female. The average postquit weight gain of 10 pounds often sabotages early attempts at smoking cessation and may cause resistance to treatment or relapse after treatment completion. Yet, research has shown that treatment for smoking cessation that includes behavioral approaches to limiting weight gain are usually ineffective and can actually interfere with smoking cessation efforts. Researchers at the University of Pittsburgh School of Medicine have now reported the effectiveness of treatment focusing on weight gain concerns, rather than on preventing weight gain. They conducted a random controlled trial in which 219 women who were concerned about weight gain were randomly assigned to one of three treatments: 1) group smoking cessation counseling (standard group) in which weight gain was not explicitly addressed; 2) group smoking cessation counseling plus behavioral weight control to prevent weight gain (weight control group); and 3) group smoking cessation counseling plus cognitive-behavioral therapy to directly reduce weight concern (CBT group). The CBT group received therapy to modify their attitude toward weight gain and to help them accept a modest weight gain in light of benefits of quitting; dieting was discouraged. Ten sessions were conducted over 7 weeks. At the end of 1 year, abstinence rates were significantly higher for the CBT group (21 percent abstinence) than the standard group (9 percent), but abstinence rates for the weight control group (13 percent) were not significantly better than the standard group. Interestingly, and unexpectedly, weight gain at the end of 1 year was significantly less in the CBT group (6 pounds) than the standard group (17 pounds), but weight gain in the weight control group

(12 pounds) did not differ significantly from that of the standard group. Thus, CBT to reduce weight concerns, but not behavioral weight control counseling to prevent weight gain, significantly improved smoking cessation outcome in weight-concerned women and significantly decreased weight gain.

**The Antidepressant, Buproprion, May Help Smokers, Especially Females, Overcome the Effects of Genetic Predisposition on Relapse Rates**

A study at the University of Pennsylvania indicates that smokers with a specific genetic variant may be more vulnerable to cigarette cravings and relapse when trying to quit smoking. The researchers found that smokers with a decreased activity variant of the CYP2B6 gene reported greater increases in cravings for cigarettes following the quit date, and were about 1.5 times more likely to relapse during the treatment phase. This study also provides preliminary evidence that buproprion may help smokers, especially females, overcome the effects of genetic predisposition on relapse rates. Among women with the CYP2B6 polymorphism, 54 percent of those who were treated with buproprion were abstinent at the end of treatment, compared with 19 percent of those who received placebo. For men with the mutation, 42 percent who were treated with buproprion and 38 percent with placebo were abstinent at the end of treatment. This sex difference could be due to buproprion's effect on abstinence-induced negative mood which is more common among women.

## *Adolescents*

Early adolescence is a time when many individuals begin experimentation with various substances, and indeed many become addicted. The study of adolescents is included in virtually all areas of drug abuse research and, increasingly, is taking a gender-based approach. The research findings from NIDA-supported research from the past 2 years, highlighted below, describes findings on sex differences in use patterns, sex differences in predictors and progress to drug abuse, as well as sex differences in the clinical aspects of drug abuse in adolescents. These findings join a growing body of drug abuse research suggesting that the trajectories to drug abuse are not identical in boys and girls and that taking a gender-based approach to prevention and treatment interventions can perhaps lead to better outcomes in boys and girls.

**Gender Gap in Inhalant Use is Narrowing**

Researchers at Colorado State University investigated inhalant use in 35,094 adolescents from three ethnic populations from across the United States (Mexican American, American Indian, and non-Latino white) who were studied over the period from 1988-1997. The data are clear that girls are equally, if not more, susceptible to inhalant use than boys. For Mexican American youths, there were no gender differences in either lifetime or 30-day prevalence. For the non-Latino white youths, there were no gender differences on the 30-day measure. Among American Indian youth, for both lifetime and 30-day prevalence, girls were more likely to have used inhalants than boys. Thus, the current data suggest that the historically higher rates of inhalant use for boys as compared to girls no longer prevail, indicating that girls should be included in all prevention efforts.

**Inner-city Girls in New York Engage in Less Polydrug Use than Boys, Regardless of Ethnicity**

Cornell University researchers assessed polydrug use in a cohort of 2,354 inner-city adolescents in 22 urban schools in New York throughout middle school. Students completed self-report questionnaires with measures of drug use (smoking, marijuana use, and drinking). In general, girls engaged in less polydrug use than boys, independent of ethnicity. This finding demonstrates that, in some cases, aggregating data across gender may obscure important differences in drug use between boys and girls, and may have implications for prevention.

**Early Pubertal Maturation Represents a Risk Factor for Substance Abuse in Adolescent Girls**

Researchers at Pennsylvania State University have found that the timing of the onset of puberty appears to be a risk factor for substance abuse in girls. Data from 966 adolescent girls involved in the National Longitudinal Study of Adolescent Health revealed important differences between early-maturing girls and their on-time and late-maturing counterparts in initiation of substance use. Twenty percent of the 7th grade girls were identified as early-maturers based on body changes (increased breast size and body curviness). During 7th grade, girls in the early-maturing group were three times more likely to be in the most advanced group of substance users (involving alcohol use, drunkenness, cigarette use, and marijuana use) than were those in the on-time/late groups. Between 7th and 8th grade, early developers were significantly more likely to transition out of the "No Substance Use" stage than on-time/late developers (47 percent vs. 22 percent, respectively), and were more likely to advance in substance use in general, regardless of level of use at grade 7. In a related study, researchers at the University of Kentucky administered questionnaires to 1,002 girls and boys who were followed from the 6th to the 10th grades. In girls, but not boys, early pubertal onset was associated with greater cigarette use in grades 7, 8, and 9, and lower self esteem in grade 7. In boys, but not girls, early pubertal onset was associated with elevated alcohol use in grades 9 and 10. Taken together, these studies suggest that early maturing girls are at high risk for the worst substance use trajectories, and that pubertal timing could be used a marker to identify girls at high risk.

**Elementary School Alcohol and Other Drug Use Increases Middle School Risk Differently in Girls and Boys**

Researchers at the University of California at Berkeley found gender differences in the relationship between alcohol, tobacco, and other drug (ATOD) use in elementary school and continued ATOD use in middle school in a sample of 331 ethnically and geographically diverse students from a range of low socioeconomic status backgrounds living in rural, urban, or inner-city environments. Girls, but not boys, who used alcohol in elementary school were at significant increased risk for alcohol use in middle school. Elementary school use of cigarettes by boys increased their likelihood of middle school tobacco use by almost nine-fold; for girls, threefold. There was a marginally significant increased risk of middle school marijuana use by boys who reported use during elementary school, but girls did not report marijuana use in either elementary or middle school. This gender-based association of early use of ATOD with greatly increased odds of later use has important implications for the timing of drug prevention programs.

**Gender Differences in Psychiatric Comorbidity among Adolescents with Substance Use Disorders**

Studies suggest that different psychiatric comorbidity patterns among youths in drug treatment are associated with distinct outcomes. Research has shown that in many drug treatment programs, psychiatric comorbidity issues are not directly addressed in a systematic manner; thus, untreated comorbid psychiatric disorders may be contributing to post-treatment relapse rates, wherein an estimated one in two adolescents reverts to substance abuse within 90 days of treatment. Researchers at Johns Hopkins University examined gender differences in the rates of psychiatric disorders among 135 adolescents with substance use disorders. Nearly four times as many female adolescents as male adolescents had a co-occurring major depressive disorder, and nearly three times as many male as female adolescents had a co-occurring ADHD or conduct disorder. Unexpectedly, rates of ADHD and conduct disorder were fairly high among females (23.5 and 47.1 percent, respectively), despite being significantly lower than for males. These findings suggest the need for adolescent drug abuse treatment programs to incorporate strategies that address these gender-based multiple comorbidity patterns.

**Past Sexual and Physical Abuse and Substance Abuse Consequences**

Researchers at Boston University examined the association between past interpersonal trauma and drug and alcohol consequences in 359 male and 111 female patients recruited from an urban alcohol and drug detoxification unit in Massachusetts. Among substance abuse consequences were risky or illegal behavior, and the impact of substance abuse on relationships, work, and school problems, as well as adverse physical consequences associated with substance abuse. Among the 465 patients, there was an extraordinarily high frequency of physical and sexual abuse: 72 percent experienced past physical or sexual abuse, and 75 percent of them first experienced it as children. Specifically, 81 percent of women and 69 percent of men reported past physical and sexual abuse, starting at a median age of 13 and 11, respectively. Further, physical and sexual abuse was significantly related to greater substance use consequences for both women and men. For men, being under the age of 17 years at first abuse was significantly associated with more substance abuse consequences than an older age at first abuse, or no abuse. For women, the association of physical and sexual abuse with substance use consequences was similar across all age groups. The mechanisms by which interpersonal violence influence substance use consequences in women and men may differ, suggesting that substance abuse prevention and treatment programs may benefit from gender-specific components.

**Female Juvenile Arrestees More Likely to Report Dependence, But Less Likely to Report Need for Treatment than Males**

Researchers at the University of Illinois at Chicago examined gender differences in drug use, self-reported dependence, and perceived need for treatment in a national sample of 4,644 juvenile arrestees who were 9 to18 years old. Significantly more girls self-reported dependence than boys, but they were no more likely to report a need for treatment. Among arrestees reporting current frequent drug use, girls were significantly less likely than boys to report a need for treatment. Among the most severe drug users, girls were 7.1 times as likely as boys to say they were dependent, and were more likely than boys to report a need for treatment. These findings that juvenile arrestees' perception of their drug dependence and of their need for treatment differs by gender and by drug problem severity especially highlights the need for girls to receive treatment before their substance abuse becomes severe.

### *Treatment and Services*

Over the past several years, NIDA-supported treatment and services research has increasingly been adopting a gender-based approach. This research approach is revealing widespread gender differences, including treatment entry characteristics, treatment and services needs, barriers to treatment, treatment engagement and retention, treatment outcomes, and relapse predictors. Such research shows, for example, that women may be less likely to enter treatment than men, have shorter lengths of stay, and lower rates of treatment completion. NIDA-supported treatment and services research also is focusing on targeted groups of women, including pregnant and postpartum women, women offenders, homeless women, minority women, and those experiencing current and past violence and trauma. NIDA-supported published research over the last 2 years, highlighted below, includes research on treatment dropouts, the role of a woman's family status in her completion of treatment, treatment needs of methamphetamine-dependent women, and special treatment and services issues regarding women offenders and pregnant and postpartum women. Continuing research into the specific needs of women who need treatment is necessary in order to increase success at getting women to begin treatment and, once there, to complete treatment and have successful outcomes.

**Treatment Dropouts More Likely to be Female**

Researchers at the University of Texas examined factors affecting treatment attrition in 165 individuals seeking treatment

for cocaine dependence. Of those who initiated treatment, 65 percent dropped out before completing all 20 therapy sessions. Treatment dropouts were more likely to be female, to be separated from their spouses, to have poorer family and social functioning, and to have fewer years of education. Individuals with higher education levels, and those with poorer psychiatric functioning, tended to remain in treatment longer. These findings have direct implications for identifying individuals at higher risk for attrition from outpatient substance abuse programs.

**A Women's Family Status Impacts Her Completion of Substance Abuse Treatment**

The impact of a woman's family status (i.e., pregnant, living with dependent children, children in foster care) on the likelihood that she would complete drug abuse treatment was examined by researchers at the Piedmont Research Institute in 9,142 women in Illinois who completed intake for publicly funded treatment. More than half of the women failed to complete treatment. The likelihood of not completing treatment was greatest for women who were pregnant, had custody of minor children, were African American, or were younger than age 21. African American women who had children in foster care, however, were more likely to complete treatment than African American women in general, or women of other races. Women's needs are often overlooked and underserved in the substance abuse treatment services. In particular, pregnancy and child-care needs, and their impact on women's completion of treatment, must be understood and addressed in the treatment system.

**Methamphetamine-dependent Women More Likely to Report a Syndrome of Depression and Suicidal Ideation and a Need for Psychiatric Assistance**

Research has shown that psychiatric comorbidity among drug users is associated with poorer treatment outcome and a higher likelihood of relapse. In a study of 1,580 arrestees sampled from the 14 most populous counties in California, increased risk for depressive symptoms was observed for both women and men reporting methamphetamine dependence, compared to those not reporting dependence. Further, women, but not men, reporting methamphetamine dependence were more likely than those not reporting methamphetamine dependence to report suicidal ideation and a need for psychiatric assistance at the time of the interview, which occurred within 48 hours of arrest. These findings raise questions of whether the depression and suicidal ideation preceded or followed the onset of methamphetamine use, and whether antidepressant medications would be efficacious in the treatment of methamphetamine dependence for individuals with co-occurring depression.

## *Women Offenders*

Drug-abusing women sometimes encounter treatment either within the prison system or following incarceration. Although women compose only 11 percent of the U.S. jail population, the rate of incarceration is rising faster among women than among men, and female arrestees are more likely than male arrestees to be found drug positive. In fact, it is estimated that about two-thirds of female arrestees use illicit drugs. NIDA-supported published research over the last 2 years on women offenders, described below, has included investigation of the services needs of substance-abusing women in jail, factors that affect their retention in prison-based treatment programs, and factors that affect their abstinence in the first week after treatment.

**The First Week after Drug Treatment: Factors Influencing Abstinence among Women Offenders**

Researchers at the National Development and Research Institutes conducted a study examining abstinence during the first week after leaving two community-based treatment programs in Portland, OR. Among 165 women offenders who were mandated to treatment, over two-thirds of the women abstained from drug use during the first week after treatment, despite their long histories of drug use and other serious

problems. Women who remained abstinent during the first week after treatment, compared with those who did not, were more likely to have remained in treatment longer, received a plan to make a successful transition out of treatment, avoided associations with other drug users after leaving treatment, and obtained encouragement from individuals and groups in support of abstinence.

**Women's Perceptions about Quality of Treatment Experience Important for Staying in a Prison-based Treatment Program**

To determine why some women offenders complete prison-based drug treatment and others leave early, perceptions of various aspects of the quality of the treatment experience were compared in 101 women offenders in Portland, OR. Researchers found that the two groups differed in terms of their perceptions about the quality of treatment experience, but did not differ in their background characteristics or previous experience with drug treatment. Clients who completed the program had a more favorable perception of staff, perceiving the counselors as supportive, and felt empowered by the experience in treatment. About half of the clients left prematurely, largely because of conflicts with the program's rules. Because many women drop out of treatment, programs need to consider strategies that will enhance the likelihood that these clients stay longer so that the treatment can have optimal impact.

**Services Needs of Substance Abusing Women in Jail**

In a study of self-reported service needs of 165 women held in a large urban county jail in Ohio, researchers at the University of Akron found that 50 percent of the women reported a need for substance abuse services. Compared to women who did not report such a need, those women were more likely to report the need for housing, medical care, education, mental health services, family support, and parenting assistance when released from jail. Housing was the need most frequently mentioned; 84 percent of drug abuse treatment-seeking women reported a need for housing compared to 45 percent of non-treatment seeking women. This study suggests that successful drug treatment of incarcerated women must consider the multidimensional needs of these women in order to break the cycle of drug use and incarceration.

### *Pregnant and Postpartum Women*

Drug use during pregnancy places the woman at risk for maternal complications; the infant at risk for low birthweight and small head circumference; and the baby and developing child at risk for problems with attention, emotional regulation, and advanced problem solving. Thus, identification of drug use during pregnancy, as well as effective drug abuse treatment, are essential to the health and well being of mother and child. Self report of drug use in pregnancy is often problematic because of the inaccuracy of recall and because of the woman's fear of losing custody of her children. A recent NIDA study, described below, has found that meconium testing, when used in conjunction with maternal self report, results in improved accuracy for the identification of prenatal exposure. Other studies have investigated the effectiveness of incentives in enhancing both treatment attendance and abstinence in pregnant women, the identification of special treatment needs for pregnant women with PTSD, and the usefulness of buprenorphine for treatment of opioid-dependent pregnant women.

**Meconium Testing Improves Identification of Infants Prenatally Exposed to Drugs Over Maternal Self Report**

Researchers at Brown Medical School evaluated maternal self report of drug use during pregnancy and meconium assay as methods to determine exposure status to cocaine, opiates, and other illicit drugs in 8,527 newborns participating the Maternal Lifestyle Study, which has sites in Detroit, Memphis, Miami, and Providence. Results indicate that accurate identification of exposure to illicit drugs in newborns is likely to be improved when meconium testing is used in conjunction with a maternal

hospital interview. For example, 254 mothers denied use, but their infants had positive meconium confirmation for cocaine/opiates, thus allowing identification of an additional 38 percent of the drug-exposed infants by means of meconium testing. Many questions still remain, however, about the disposition of drugs in meconium and, therefore, further research is necessary.

**Drug Use during Pregnancy and Short-term Maternal Outcomes**

In a separate study, Maternal Lifestyle Study researchers also found that those women who used cocaine or opiates during pregnancy had a significantly higher risk of infections, including: syphilis, gonorrhea, hepatitis, and HIV; psychiatric, nervous, and emotional disorders; and abruptio placenta. The prevalence of these risk outcomes, however, was lower than typically reported in other studies examining drug use during pregnancy, perhaps because a high percentage of the women made use of available prenatal care services: 77 percent of the exposed mothers and 97 percent of nonexposed mothers had at least one prenatal care visit. The women may also have moderated their drug use behavior during pregnancy to minimize the potential negative impact of their lifestyles on their infants. The women were largely polydrug abusers, with approximately 93 percent admitting to using other drugs that are known to have a negative impact on fetuses, particularly tobacco and alcohol. These results support the need for early, comprehensive prenatal care for drug-using pregnant women to prevent or treat the health hazards that accompany drug exposure, thereby optimizing maternal-infant outcome.

**Clinical and Psychosocial Characteristics of Substance-dependent Pregnant Women with and without PTSD**

Researchers at Johns Hopkins examined clinical and psychosocial characteristics and posttraumatic stress disorder (PTSD) symptomatology in a sample of pregnant women who were severely drug dependent. Among the 123 women, lifetime prevalence of PTSD was 19 percent. Compared to women without PTSD, those with PTSD had received more previous drug treatment, were more likely to report a previous suicide attempt, and reported greater need for psychiatric treatment. The most salient predictors of PTSD status were lifetime sexual abuse and family or social problems. The results suggest that pregnant, drug-dependent women with comorbid PTSD may benefit from specialized treatment services for trauma and/or abuse issues.

**Incentives Enhance Treatment Attendance and Abstinence in Methadone-maintained Pregnant Women**

Methadone maintenance for heroin dependence during pregnancy is associated with many benefits for both mother and baby. Methadone-maintained pregnant women, however, often use other drugs (e.g., cocaine) that may exert a detrimental effect on the fetus. Researchers at Johns Hopkins University examined the effectiveness of a short-term contingency management program designed to eliminate cocaine use in heroin-dependent pregnant women and to increase their attendance in a methadone-maintenance program. The women were randomly assigned to either an escalating voucher incentive schedule (women received a voucher exchangeable for appropriate goods and services for each day they provided a drug-free urine sample and full-day treatment attendance) or a non-incentive condition. Over the 14-day program, the escalating voucher incentive schedule significantly increased full-day treatment attendance, as well as both cocaine and heroin abstinence compared to the non-incentive schedule. These findings suggest that reinforcing the co-occurrence of treatment attendance and abstinence from illicit drug use is effective and could be an important adjunct to methadone pharmacotherapy for treating pregnant heroin-dependent women.

**Buprenorphine Treatment of Pregnant Opioid-dependent Women Improves Maternal and Neonatal Outcomes**

Researchers at Johns Hopkins University examined both maternal relapse, as well as neonatal safety outcome measures, in

three pregnant opioid-dependent women who received buprenorphine for the treatment of their opioid dependence during pregnancy. The researchers found that buprenorphine, in combination with comprehensive prenatal care, was safe and effective in treating opioid dependence in these women. Prenatal exposure to buprenorphine was associated with normal birth outcomes and a mean hospitalization stay of 4.33 days (minimum possible was 4 days), and the infants exhibited only a relatively mild neonatal abstinence syndrome, requiring no pharmacological treatment. These results are promising when compared to infants born to mothers maintained on methadone during pregnancy, who experience a high incidence of neonatal abstinence syndrome, often requiring extensive treatment and hospitalization.

### *HIV/AIDS*

In the United States, a greater percentage of women acquire HIV directly or indirectly from injecting drug use compared to men. According to the CDC (*HIV/AIDS Surveillance Report*, 2001; 13(1)), 40 percent of the cumulative AIDS cases in adult females were among injecting drug users (IDUs), whereas IDUs accounted for 30 percent of the cumulative AIDS cases in adult males. An additional 15.6 percent of AIDS cases among women, compared to 1.5 percent of AIDS cases among men, were associated with sex with IDUs. In all, AIDS cases among U.S. women are much more likely to be directly or indirectly (through sex with an IDU) related to injecting drug use as compared to men (56 percent vs. 31 percent). Among youth in the age range 13 to 19 years, females represent 61 percent of HIV infection. Among males aged 13 to 24 years, men who have sex with men represent 49 percent of reported AIDS cases, injection drug use represents 10 percent, and infection through heterosexual contact represents 9 percent. For females of that age range, infection through heterosexual contact represents 45 percent of reported AIDS cases, and injection drug use represents 11 percent.

The gender differences in transmission of HIV clearly points to the needs for gender-specific approaches in understanding risk factors and in developing interventions. Recent NIDA research has examined factors associated with obtaining syringes from safer sources and factors associated needle-sharing behavior among IDUs. Researchers also have investigated the role sexual risk behaviors in seroconversion among IDUs, the role played by alcohol on these risk behaviors, and the function of health and/or social service contacts as a protective factor for homeless, injection drug-using women. Recent NIDA studies among youth have examined gender differences in health and risk behavior among youth living with HIV, gender differences in sexual risk behavior in an urban minority population of African American youth, and the manner in which the use of various drugs by youth relates to sexual risk behaviors and network characteristics. A NIDA study aimed at HIV prevention characterized the attitudes of drug-involved women towards vaginal microbicides for the prevention of HIV and STDs, a preventive approach that could be used without the knowledge or cooperation of a male partner. And a study with important treatment implications found gender differences in the relationship between the initial viral load following HIV seroconversion and the risk of progression to AIDS.

#### Being Female Associated with Obtaining Needles from Safe Sources Only

Researchers at Johns Hopkins University examined factors associated with obtaining sterile syringes from a needle exchange program and other safe sources, such as pharmacies or hospitals, versus obtaining needles from unsafe sources, such as street needle sellers. Of the 741 Baltimore IDUs recruited, 85 percent of participants obtained needles from street needle sellers, whereas only 8 percent of participants obtained their needles exclusively from safe sources. IDUs who sold needles reported that it was easy to make used needles appear to be unused, and some admitted to selling used syringes as new. Being female, less frequent needle

sharing and shooting gallery attendance were associated with obtaining needles from only safe sources. Specifically, 11.5 percent of women, but only 6.7 percent of men, reported using safe sources only to obtain needles. Among HIV-seropositive respondents, women were nearly four times more likely than men to exclusively visit safer sources for needles.

**Women Injecting Drug Users at Particularly High Risk for Needle Sharing**

Researchers at Johns Hopkins conducted interviews with 1,184 injecting drug users (IDUs) who participated in the Baltimore Needle Exchange Program from 1995-1997. Participants were asked on several occasions to give the initials of up to five of their closest friends, and asked whether they had injected drugs, shared syringes, had sex, or consumed alcohol with each of these friends. Of the 17.1 percent of IDUs who reported using a syringe after someone else, 78.3 percent reported syringe sharing with close friends. Although syringe sharing occurred within integrated networks at a particular point in time, these friendship networks had considerable turnover, with less than 30 percent of the friends being repeated nominations as close-tie friends. Thus, while sharing tended to occur with strong ties, there was considerable change in the identity of these strong ties. This was particularly true for women, who reported higher sharing rates and higher sharing with strong-tie friends but only marginally less turnover in networks (30 percent repeated nominations in males vs. 26 percent in females).

**Social Networks of Women Injecting Drug Users May Facilitate HIV Risk**

Another study at Johns Hopkins indicates gender differences in the social networks and syringe sharing among 508 IDUs in Baltimore. On average, women's overall social networks were significantly larger than mens. Approximately 40 percent of the members of women's and men's social networks were active and daily drug users. Importantly, however, women shared syringes with a significantly larger proportion of network members than men (25 vs. 17 percent, respectively). Women's larger networks with a high percentage of drug users, combined with their high rates of network needle sharing, could serve to increase their risk of HIV.

**Sex Differences in Risk Factors for HIV Seroconversion among Injecting Drug Users**

Researchers at Johns Hopkins University followed a cohort of 1,874 HIV-negative-IDUs in Baltimore from 1988 to 1998 in order to investigate drug-related and sexual risk factors for HIV. Incidence of HIV seroconversion did not significantly differ by sex. Among both women and men, significantly higher HIV incidence rates occurred among those who injected cocaine alone or in combination with other drugs, injected daily or more, shared injection paraphernalia, had multiple needle-sharing partners, and had a sexually transmitted disease. Higher rates of seroconversion occurred among both women and men aged 30 years or younger at enrollment. For men only, homelessness, number of needle-sharing partners, and shooting gallery attendance were associated with an increased risk of HIV seroconversion. Also, for men only, both higher income and higher levels of education were inversely associated with HIV seroconversion. Among women but not men, HIV incidence was elevated for those who reported using cocaine, and recent enrollment in a methadone maintenance program was inversely associated with HIV seroconversion. The most striking gender difference in risk factors was in terms of sexual risks. Male IDUs, who had recently engaged in homosexual activity, were more than twice as likely to seroconvert than those who did not. Among female IDUs, HIV incidence was more than double among those who reported recently having sex with another IDU. Further, incidence of HIV was double among women who reported a STD in the prior 6 months, compared with those who did not. Also among women, condom use, which is highly correlated with high-risk sexual behaviors (e.g. sex trade), was significantly associated with an increased risk of HIV

seroconversion. Thus, whereas drug-related risk behaviors and homosexual activity were the most important predictors of HIV seroconversion among men, factors consistent with high-risk heterosexual activities were the main predictors among women.

**Trading Sex for Money is Strongest Predictor of HIV Seroconversion in Women Injecting Drug Users**

Among 1,192 male and female street-recruited IDUs in San Francisco from 1986 to 1998, researchers at the University of California–San Francisco, compared those 58 individuals who seroconverted between visits to the 1,134 controls who remained seronegative. The main risk factors for seroconversion among IDUs were sexual behaviors. The strongest predictor of seroconversion for men was having sex with men; men who had sex with men were 8.8 times as likely to seroconvert as heterosexual men. For female IDUs, the strongest predictor of HIV seroconversion was trading sex for money. Specifically, women who reported having traded sex for money in the past year were 5.1 times as likely as others to seroconvert. Further, women younger than 40 years of age were more likely to seroconvert than those 40 years or older, and women who reported having a steady sex partner who injected drugs were less likely to seroconvert than other women.

**Increased Alcohol Consumption Associated with Risky Sexual Behavior in Dependent Drug Users**

In a study of 364 dependent drug users in an inpatient detoxification program, researchers at Boston University examined whether alcohol use is a modifier of HIV-risk behaviors, specifically, drug-risk behaviors and sexual-risk behaviors. Although there was no association between alcohol consumption and HIV drug-risk behavior, alcohol use was associated with HIV sexual-risk behavior in both male and female drug users, and sex-risk behaviors increased slightly with higher alcohol use levels. At the highest level of alcohol consumption, there was a significant difference in sex-risk behaviors for men and women, suggesting that women who consume more alcohol on a daily basis are more likely to engage in sexual behavior placing them at higher risk for HIV infection than men.

**Among Homeless Women, Substance Abuse Positively Associated with Injection Drug Use and Trading Sex**

Researchers at the University of Pennsylvania and UCLA investigated whether homeless women with health and/or social service contacts were less likely to engage in HIV-risk behaviors (e.g., injection drug use, trading sex for drugs or other commodities) than those without such contacts. Similar to previous research with homeless women, in this sample of 974 women there was a high prevalence of HIV-risk behavior activity. In the previous year, 8 percent had injected drugs, 64 percent had engaged in unprotected sex, and 20 percent had traded sex. A large proportion of the women screened positive for drug abuse or dependence (48 percent) and alcohol abuse or dependence (40 percent). Homeless women who were drug abusers were nearly ten times more likely to trade sex than were other homeless women, and those with alcohol-dependence problems were five times more likely to inject drugs. Homeless women with a case manager were less likely than those without one to have injected drugs within the past year, but were no less likely to engage in unprotected sex or trade sex. Homeless women with substance abuse problems are especially vulnerable to HIV transmission, and efforts should be focused on providing access to more intense case management and drug treatment programs for this group.

### *Adolescents*

**Gender Differences in Health and Risk Behavior among Youth Living with HIV**

Lifetime and current health practices and risk behaviors were examined among 350 youth living with HIV (YLH), aged 14 to 23 years, in New York, Los Angeles, San Francisco, and Miami. Compared to females, males were more likely to use drugs and to be HIV symptomatic, had more lifetime and recent sexual partners, used condoms less in the

past 3 months, and were less likely to disclose their HIV status. Males, despite having more sexual partners and more drug use than females over their lifetimes, were nevertheless more likely than females to reduce their number of sexual partners and drug use since learning their HIV status. Youth who were recently sexually active (81.3 percent) had multiple partners. Most of the sexually active YLH used condoms consistently (81.6 percent). YLH who were symptomatic or had an AIDS diagnosis were likely to have recently had more seropositive sexual partners than the asymptomatic youth. Youth disclosed their serostatus to about half of their sexual partners (53.9 percent), although females, Latinos, and YLH with AIDS were more likely to disclose their serostatus than were other groups. YLH with AIDS used fewer hard drugs than those without an AIDS diagnosis. Over half of males and about a third of females who had used hard drugs in their lifetime had stopped using them since learning of their HIV status.

**Drug-using Youth at Substantially Higher Sex Risk for HIV, Especially Females**

In order to determine how stigmatized drug use is related to sexual risk behaviors and network characteristics among youth in an inner-city New York neighborhood, researchers at the National Development and Research Institutes conducted in-person interviews with both a sample of 363 household youths and a sample of 165 targeted street-recruited 18 to 24 year olds who were cocaine, heroin, crack, or injection drug users. Drug use in the preceding 12 months was categorized from lowest to highest social stigma as none, marijuana, noninjected cocaine, noninjected heroin, crack, and injected drugs. Findings revealed that users of any drug were at substantially higher sex risk than those who use no drugs. For example, the proportion of male marijuana users who had concurrent partners was more than double that for those who used no illicit drugs. For females, the proportion was nearly quadruple. Further, users of the more stigmatized drugs had more sex partners. They were also more likely to report a history of concurrent sex partners, sex with someone who also had engaged in sex with a network member, commercial sex work, and unprotected sex. Crack use and drug injection were more strongly associated with increased sex risk among females than among males. These data indicate that any drug use in this sample increased HIV sex risk and that the risk was greater for females than males, thus highlighting the need for gender-specific interventions.

**Gender Differences in HIV-related Sexual Risk Behavior among Urban African American Youth**

Researchers at UCLA and the University of Michigan assessed alcohol and other drug (AOD) use during sexual encounters, sexual partner's age, perceived HIV risk, and perceived condom effectiveness among 388 sexually active African American youth selected from the four public high schools in the second-largest school district in Michigan. Four risk groups were identified: low risk, monogamy strategy, condom strategy, and high risk. The high-risk group included more males (61 percent), and the monogamy group included more females (75 percent). High-risk males reported more AOD use during sexual activity than all females, and low-risk or condom strategy males. Females had older partners, rated condoms as less effective, and perceived lower HIV/AIDS risk than males. These results suggest different patterns of sexual activity and condom use among urban African American adolescent males and females, which may have implications for HIV prevention.

## *Prevention and Treatment Issues*

**Drug-involved Women as Potential Users of Vaginal Microbicides for HIV and Sexually Transmitted Disease Prevention**

A survey of potential users' perspectives on vaginal microbicides was conducted among 743 women – in Bridgeport, CT, Providence, RI, and San Juan, PR – who were at high risk for HIV, including IDUs and sexual partners of male IDUs. In order to be included in the study, the women had either used cocaine or heroin more than four times per month in the past 6 months, were not in inpatient

drug treatment at the time of the study, or had a primary sexual partner in the past 6 months who was a drug injector. Ninety percent of the women said they would be very likely to use microbicides with paying partners (who paid for sex with money or drugs), and 78 percent would with primary partners. Even after potential product characteristics were rated as unacceptable, such as irritation or burning, women expressed a high likelihood of potential use. More than 80 percent of women said they would want their primary partners to know of their microbicide use, and 42 percent said that they would want their paying partners to know. Women's concern about a paying partner's violent response to suggested use of risk-reduction measures was inversely related to predicted likelihood of microbicide use.

**Current Treatment Guidelines May Lead to Differences in Eligibility for HIV Treatment According to Sex**

Research has shown that in men viral load after HIV seroconversion is a predictor of the risk of progression to AIDS, and this has led to the use of viral load as the basis for the current guidelines for the initiation of antiretroviral therapy, which are applied uniformly to men and women. Researchers at Johns Hopkins University have now prospectively compared the relation between the initial viral load following HIV seroconversion and the risk of progression to AIDS in a cohort of 46 female and 156 male IDUs. They found that the median viral load after seroconversion was significantly lower in women vs. men (15,103 vs. 50,766 copies per millimeter), but neither the rates of progression to AIDS nor the risk of progression to AIDS differed significantly according to sex. Further, the CD4+ lymphocyte counts did not differ by sex. While viral load had a similar qualitative predictive value for progression to AIDS in men vs. women, the same absolute viral load conferred different risks of AIDS in men vs. women. For example, an initial viral load of 17,149 copies per milliliter was associated with progression to AIDS in women but not in men, while the median viral load among men who did not progress to AIDS was 40,634 copies. Given the recommendation that treatment should be initiated when the viral load reaches 20,000 copies per milliliter, 74 percent of the men, but only 37 percent of the women, in this study would have been eligible for therapy at the first visit after seroconversion. Thus, treatment guidelines that are based on the viral load, rather than the CD4+ lymphocyte count, will lead to differences in eligibility for antiretroviral treatment according to sex.

## Initiatives

NIDA has engaged in a variety of activities to promote research on women and gender differences and to disseminate research findings in this area. Many of these activities, some of which are described below, involved program announcements, publications, talks, seminars, and special programs targeted at junior investigators. Many efforts have been accomplished by NIH collaborations, including the NIH Office of Research on Women's Health, as well as collaboration with non-federal organizations, including the American Psychological Association and the College on Problems of Drug Dependence.

*Program Announcements (PAs)*

NIDA issued several program announcements during 2001 and 2002 that solicit research that addresses sex and gender differences and issues specific to women:

- **Neuroscience Research on Drug Addiction (PA 02-085)**
- **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Gender Differences (PA 02-055)**
- **Drug Abuse Health Services Research (PA 01-097)**
- **Prescription Drug Abuse (PA 01-048)**
- **Collaborative Clinical Studies in Drug Abuse (PA 01-039)**
- **Drug Abuse Aspects of HIV/AIDS and Other Infections (PA 01-023)**

*Publications*

- **A Collection of NIDA Notes: Articles that Address Women's Health and Gender Differences**

  This is a compilation of articles from the *NIDA Notes* newsletter. This publication was originally published in 1996 and is revised periodically, most recently in 2001.

- **Successfully Including Women in Clinical Trials: A Guide for Researchers**

  NIDA's Clinical Trial Network published the brochure.

- **Women and Gender Research Website**

  The website became operational on NIDA's website in April 1998. Topics include an overview of NIDA'S research program in this area, research findings covering a wide range of topics, a list of publications that either focus on this subject or contain relevant information, and information on funding opportunities in the area of women and gender differences. This site is updated on a regular basis and continues to be an important resource.

*Fostering the Next Generation of Researchers*

NIDA has actively sought to increase the number of new drug abuse investigators who engage in research on women and gender differences through the following programs:

- **Women and Gender Junior Investigator Travel Awards**

  Since 1999, NIDA has given travel awards to junior investigators to attend the annual meeting of the College on Problems of Drug Dependence and present their research on women and/or gender differences. In 2001, NIDA made travel awards to 30 investigators for the annual meeting in Scottsdale, AZ, in June 2001, and again for the annual meeting in Quebec in June 2002.

- **Dissertation Awards**

  In 2002, NIDA issued the program announcement, "Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Gender Differences" (PA 02- 055), which provides support for predoctoral students whose dissertation on drug abuse focuses on women and/or gender differences.

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

  Under this ORWH-led initiative (RFA, OD-99-008) that supports 12 grants funded in 2000, NIDA is providing cofunding for the three grants that provide mentoring to junior faculty members wishing to pursue a program of drug abuse research on women's health and gender differences. The NIDA BIRCWH sites are the University of Kentucky, the Virginia Commonwealth University, and Yale University.

*Other NIH Collaborations*

- **ORWH SCOR Program**

  Eleven centers were established under the ORWH-led initiative, "Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health" (RFA, OD-02-002). NIDA is providing cofunding for the two centers that focus on drug abuse: "Sex and Gender Factors in Drug Abuse" at the Medical University of South Carolina and "Sex, Stress, and Cocaine Addiction" at Yale University.

- **Maternal Lifestyle Study**

  The Maternal Lifestyle Study (MLS), a multicenter project funded by NICHD and NIDA since the early 1990s, is a longitudinal study investigating the health and development of children exposed to cocaine and opiates during pregnancy. This research also examines maternal outcomes associated with

these pregnancies. Measures include a range of child and maternal outcomes, as well as numerous potentially confounding social and environmental factors. The largest study of its type, MLS has sites in Detroit, Memphis, Miami, and Providence. The children have been followed since birth, and the oldest are now 9 years of age. Given its large sample size, the MLS also permits careful study of maternal perinatal complications and pregnancy outcomes.

- **Women's Interagency HIV Study**

  This NIAID, NIDA, NICHD, NCI, and NIDCR cooperative agreement supports a very unique multidisciplinary, multisite study of HIV/AIDS progression in a large cohort of women. Since a large percentage of women at risk for HIV/AIDS are drug abusers, this study provides information on women for whom drug abuse is a factor in their HIV/AIDS.

*Seminars*

NIDA's Women & Gender Research Group sponsored the following seminars in the NIH Neuroscience Center:

- **Gender Differences, Women Drug Abusers and HIV Risk: Lessons Learned and Future Prospects**
  **February 5, 2001**
  Research Triangle Institute
  Wendee M. Wechsberg, Ph.D.

- **Gender Differences in Marijuana and Cocaine Abusers: Evidence from Cerebral Blood Flow and EEG Measures**
  **April 24, 2001**
  Intramural Research Program, NIDA
  Ronald J. Herning, Ph.D.

- **Prevention of Post-rape Psychopathology and Drug Abuse**
  **May 24, 2001**
  Medical University of South Carolina
  Heidi Resnick, Ph.D.

*Meeting Cosponsorships*

- **Research Opportunities for Gender Issues in the Clinical Trial Network**
  **May 14-15, 2001**

  NIDA's WGRG and the Clinical Trial Network (CTN) cosponsored the meeting. Researchers and community treatment providers nationwide shared information on gender differences issues in the research treatment field. NIDA staff gave two presentations: "Women in Cultural Context: The Hope of the CTN" and "Gender Differences in Drug Abuse Research."

- **Enhancing Outcomes in Women's Health**
  **February 2002**
  Washington, DC

  NIDA was a cosponsor of the American Psychological Association conference. NIDA's WGRG organized and chaired three symposia: "The Convergence of Drug Abuse, Sex, and Violence;" "Gender Issues in Drug Abuse Prevention and Treatment Interventions;" and "Intervention Approaches with Women in Diverse Populations at Risk for Drug Abuse."

*Meeting Presentations*

- **How Does Gender Matter in Clinical Trial Network Research?**
  **January 2001**
  Clearwater, Florida

  NIDA staff gave an invited talk at the Clinical Trial Network Steering Committee meeting.

- **The Effects of Sex Hormones on Nicotine Dependence Society for Research on Nicotine and Tobacco**
  **March 2001**
  Seattle, Washington

  NIDA staff co-organized and chaired this symposium.

- **Roundtable Discussions: Hot Topics in Drug Abuse Research**
  **April 2001**
  Minneapolis, Minnesota

  NIDA staff hosted "Gender Issues" at the Society for Research on Child Development's annual meeting.

- **Bridging Neurobiological, Behavioral, and Prevention Science Workshop**
  **May 2001**
  Washington, DC

  NIDA staff hosted the roundtable "Gender: How Does It Matter for Prevention Science?" at this workshop.

- **When Mars Meets Venus: Gender Differences in Drug Dependence**
  **June 2001**
  Scottsdale, Arizona

  NIDA staff served as discussant in the symposium at the annual meeting of the College on Problems of Drug Dependence.

- **Gender Issues Topic Table at the 2nd National Conference on Drug Abuse Prevention Research**
  **August 2001**
  Washington, DC

  NIDA staff served as leader.

- **Gender-specific Issues in the Addictions**
  **August 2001**
  San Francisco, California

  NIDA staff served as discussant for this symposium at the annual meeting of the American Psychological Association.

- **Women and Substance Abuse**
  **October 2001**
  Marina Del Rey, California

  NIDA staff gave keynote address, "Developmental Vulnerabilities for Women and Substance Abuse," in this California Society of Addiction Medicine: State of the Art in Addiction Medicine workshop.

- **Hispanic Drug Abuse Research: Advancing the Field**
  **November 2001**
  Washington, DC

  NIDA staff served as cohost of the Women and Drug Abuse Special Interest Luncheon Table at the National Hispanic Science Network on Drug Abuse at its first National conference.

- **Annual Meeting of the Society for Neuroscience**
  **November 2001**
  San Diego, California

  NIDA staff presented a poster, "Gender Matters in Neuroscience: Investigations of Drug Abuse."

- **Gender Issues Workshop**
  **March 2002**
  New York, New York

  NIDA staff gave an invited talk, "Gender-related Issues in Drug Abuse," in this workshop held at the NIDA conference "Blending Clinical Practice & Research: Forging Partnerships to Enhance Drug Addiction Treatment."

- **The Clinical Implications of Gender for Addiction**
  **April 2002**
  Atlanta, Georgia

  NIDA staff gave an invited talk, "Gender Differences in Vulnerability to Addiction," in this symposium at the Annual Medical-Scientific Conference of the American Society of Addiction Medicine.

- **24th Annual Substance Abuse Librarians and Information Specialists Conference**
  **April 2002**
  Washington, DC

  NIDA staff gave an invited talk, "Gender Differences Issues in Drug Abuse."

*APPENDIX A*

# *Office of Research on Women's Health Research Awards*

## FY 2001 ORWH RESEARCH INITIATIVES

### *Aging*

▶ Title: *Age Difference of Spouses and Long-term Care* NIA
P.I.: Darius Lakdawalla, Ph.D.
RAND, Santa Monica, CA

The magnitude of long-term care expenditures, $100 billion annually, makes it imperative for us to understand past and future trends in long-term care demand. The aim of the proposed research is to examine how the declining age gap between spouses will affect future trends in the demand for long-term care. It has been well established that the presence or absence of a healthy spouse is a major determinant of nursing home entrance: a disabled person married to a healthy spouse is about half as likely to enter a nursing home as a disabled person without a health spouse. In turn, the availability of healthy spouses may have been substantially affected by the shrinking age gap between spouses over the twentieth century. A woman born in 1900, on average, ended up with a husband who was 4.2 years older than she. The same woman born in 1950, however, would have ended up with a husband just 2.5 years older. The investigators propose to show that this decline has two effects: 1) all elderly couples will tend to stay married longer, because they are more closely matched in age; and 2) today's elderly women will tend to have younger, healthier husbands, but today's elderly men will tend to have older wives. The first effect will reduce nursing home demand, while the second has an ambiguous effect. The investigators propose to quantify both effects and estimate their overall effect on nursing home demand. Life table data from the Social Security Administration will be used to compute the effect of the changing age gap on the prevalence of marriage among the elderly. Data from the Action for Health in Diabetes (AHEAD) study will be used to estimate the probability of nursing home entrance by disability, marital status, and the age of a married person's spouse. As part of this analysis, Census data will be utilized to impute data on the ages of deceased spouses absent from AHEAD. This analysis quantifies the effect of the changing age gap of the probability of nursing home entrance for married people. Using estimates of the changing probability of being married, and the changing probability of nursing home entrance for married people, the total effect of the changing age gap on overall nursing home demand will be computed.

*1R03AG19900-01 Award Amount: $86,538 Basic*

- Title: *A Fall Prevention Program for High-risk Elderly Women* NINR
  P.I.: Jean F. Wyman, Ph.D., R.N.
  University of Minnesota, Minneapolis, MN

  The long-term objective of this study is to develop cost-effective, community-based strategies for the prevention of falls in high-risk elderly women. Specific aims are 1) test the efficacy of a fall prevention program for high-risk elderly women on fall rates over 1 and 2 years; 2) determine the effects of the fall prevention program on postural competence, functional performance, and a variety of other outcome measures; and 3) identify demographic, clinical, personal, functional, and postural competence variables that predict long-term exercise adherence for participants in the fall prevention program. The participants will be 250 community-dwelling women, aged 70 and over, who are mentally intact, ambulatory, with postural instability – and at least one other fall risk factor – not currently involved in regular exercise, and medically stable with physician approval for independent exercise participation. This study will provide information on the efficacy and cost of simple interventions designed to prevent falls and fall-related injuries, reduce preclinical disability, maintain long-term exercise adherence, and improve quality of life for older women.

  *5R01NR005107-02 Award Amount: $150,000 Clinical*

### *Adolescent Health*

- Title: *The National Study of Adolescent Health – ADD Health* NICHD
  P.I.: Richard Udry, Ph.D.
  University of North Carolina–Chapel Hill, Chapel Hill, NC

  The National Study of Adolescent Health: Survey 2000, is being conducted by investigators at the University of North Carolina, Chapel Hill, to investigate a broad set of research questions on the health of young men and women as they make the transition to adulthood. This survey is a followup to the National Longitudinal Study of Adolescent Health (ADD Health). ADD Health was conducted in 1994-1996 to provide comprehensive information on adolescent health and behavior and the social contexts in which adolescents develop. ADD Health was funded through a 5-year grant supporting one wave of in-school data collection (1994; N=90,000); two waves of in-home data collection (N=20,000 and 16,000, respectively, in 1995 and 1996); one wave of home interviews with parents of 18,000 respondents in 1995; two waves of data collected from school administrators; and linking of existing data on local communities. Survey 2000 is supported by a grant from the National Institute of Child Health and Human Development, with cofunding support from the DHHS Office of Population Affairs and the Office of the Assistant Secretary for Health, and will re-survey 20,000 adolescents who initially participated in previous in-home interviews.

  *5P01HD031921-08 Award Amount: $50,000 Cross-sectional survey*

## *Alcohol and Other Substance Abuse*

▶ Title: *Alcohol, HIV-risk Behaviors, and Sexual Victimization* NIAAA
P.I.: Maria Testa, Ph.D.
Research Institute on Addictions, Buffalo, NY

This application suggests that childhood sexual abuse and risk-prone personality (high sensation-seeking, high negative affect, low assertiveness) lead women to engage in risky behaviors (heavy alcohol and drug use, and high levels of sexual activity and exposure to risky settings, such as bars) which in turn increase the likelihood of experiencing both sexual victimization and HIV/STD infections. There will be a three-wave, cross-legged panel design using a representative sample of 1,000 unmarried women, ages 18 to 30, recruited from random digit dialing.

*5R01AA12013-04 Award Amount: $100,000 Clinical*

▶ Title: *Sexual Identity and Drinking: Risk and Protect Factors* NIAAA
P.I.: Tonda L. Hughes, Ph.D.
University of Illinois at Chicago, IL

This study will use an existing survey instrument to examine and compare risk and protective factors for heavy drinking and alcohol-related problems in lesbians and heterosexual women. The study will include data from 600 women, 18 years of age or older.

*5K01AA00266-03 Award Amount: $55,224 Clinical*

▶ Title: *Women with Schizophrenia and Co-occurring Substance Use Disorders* NIDA
P.I.: Jean Gearon, Ph.D.
University of Maryland, Baltimore, MD

The primary goals of this project are: 1) to determine if women with schizophrenia and co-occurring substance use disorders are more vulnerable to HIV (e.g., engage in more high-risk behaviors) and violent victimization than either women with major depression and co-occurring substance use disorders, or women with substance use disorders only and no history of serious and persistent mental illness; 2) to determine if women with schizophrenia, who abuse substances, experience more violent victimization than women with major depression and co-occurring substance, use disorders, or women with substance abuse disorders alone and no history of serious and persistent mental illness; and 3) to examine the causal sequencing between cognitive functioning, social competency, negative symptoms, and HIV risk and victimization.

*5R29DA011199-03 Award Amount: $20,000 Clinical*

## *Cancer*

▶ Title: *Growth Regulation of the Normal and Malignant Endometrium* NCI
P.I.: Leslie Gold, Ph.D.
New York University School of Medicine, New York, NY

The broad long-term objectives of this study are to elucidate mechanisms that cause loss of growth inhibition by TGF-α in endometrial adenocarcinoma (ECA), and to define hormone regulation of TGF-α through stroma/epithelial interactions in the endocumetrium. ECA is induced by estrogenic (E2) agents causing hyperproliferation of uterine epithelial cells (UtE). Progesterone (Pg) is therapeutic due to its growth inhibitory effect. TGF-α-mediated growth inhibition is transduced by two cooperating receptors (RI, RII) and the downstream signaling/transcription factors, Smad2/3, that activate genes that block cell cycle progression, such as the cyclin-dependent kinase inhibitor, $p27^{kip1}$. The investigators have shown that UtE, isolated from all grades of ECA, escape negative growth control by TGF-α by incurring multiple defects in the TGF-α response pathway, including loss of: TGF-α RII, activated Smad2, and $p27^{kip1}$. Moreover, in complex hyperplasia (CH), the precursor to ECA, these proteins are already decreased. Thus, disruption of TGF-α action occurs early in endometrial carcinogenesis, providing an opportunity to understand molecular events leading to dysregulated growth. The principal investigator will use primary cultures of normal, CH, and ECA UtE and co-cultures with stromal cells (UtS), which, unlike ECA cell lines, retain many *in vivo* differentiation characteristics. *Specific Aim I*, will determine the molecular mechanisms causing TGF-α receptor downregulation (e.g., transcriptional, translational) and test for defective Smad2/3 signaling using a TGF-α-promoter-responsive reporter assay. TGF-α function by transient transfection of RII cDNA into ECA UtE will be regained. *Specific Aim 2* will test the hypothesis that loss of $p27^{kip1}$ in ECA is by degradation via ubiquitin-proteasome pathway, which is E2-driven directly through as a MAP kinase via the Ras/MAPK/ERK1 pathway that TGF-α normally prevents p27 degradation. Tissue/cell lysates, inhibitors of proteasomes and MAPK, and immunoanalytical techniques will be used. Using single cell and co-cultures, we show that UtS from normal, but not malignant, endometrium mediates Pg-induced growth inhibition of normal UtE. *Specific Aim 3* will test the hypotheses that UtS paracrine-mediates Pg-induced growth inhibition of UtE by release of TGF-α in response to Pg. Co-cultures of normal and "malignant" UtS and UtE and novel *in vivo* chimeric tissue recombinants composed of UtS from both Pg receptor knock-out (PRKO) and wild-type mice and human UtE, that are hormonally manipulated as transplants in nude mice and UtE then analyzed for growth will be used. These studies should elucidate molecular mechanisms of endometrial carcinogenesis, hormonal (dys) regulation of endometrial growth, and identify targets for prevention and therapeutic intervention.

*1R01CA89175-01A1 Award Amount: $100,000 Basic*

▶ Title: *Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines* NCI
P.I.: Douglas R. Lowy, M.D.
National Cancer Institute, Bethesda, MD

This project will perform the early phase clinical trials of two HPV16-based papillomavirus vaccines. L1 is a major structural papillomaviral protein that can self assemble into virus-like particles (VLPs). It is thought that L1 VLP will only protect by preventing primary infection. To add another level of protection, a chimeric VLP was developed by adding the L2 minor capsid protein to the L1. After preclinical vaccine results, an early-phase human trial of L1 HPV16 VLP vaccine is being tested. There are four groups of 12 normal volunteers, 18 to 29 years old. In each group, ten volunteers received the vaccine and two received a placebo in a double-blind fashion.

*Award Amount: $300,000 Clinical*

▶ Title: *Symptom Intervention for Older Women with Breast Cancer* NINR
P.I.: Susan M. Heidrich, Ph.D.
University of Wisconsin Madison, Madison, WI

Older women, especially those over age 75, are the fastest growing segment of the population. Many of these women will be living with breast cancer because the incidence of this disease increases with age. Unfortunately, the research on adaptation to illness, symptom management, and quality of life of women with breast cancer has focused on women under 65. Unlike younger women, older women with breast cancer experience symptoms of their disease and its treatment concurrent with symptoms of age-related chronic illnesses. Thus, they are faced with the unique challenge of sorting out and managing a variety of complex and sometimes confusing symptoms. We propose to test an individualized representational intervention (IRIS) to improve symptom management and quality of life in older women with breast cancer. The theoretical basis of the intervention is Leventhal's Common Sense Model, with the addition of strategies for conceptual change. Leventhal's Common Sense Model suggests that individuals' representations of their symptoms are critical determinants of how they cope with them. By addressing women's representations, we hope to change beliefs that interfere with adequate symptom management; assist women in developing individualized, effective symptom management strategies; and thereby improve quality of life. Participants in this study will be women aged 65 and older who are at least 1-year post-diagnosis of breast cancer. They will be randomized to one of three conditions: an IRIS delivered by an advanced practice nurse in a counseling interview, an attention-only control group, or usual care. Measures of symptom distress, helpfulness of symptoms management activities, and quality of life will be taken at baseline, 6-weeks, and 10-weeks post-intervention. We predict that IRIS will improve symptom management, which will, in turn, improve quality of life for older women with breast cancer.

*1R01NR07741-01 Award Amount: $100,000 Clinical*

### *Cardiovascular Disease*

- Title: *Evidence Report – Gender Differences in Cardiac Care* AHRQ
  P.I.: Deborah Grady, M.D.
  Regents of the University of California, San Francisco, CA

  The Phase II project builds upon the findings and recommendations from the initial study that identified the scientific evidence and basis relating to sex and gender differences in coronary heart disease, its diagnosis, and subsequent treatment. The recommendations, considered by the Evidence Practice Centers and AHRQ, in order to complete a comprehensive evidence report on the prioritized set of questions that focus on the gender-based difference in diagnosis and treatment, both in-hospital and chronic, related to coronary heart disease. The study population is adult females, including major racial and ethnic minorities and the elderly.

  *Award Amount: $250,000 Collaborative Federal Agency Review*

- Title: *Hormonal Regulation of Angiotensin Receptors* NIA
  P.I.: Kathryn Sandberg, Ph.D.
  Georgetown University, Washington, DC

  The sexual dimorphism associated with many cardiovascular and renal disease, related to aging, is well documented with the risks being significantly higher for men than women. Two of the major risk factors in these diseases are felt to be increased activity of the renin angiotensin system (RAS) and estrogen deficiency. Furthermore, there is accumulating evidence that estrogen may have a regulatory influence on the RAS. In view of its considerable potential physiologic and pathophysiologic significance, the principal investigator will investigate how estrogen regulates the activity of the RAS. Specific hypotheses to be tested in the proposed studies are: 1) estrogen downregulates the density of the type 1 angiotensin receptor subtype ($AT_1$) expressed in adrenal and kidney tissues, and thereby attenates tissue responsiveness to the hormone, angiotensin II (Ang II); 2) estrogen mediates its effects on $AT_1$ receptor expression in these tissues via the estrogen type ($_{Er}$) receptor; 3) estrogen has direct effects on $AT_1$ receptor expression by modulating receptor transcriptional and/or post-transcriptional mechanisms; 4) estrogen also acts to decrease $AT_1$ receptor expression by modulating the local production of Ang II; and 5) the ability of estrogen to downregulate Ang II activity in the adrenal and kidney is attenuated in animal models of salt-sensitive hypertension and aging. *Aim 1* is to determine the effects of estrogen on $AT_1$ receptor density in the adrenal and kidney of the rat using quantitative autoradiography under a variety of perturbations of the RAS. In *Aim 2*, the effects of estrogen on adrenal and kidney tissue responsiveness to Ang II by measuring the effects of estrogen on Ang II-induced changes in aldosterone secretion and renal hemodynamics will be determined. *Aim 3* will focus on determining the specific mechanisms by which estrogen reduces the density of $AT_1$ receptors. The effect of estrogen on $AT_1$ receptor synthetic and degradative pathways, and its effects on the components of the plasma and tissue RAS, will be determined. Which estrogen receptor subtype mediates the effects of estrogen will also be determined. In the final aim, *Aim 4*, the effects of estrogen on adrenal and kidney $AT_1$ receptor density and function in relevant animal models of salt-sensitive hypertension and aging will be studied. These studies will answer important questions about whether some of the well-documented cardio- and renal-protective effects of estrogen may occur via downregulation of $AT_1$ receptors in the adrenal and kidney, two key effector organs of the RAS.

  *1R01AG19291-01 Award Amount: $100,000 Basic*

▶ Title: *Cardiovascular Disease Risk and Health in Postmenopausal Phytoestrogen Users* NHLBI

P.I.: Donna C. Kritz-Silverstein
University of California–San Diego, San Diego, CA

In the United States, heart disease is the leading cause of death in postmenopausal women. Estrogen replacement therapy is beneficial for heart disease risk factors, as well as for bone density. However, a large proportion of postmenopausal women are not compliant with therapeutic regimens. Phytoestrogens are naturally occurring compounds found in plants and soy products that have estrogenic effects, and may represent an alternative treatment for the prevention of heart disease and osteoporosis in postmenopausal women. However, few intervention trials have examined the extent to which it is possible to improve heart disease risk factors, bone density, and quality of life in postmenopausal women through use of a dietary supplement of phytoestrogen. The proposed randomized, double-blind, placebo controlled study is designed to determine the acceptability and benefits of use of a dietary supplement of phytoestrogen (genistein) versus placebo on heart disease risk factors, bone density, and psychosocial outcomes in postmenopausal women, aged 45 to 74. Approximately 300 women will be screened in order to enroll 200 (100 treatment, 100 placebo) who will each be followed for 1 year. Data will be collected at screening and baseline visits, 1 and 3-month followup telephone calls, and 6- and 12-month followup clinic visits. Measures of HDL, and other heart disease risk factors, hip and spine bone density, and depression, life satisfaction, and quality of well being will be obtained. Cross-sectional and longitudinal comparisons of treatment and placebo groups will be performed before and after adjustment and stratification for potentially confounding covariates. It is expected that women treated with phytoestrogen will have higher HDL and bone density, and more favorable psychosocial outcomes. It is also expected that women using phytoestrogen will have more favorable total cholesterol, LDL, triglycerides, Lp(a), fibrinogen, blood pressure, fasting and postmenopausal challenge glucose and insulin, and fat distribution. Given that women can expect to live one-third of their lives after menopause, the investigators point out that it is important to know how Phytoestrogen may modify heart disease risk factors and bone density. They further state that by defining the influence phytoestrogen use has, this study would contribute to the understanding of how to prevent cardiovascular disease and osteoporosis in postmenopausal women, and thereby improve their quality of life.

*3R01HL057790-04 Award Amount: $144,795 Clinical*

### *Diabetes*

- Title: *Diabetes Prevention Program Primary Prevention Program Data Coordinating Center* NIDDK
  P.I.: Sarah Fowler, Ph.D.
  George Washington University, Washington, DC

  The Diabetes Prevention Program is a multicentered, randomized trial designed to determine whether type 2 diabetes can be prevented or delayed in a population of high-risk individuals. Included in the high-risk population are women with a history of gestational diabetes mellitus (GDM) and individuals with impaired glucose tolerance. There are 3,234 participants enrolled in the three-arm study with two active treatment groups (metformin and lifestyle) compared to placebo controls. Of the total recruited, 68 percent were women – 13 percent of these had a history of GDM, and nearly 50 percent were from minority populations.

  *5U01DK048489-08 Award Amount: $67,500 Clinical*

- Title: *Diabetes Prevention Program Primary Prevention Trial* NIDDK
  P.I.: David Marrero, Ph.D.
  Indiana University–Perdue, University at Indianapolis, Indianapolis, IN

  The primary goal of the proposed project is to determine, via a collaborative multicenter trial, whether interventions can: 1) prevent persons with impaired glucose tolerance (IGT) or a history of gestational diabetes mellitus (GDM) from developing non-insulin-dependent diabetes mellitus (NIDDM); and 2) prevent the worsening of glucose tolerance in people with newly diagnosed NIDDM. Because of the ethnic diversity of the study populations, a secondary goal is to design the interventions to be sensitive to varying social, ethnic, and cultural values. With the use of the Regenstrief Medical Record System, we have identified three potential high-risk populations: a) 6,721 persons with a prior history of diabetes with random blood glucose values of 108 to 160 mg/dl and concomitant risk factors for NIDDM, of whom 54 percent are African American, b) 3,688 patients with NIDDM in whom we will contact their first-degree relatives, and c) between 530 to 600 women with a history of GDM projected to be available by enrollment, 34 percent of whom are African American. We plan to evaluate, using a randomized control group comparison design, the relative effectiveness of the proposed interventions in reducing conversion to NIDDM in persons with IGT, and deterioration of glucose tolerance in newly diagnosed NIDDM as primary end points and macrovascular risk factors, coronary events, and overall mortality as secondary end points.

  *5U01DK048406-08 Award Amount: $67,500 Clinical*

▶ Title: *Diabetes Prevention Program* NIDDK
P.I.: Harry Shamoon, M.D.
Yeshiva University, New York, NY

By selecting populations at higher than average risk for the ultimate development of NIDDM, the Diabetes Center at the Albert Einstein College of Medicine will test the following hypothesis: The reduction in risk of developing NIDDM in persons at high risk for the development of diabetes will be dependent on treatment which affects insulin resistance, islet B-cell dysfunction, and/or hepatic glucose production. Interventions which include diet, exercise sulfonylurea drugs, and metformin in a factorial design can address this hypothesis. The Albert Einstein Center has a large, identified population of individuals from racial and ethnic minority groups in the Bronx and Westchester Counties who receive their medical care in Einstein-affiliated programs; an identified and well-characterized population of women who had gestational diabetes diagnosed between 1988 and the present, and an annual accrual of an additional cohort of women with gestational diabetes; members of the treatment team with specific competence in diabetes in Hispanic and in African American individuals; and expertise in related areas, such as hypertension control, cardiovascular risk reduction, and behavioral techniques intended to achieve therapeutic goals.

*5U01DK048349-08 Award Amount: $21,000 Clinical*

▶ Title: *Diabetes Prevention Program* NIDDK
P.I.: Janet A. Tobian, M.D.
University of Chicago, Chicago, IL

This grant is a multicenter trial in which subjects would be screened for inclusion and exclusion criteria. A primary prevention subgroup will consist of subjects with impaired glucose tolerance (IGT) by National Diabetes Data Group (NDDG) criteria with a fasting plasma glucose (FPG) equal to or more than 110 mg/dl. A secondary intervention subgroup will consist of individuals with NIDDM by NDDG criteria and a FPG 140 mg/dl. The subjects will be randomized in a 2 x 2 factorial design to: 1) intensive program of diet, exercise, and stress reduction versus standard dietary and exercise advice, as well as, 2) therapy with either glipizide or placebo. We propose that the diet and exercise intervention be modeled after the PATHWAYS program (diet, exercise, and stress management) which has been validated as an effective method of weight reduction in inner-city African American women. Individuals will be followed to test whether these interventions can: 1) prevent the worsening of glucose tolerance in these subjects over 5 years, and 2) reduce cardiovascular morbidity and mortality.

*5U01DK048381-08 Award Amount: $22,000 Clinical*

- Title: *NIDDM Primary Prevention Trial* NIDDK
  P.I.: Neil White, M.D.
  Washington University, St. Louis, MO

  The proposed intervention is centered on an intensive, multidisciplinary program to promote long-term weight loss and increase physical activity among 200 volunteers who work in or live near the Washington University Medical Center in St. Louis. The proposed intervention is designed to minimize physical discomfort and lifestyle disruption; to emphasize gradual, moderate changes in the foods usually eaten; to maximize continued adherence over 5 years; and to be acceptable to both white and African American volunteers. In order to sustain this weight loss long term, it is proposed to have the intensively managed patients seen regularly by trained members of a multidisciplinary team that will consist of an exercise technician, a nutritionist, a nurse, and a social worker trained in behavioral medicine. Volunteers randomized to the control group will be seen quarterly and provided with state-of-the-art educational and motivational materials that will include recommendations for weight loss, increase physical activity, and a prudent diet low in saturated fats and cholesterol.

  *5U01DK048400-08 Award Amount: $22,000 Clinical*

### *Eating Disorders*

- Title: *Meditation-based Treatment for Binge Eating Disorder* NCCAM
  P.I.: Jean Kristeller, Ph.D.
  Indiana State University, Terre Haute, IN

  As many as 30 percent of individuals seeking treatment for obesity meet DSM-IV criteria for binge eating disorder (BED). BED is marked by recurrent episodes of binging, accompanied by feelings of loss of control, and involves chronic disregulation of physiological, emotional, and behavioral systems. Meditation-based interventions have been used successfully to treat disorders with similar addictive and disregulatory characteristics, but have not been applied to treating BED. Data from an uncontrolled pilot study suggests that such an intervention can have marked immediate impact on decreasing episodes of binge eating and other associated characteristics in obese women. Therefore, this study incorporates appropriate comparison conditions to further investigate the efficacy of a mindful, meditation-based intervention as a treatment component for treating BED symptoms. Exploratory aspects include further development of a manual, establishment of effect size (in comparison to appropriate comparison groups), inclusion of a more diverse population, and of measures that address: 1) individual differences in treatment response, 2) possible mechanisms, 3) time course of response, and 4) impact on medical and health variables. Women (approximate N=162) from two communities will be randomly assigned to three conditions: 1) an 8-week manualized mediation-based group intervention, 2) a psychoeducational comparison condition, or 3) a waiting-list control. Primary outcome variables will be changes in binge-eating behaviors, and associated measures of depression, anxiety, self esteem, and diet; secondary variables include medical variables sensitive to dietary change (i.e., weight, blood pressure, lipid profile, blood glucose levels), and process variables related to meditation practice (the Tellegen Absorption Scale, perceived value, use of the meditation practice), and experiences of increased control and awareness. Participants will be evaluated pre- and post-treatment, and at 1-, 3-, and 6-months followup. This data would then support the further investigation of a meditation-based intervention as part of a more comprehensive treatment program for BED.

  *1R21AT00416-01 Award Amount: $172,095 Clinical*

▶ Title: *Nociception in Bulimia Nervosa* NIDDK
P.I.: Patricia Faris, Ph.D.
University of Minnesota, Minneapolis, MN

This application proposes to further study the role of vagal afferents in the perpetuation of binge eating and vomiting. Previously proposed was that the pathophysiology of bulimia nervosa involved dysregulation of the afferent vagus nerve. This hypothesis was tested using two main strategies: 1) the use of somatic pain detection as a physiological marker of vagal afferent activity; and 2) the use of ondansetron (a 5 HT3 antagonist known to reduce vagal neurotransmission) as a pharmacological challenge test of vagal modulation of both the bulimic behaviors and on elevated pain detection thresholds. The principle findings from these studies are: 1) pain detection thresholds rise dynamically across the interval between bulimic binge and vomit episodes, apparently reaching their zenith as the next bulimic episode is approached and dropping to their nadir in close temporal association with having recently engaged in a bulimic episode; and 2) ondansetron treatment was associated with a significant moderation in both the cyclic fluctuations in pain detection thresholds and the primary disorder symptom of binge and vomit episodes per week in a group of patients with severe and chronic bulimia nervosa under randomized, placebo controlled, double-blind conditions. The overall hypothesis will be tested through an interactive combination of clinical pharmacology and psychophysiological approaches. *Specific Aim I* will investigate the association between disorder severity as indicated by binge and vomit frequencies and dynamic changes in pain detection thresholds. The approach of this aim is based on the idea that if dynamic increases in vagal activity drive bulimic episodes, then the rate of cyclic changes in vagal activity should be a significant statistical predictor of the frequency of bulimic behaviors. *Specific Aim II* will investigate the effect of psychotherapeutic intervention on physiological indices of vagal activity, namely thresholds for pain detection and induction of satiety. The approach of the aim is based on the idea that if vagal hyperactivity represents the critical factor involved in symptom production, then any therapeutic method resulting in a decrease in symptoms would be predicted to be accompanied by a demonstrable correction in vagal function. In addition to generating important basic science information on vagus nerve function in bulimia nervosa, these studies will also provide insight into the utility of ondansetron in the clinical treatment of this debilitating disorder.

*2R01DK52291-06A2 Award Amount: $200,000 Clinical*

## *Endocrinology*

▶ Title: *Mechanisms of Steroid Hormone Action in the Brain* NIDDK
P.I.: Marc J. Tetel, Ph.D.
Skidmore College, Saratoga Springs, NY

The ovarian hormones, estradiol and progesterone, act in brain to mediate complex behaviors, such as female reproductive behavior in rodents. Understanding how these ovarian hormones act in brain is essential to understanding their role in various mental health disorders, such as depression. However, the cellular and molecular mechanisms by which steroid receptors mediate the effects of these hormones in brain are not well understood. Recently, a novel class of proteins has been identified, known as nuclear receptor coactivators, that dramatically enhance the transcriptional activity of steroid receptors. While research has led to a much greater understanding of the molecular mechanisms of these coactivators in steroid receptor action *in vitro*, very little is known about coactivator function *in vivo* in brain to regulate hormone-dependent gene expression and behavior. This proposal investigates the function of three important coactivators – steroid receptor coactivator-1 (SRC-1), SRC-3, and CREB binding protein (CBP) – in estrogen receptor (ER) action in brain and the regulation of behavior.

*Aim I* will determine if SRC-3, which has recently been shown to be essential for female reproductive physiology, is expressed in steroid receptor-containing neurons in brain regions known to regulate reproductive behavior. In support, it has been found that SRC-1 and CBP are expressed in steroid-sensitive cells in behaviorally relevant brain areas. Aim I will also test the hypothesis that these three coactivators physically interact with neural ER in a hormone-dependent manner. *Aim 2* will use antisense oligonucleotides to suppress SRC-1, SRC-3, and CBP expression to investigate the function of these coactivators in ER-mediated activation of three behaviorally relevant genes: the progesterone receptor, preproenkephalin, and oxytocin receptor genes. *Aim 3* will use the same antisense approach to test the hypothesis that these nuclear receptor coactivators are critical for the expression of estradiol-induced female reproductive behavior.

Consistent with these hypotheses, our preliminary results indicate a functional role for these coactivators in estrogen-dependent gene expression in brain and hormone-dependent reproductive behavior. These studies will greatly enhance our understanding of how these novel coactivators function with steroid receptors in brain to activate behaviorally relevant genes and regulate complex behaviors. Finally, these nuclear receptor coactivators have been implicated in human disorders, including a form of mental retardation (Rubinstein-Taybi syndrome), and hormone-dependent diseases, such as breast cancer. Studying how these coactivators function *in vivo* and, moreover, in brain, will greatly increase our limited knowledge of the role of these coactivators in human disorders.

*1R55DK061935-01 Award Amount: $100,000 Basic*

## *Gastroenterology*

▶ Title: *Cognitive Therapy as a Treatment for Irritable Bowel Syndrome* NIDDK
P.I.: Edward Blanchard, Ph.D.
State University of New York, Albany, NY

Recent research suggests that cognitive therapy (CT) is highly effective (70 to 80 percent clinically improved) in the short term (3 months) as a treatment for irritable bowel syndrome. This application seeks to replicate and extend previous small-scale studies by conducting a controlled clinical trial of CT vs. a self-help support group as an attention placebo control and followup of the treated patients for at least 12 months.

*5R01DK54211-03 Award Amount: $100,000 Clinical*

▶ Title: *Neurotensin's Role in Models of Irritable Bowel Syndrome-related Hyperalgesia* NIDDK
P.I.: Robert E. Carraway, Ph.D.
University of Massachusetts, Worcester, MA

Neurotensin (NT), a gastrointestinal peptide, participates in modulating pain perception, mediating stress responses, and regulating digestive motility and secretion. NT works closely with mast cells which coordinate neuroendocrine immune activities in the gut. This project hypothesizes that NT-mast cell interactions are involved in physiological visceral perception and/or pathological visceral hyperalgesia. It is likely that multiple chemical mediators are involved in visceral hypersensitivity associated with stress-related functional bowel disorders. This proposal will address the potential role of neurotensin as a key mediator of the pathological hyperalgesia associated with irritable bowel syndrome using animal models of post-stress and post-inflammatory bowel hypersensitivity. The hypothesis will be tested using NT receptor antagonist, an NT-knockout mouse model, and a mast cell-deficient mouse model.

*3R01DK56999-01S1 Award Amount: $50,000 Basic*

▶ Title: *Regional Cerebral Activation with Visceral Pain in Irritable Bowel Syndrome Controls* NIDDK
P.I.: Howard R. Mertz, M.D.
Vanderbilt University, Nashville, TN

Recent data have demonstrated abnormal activation of limbic and paralimbic pain centers in irritable bowel syndrome (IBS) in response to rectal pain. Conversely, non-limbic pain centers – including the VPL-thalamus, sensory cortex, and insular systems – are critical to the generation of symptoms in IBS. This project will compare the activity of the limbic system in IBS and controls in response to graded rectal distention (non-painful and painful). Activity in non-limbic pain centers and autonomic outflow centers will be compared between IBS and controls. Understanding the function of the limbic and non-limbic pain centers in healthy and disease states, and the effect of stress and medication on the pain experience, may lead to improved pharmacological and behavioral therapies for visceral pain, including IBS.

*3R21DK57047-01S1 Award Amount: $25,000 Clinical*

- Title: *Effect of Menstrual Cycle and Irritable Bowel Syndrome on Central Nervous System Processing of Gut Stimuli* NIDDK
  P.I.: Ann Ouyang, M.D.
  Milton S. Hershey Medical Center, Hershey, PA

  Recent evidence suggest that patients with irritable bowel syndrome (IBS) have heightened sensitivity to visceral stimuli. Little is known about factors affecting visceral sensitivity, reasons for the higher female prevalence, or the central nervous system processing of visceral sensitivity stimuli, and if this process is altered in IBS. The investigators hypothesize that: 1) menstrual cycle stage affects visceral sensitivity in both control female subjects and in subjects with IBS; 2) the areas of the brain which are activated by visceral stimulation are dependent on both the degree of distension and by the perception that the stimulus is painful; and 3) the areas of the brain activated in IBS subjects, when the stimulus is painful, differ from areas activated in control subjects, and that this difference may be due to the effect of anxiety. Specific aims of the study are: 1) to determine the effect of menstrual cycle on the perception of rectal balloon distention and transcutaneous nerve stimulation (TNS) in subjects without bowel symptoms (controls); 2) to determine the effect of menstrual cycle on these responses in subjects with IBS; 3) to compare the responses between controls and IBS subjects; 4) to determine the regions of the brain activated in response to rectal (non-painful and painful) and non-visceral (TNS) stimulation; and 5) to determine the influence of the state of anxiety on these parameters. An understanding of cerebral processing of non-painful and painful visceral stimuli will be helpful in defining the pathway for perceiving pain in the IBS and other functional gut disorders, and for directing therapy appropriately.

  *3R21DK57053-02S1 Award Amount: $50,000 Clinical*

- Title: *Biofeedback for Fecal Incontinence and Constipation* NIDDK
  P.I.: William E. Whitehead, Ph.D.
  University of North Carolina, Chapel Hill, NC

  Among constipation patients, half are reported to have pelvic floor dyssynergia, a condition marked by an inability to relax pelvis floor muscles during evacuation. Biofeedback has been recommended for the treatment of both conditions because uncontrolled studies over the past 10 to 25 years suggest that these treatments are as effective as medical or surgical management and involve no risk. However, placebo-controlled trials are lacking in this area. The aims of the proposed research are: 1) to compare biofeedback to alternative therapies for which patients have a similar expectation of benefit; 2) to identify which patients are most likely to benefit; and 3) to assess the impact of treatment on quality of life. Two long-term, prospective, single-blind studies will be conducted. *Study I* will compare biofeedback for the treatment of fecal incontinence to a standard therapy, Kegel exercises. *Study II* will compare biofeedback for pelvic floor dyssynergia to a skeletal muscle relaxant drug (diazepam) and to placebo medication. These studies will help to establish the efficacy of biofeedback on the treatment of defecatory disorders.

  *3R01DK57048-01S2 Award Amount: $75,000 Clinical*

## *Genitourinary*

▶ Title: *Urine Loss and Prolapse in Nuns and Their Parous Sisters* NICHD
P.I.: Gunhilde M. Buchsbaum, M.D.
University of Rochester, Rochester, NY

Urinary incontinence (UI) and pelvic organ prolapse (POP) are common health problems in older women, for which the etiologies are poorly understood. Injuries to the pelvic floor at the time of vaginal delivery and genetic predisposition have been implicated as factors associated with UI and POP. However, the epidemiological evidence for these relationships is scant and controversial. Data from the investigators survey study of 149 nulliparous nuns found the same prevalence of stress urinary incontinence as was reported for parous women. The major objective of our proposed study is to determine whether vaginal delivery and familiarity are associated with the development of urinary incontinence and pelvic organ prolapse by comparing the prevalence of objectively confirmed incontinenence and prolapse in nuns (nulliparous women) with the corresponding rates in their biological sisters who have had at least one vaginal delivery. To achieve this objective, the investigators will: recruit the nuns' biological sisters who have had at least one vaginal delivery; collect data from nuns and their sisters about the presence of any symptoms of UI and POP, and on any risk factors for these conditions; and examine nuns and sisters for objective evidence of UI and POP. The examiner will be blinded to the subjects' identity as to nun or sister, and to the presence or absence of symptoms. Women with signs or symptoms of UI and POP will undergo further urodynamic testing. Finally, the data collected will be tested in a matched pair analysis. It will be determined whether nulliparous nuns differ from their biological sisters with regard to UI and POP. A matched pair logistic regression will be performed to obtain an adjusted estimate of the impact of familiarity and vaginal delivery in UI and POP, taking into account other risk factors.

*1R01HD41165-01 Award Amount: $331,779 Clinical*

▶ Title: *A Randomized Surgical Trial: Burch vs. Sling* NIDDK
P.I.: Linda Brubaker, M.D.
Loyola University Chicago, Maywood, IL

The Loyola team plans participation in the Urinary Incontinence Treatment Network in order to advance our understanding of the clinical care for women with stress urinary incontinence. Our multidisciplinary team has the volume and proven ability to participate in clinical trials. As requested in the Request for Applications, investigator experience, institutional support, patient volumes, and human subject safety is discussed. The Loyola team understands the significance of this important clinical trial; can recruit and retain patients of racial, economic, and ethnic diversity; has experienced investigators, including physicians, nurses, physical therapists, and urodynamic technicians; has a clinical environment and resources which will maximize chances for a successful clinical trial; has a current clinical practice which offers surgical, pharmacological, and behavioral treatment for urinary incontinence; can ensure data management and transmission; and looks forward to cooperation with the other Clincal Trial Centers in order to maximize the scientific results of this study.

*1U01DK60379-01 Award Amount: $115,000 Clinical*

- Title: *Maryland Interstitial Cystitis Clinical Trials Group* NIDDK
  P.I.: Susan Keay, M.D. and John Warren, M.D.
  University of Maryland School of Medicine, Baltimore, MD

  Interstitial cystitis (IC) is a chronic disease characterized by pain, urgency, and frequency, and by bladder findings of ulcers, glomerulations, and diminished capacity. The etiology(ies) is unknown and numerous treatments have been examined by only a few in well-designed trials. Patients would benefit from scrutiny of existing and novel treatments, the mission of the IC Clinical Trials Group (IC CTG). Critical to the IC CTG is the ability to recruit IC patients for well-designed clinical trials. Over the last 7 years, work with IC patients has been to explore the pathogenesis of IC. The investigators have discovered a urine peptide which inhibits the growth of human bladder epithelial cells *in vitro* in 85 percent of IC patients vs. <10 percent controls. To explore the clinical role of this peptide, a recently modest recruitment campaign has begun and the investigators have observed a pent-up demand of IC patients and of urologists and gynecologists for IC research. Within a 2 month period, 241 patients have expressed willingness to participate in the clinical studies, and 151 urologists and gynecologists have offered to refer the investigators >500 IC patients for these studies. The Baltimore-Washington area comprises more than 6,000,000 people. This includes many IC patients and the investigators will work with the ICA and the network of urologists and gynecologists to recruit large numbers of patients during the clinical trials. To respond to this clinical opportunity, a multidisciplinary team has been developed comprised of veteran IC investigators, urologists, and urogynecologists, skilled in bladder diseases and pain syndromes. This team has experience in complex projects, randomized placebo-controlled double-masked trials, large data sets, and collaborative ventures. This group will bring to the IC CTG experienced, motivated, and dedicated investigators; a new cadre of IC patients; and a network of referring urologists and gynecologists to study management strategies for this distressing disease.

  *5U01DK054125-04 Award Amount: $100,000 Clinical*

## *HIV/AIDS*

▶ Title: *A Clinical Trial of Directly Observed Therapy for Highly Active Antiretroviral Therapy in Jailed Drug Users* NIDA

P.I.: Jacqueline P. Tulsky, M.D.
University of California–San Francisco, San Francisco, CA

HIV-infected adults in the United States corrections system are predominantly active drug users and people of color. These are the very populations with HIV who are not benefitting from effective treatments for HIV, such as highly active antiretroviral therapy (HAART). Jail may be an excellent site for the introduction of medical care for HIV to marginalized populations, particularly drug users who access care for HIV infection at lower rates than other populations of HIV-infected persons. Both primary medical care and initiation or continuation of treatment with HAART may be offered in jail. The jail setting also provides an ideal opportunity to evaluate the best way to deliver care in order to maximize the benefits, both while in jail and, perhaps more importantly, after release from jail. Directly observed therapy (DOT), in which every dose of medication is observed, has been shown to decrease HIV viral replication in incarcerated inmates. Other benefits of DOT include sustained HIV viral control that minimizes the likelihood of developing drug resistance to HAART medications started in jail. In the San Francisco city and county jails, DOT is standard care for inmates on HAART. Unfortunately, our pilot data suggest that the benefits of DOT are often not sustained after inmates are released from jail and must transition to self-administered therapy. Alternatively, a structured program of self-administered therapy in jail may be an equally effective strategy as DOT while inmates are in jail, and may enable inmates to maintain virologic control after they are released from jail.

The effects of an intervention for delivering HAART to HIV-infected persons in jail (structured, self-administered therapy), as compared to usual care (DOT), on virologic and immunologic outcomes in jail and after release from jail is proposed. The specific aims of this randomized, controlled trial of HAART in jailed drug users are: *Primary Aim 1*, to compare the effects of structured, self-administered therapy as compared to DOT on virologic and immunologic outcomes and incidence of developing new resistant mutations after release from jail; *Primary Aim 2*, to compare the effects of structured, self-administered therapy as compared to DOT on virologic and immunologic outcomes while subjects are in jail; and *Secondary Aim*, to measure other factors that may be associated with the short- and long-term virologic and immunologic outcomes. Such covariates include: demographic factors (including housing and employment), drug and alcohol use, general health status (physical and mental health status), and medications (lifetime and current HAART and medication adherence).

*1R01DA13892-01A1 Award Amount: $146,323 Clinical*

- Title: *A Contextual Model of Microbicide Acceptability* NIMH
  P.I.: Kathleen M. Morrow, Ph.D.
  Miriam Hospital/Brown Medical School, Providence, RI

  Women are the fastest growing segment of the HIV/AIDS population, and heterosexual vaginal intercourse is their greatest risk factor. This growth, the lack of clear efficacy of more traditional prevention strategies, and ongoing questions about the safety and efficacy of Nonoxynol-9 in the prevention of HIV transmission, demands increased attention to the development of safe, effective vaginal microbicides. As these products are developed and investigated, it is also essential to establish an understanding of how acceptability and use of the products are decided by consumers. The common, one-factor approach of equating acceptability and use fails to capture the complex, contextual nature of microbicide acceptability and use. The present study applies a theoretical framework for understanding acceptability and, ultimately, its use among women at risk. Guided by the social ecology model, the investigator considers both product and person-in-context variables. The objective of this work is to elucidate how personal, social, relational, and political variables to one another and to a woman's decision to use a microbicidal product. Further, this study will address a limitation in the current state of microbicide acceptability research. That is, the present research will both contribute to a social ecological model of microbicide acceptability and develop a psychometrically sound, quantitative microbicide acceptability instrument. This tool will enable future research to quantify relationships and pathways between person-in-context factors, product characteristics, intention to use, and actual use of microbicides. The instrument will enable the investigators to compare factor structures across risk groups and will also provide the field with a high-quality acceptability measure that will facilitate comparison and consolidation of data across studies. By contributing both to a theoretical and applied understanding of acceptability, and furnishing a sound means of quantifying product acceptability, this work will ultimately increase efficiency of acceptability assessment in upcoming Phase II/III clinical trials of vaginal microbicides, and allow for more successful education and marketing of approved microbicidal products.
  *1R01MH64455-01 Award Amount: $100,000 Clinical*

## *Immunity and Autoimmunity*

▶ Title: *Curcumin Treatment of Fibrosis* NCCAM
P.I.: Stanley Hoffman, Ph.D.
Medical University of South Carolina, Charleston, SC

Practitioners of alternative medicine recommend curcumin, a component of the spice turmeric, as a treatment for autoimmune diseases. Scleroderma is a debilitating autoimmune disease that affects over 100,000 people in the United States, mostly women. The hallmark of scleroderma is dermal fibrosis. When accompanied by visceral organ fibrosis, significant morbidity and mortality results. Despite its widespread occurrence, little is known to suggest effective treatment. As part of a long-term objective of understanding the aberrant regulation of extracellular matrix protein accumulation in scleroderma, the investigators treated primary fibroblast cultures from the lungs of scleroderma patients with curcumin. They found that this treatment inhibits collagen accumulation and promotes cell death in these cultures while having no effect on normal lung fibroblasts. Interestingly, these effects of curcumin on scleroderma fibroblasts are enhanced in the presence of vitamin C. If curcumin were to have the same effect on scleroderma fibroblasts *in vivo* as it has in culture, then curcumin would be likely to be an effective treatment for scleroderma. While curcumin is not yet used in standard medical practice, in Chinese and Indian folk medicine turmeric is used to treat a broad range of ailments. Published articles show curcumin to have a range of potent biological activities including anti-cancer, anti-inflammatory, and antimicrobial. The use of curcumin in folk medicine, published studies on curcumin, and the investigation studies combine to indicate that curcumin is non-toxic and is a treatment already used in alternative medicine that is likely to have demonstrably positive effects on patients with scleroderma and other fibrotic diseases. In order to test the hypothesis that curcumin may be a beneficial treatment for scleroderma, in particular, and fibrotic diseases, in general, this study will: 1) use cultured fibroblasts to determine the molecular and cellular mechanisms involved in the specific effects of curcumin on cells from scleroderma patients; and 2) perform translational research using an animal model for scleroderma and lung fibrosis to determine whether curcumin is indeed effective in treating lung fibrosis *in vivo*. These experiments will demonstrate the efficacy, and the scientific basis for that efficacy, of a disease treatment already recommended by practitioners of alternative medicine.

*1R21AT00382-01A1 Award Amount: $178,750 Basic*

▶ Title: *Visual Dysfunction and Quality of Life in Patients with Multiple Sclerosis* NEI
P.I.: Laura J. Balcer, M.D.
University of Pennsylvania, Philadelphia, PA

Visual impairment is a leading cause of symptoms in patients with multiple sclerosis (MS). The extent to which vision has been affected by new therapies for MS is not known, and has been difficult to assess using traditional measures of neurologic impairment. The visual profile of MS has not been examined, and the relation of visual function to overall neurologic impairment in patients with MS has not been determined in a large, heterogeneous cohort. This proposal will accomplish the following specific aims: 1) define the visual profile of MS in a large cohort (400 patients), and determine which measures best identify visual dysfunction in patients with MS; and 2) determine the relation of visual function to vision- and disease-specific HRQOL in patients with MS.

*1R01EY13273-01A1 Award Amount: $125,000 Cohort study*

- Title: *Autoimmunity Center of Excellence* NIAID
  P.I.: Leonard Chess, M.D.
  Columbia University College of Physicians & Surgeons, New York, NY

  This center will establish an interdisciplinary basic and clinical research program to focus on the evaluation of novel therapeutic approaches to five autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, and scleroderma. The investigators hypothesize that there are four principal events involved in the immunopathogenesis of these diseases: 1) predisposing genes establish a T-cell repertoire capable of recognizing self peptides intrinsic to the autoimmune process; 2) previously tolerant autoreactive CD4+ T-cell clones become activated and expand to change the T-cell repertoire to reflect autoreactive effector T cells; 3) regulatory mechanisms, including the activation of TH1 and TH2 CD4+ T-cell subsets, as well as those involving CD8 T cells fail, through processes such as clonal deletion or changes in the cytokine milieu; and 4) pathogenic autoantibodies develop through cognitive T cell-B cell interactions which effect tissue injury. In these diseases, one would predict that reducing the clonal expansion of relevant autoreactive T cell by blockade of T-cell receptor signaling or interruption of the CD40 ligand-dependent pathway could downmodulate disease activity. Also, interruption of the inflammatory effector functions of T cell mediated by TNF or CD40L would similarly reduce disease potential. These hypotheses will be tested during the natural history of disease and during specific immune interventions.

  *5U19AI46132-02 Award Amount: $75,000 Clinical*

- Title: *Virginia Mason/University of Colorado Health Sciences Center Autoimmune Center* NIAID
  P.I.: George S. Eisenbarth, M.D.
  University of Colorado, Denver, CO

  This grant consists of three research projects. The overall objective of this application is to derive markers of autoimmune disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in genetic, immunologic, and environmental determinants that lead to disease. *Project 1* will use tetramers to analyze the peripheral antigen-specific T-cell profile in IDDM. *Project 2* will identify three cohorts of individuals at increased risk for rheumatoid arthritis and attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. *Project 3* will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

  *1U19AI50864-01 Award Amount: $200,000 Translational*

▶ Title: *Autoimmunity: Treatment by Co-stimulatory Signal Blockade* NIAID
P.I.: Samia J. Khoury, M.D.
Brigham and Women's Hospital, Boston, MA

A Center of Excellence for Autoimmunity will be established at the Brigham and Women's Hospital. Projects supported under this initiative will focus on the study of therapy of autoimmune diseases by blocking co-stimulatory signals. Investigators will focus on the CD40-CD40L pathway. The human diseases of major focus are multiple sclerosis, inflammatory bowel disease, 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. Four projects are supported. The overall goals of *Project 1* are to study, in a pilot trial, the efficacy and safety of anti-CD40L therapy in multiple sclerosis. The goals of *Project 2* are to study, in a pilot trial, the efficacy and safety of anti-CD40L therapy in inflammatory bowel disease. *Project 3* will focus on the immunologic changes associated with anti-CD40L therapy in patients with multiple sclerosis and inflammatory bowel disease. *Project 4* will study the immune mechanisms of psoriasis. Data obtained from the pilot studies will be useful in designing Phase M clinical trials, and immunologic investigations will help to identify surrogate markers for disease activity.

*5U19AI46130-02 Award Amount: $75,000 Clinical*

▶ Title: *Denver Autoimmunity Center of Excellence* NIAID
P.I.: Brian L. Kotzin, M.D.
University of Colorado Health Sciences Center, Denver, CO

A Center of Excellence for Autoimmunity will be established at the University of Colorado Health Sciences Center. The center builds on a strong research and clinical base in type 1 diabetes, celiac disease, systemic lupus, rheumatoid arthritis, multiple sclerosis, autoimmune skin disease, autoimmune pulmonary disease, and other autoimmune disorders. Under this initiative, two clinical trials will be conducted. *Clinical Project 1* will evaluate subcutaneous insulin vaccination to prevent the appearance anti-islet autoantibodies in infants at high risk for the development of autoantibodies and disease. *Clinical Project 2* will test humanized anti-C5 mAbs in patients with active lupus nephritis. Three basic components will be studied: 1) to define the T-cell specificities and distribution of insulin and islet antigen-reactive T cells in murine models and patients with type 1 diabetes; 2) to determine the effects of inhibition of IL-18 and complement on cytokine production and disease in collagen-induced arthritis and rheumatoid synovion; and 3) to define the non-MHC genetic contributions to different clinical subtypes of autoimmune polyendocrine syndrome II. These basic projects will provide important information to design future clinical trials, to monitor the effectiveness of immunologic therapies, and/or provide surrogate markers to correlate with immunologic therapies in autoimmune diseases.

*5U19AI46374-03 Award Amount: $75,000 Clinical and basic*

- Title: *Mechanism of Copaxone Therapy in Multiple Sclerosis* NIAID
  P.I.: Michael Racke, M.D.
  University of Texas Southwestern Medical Center at Dallas, Dallas, TX

  Multiple sclerosis (MS) patients are categorized on the basis of whether they have clearly defined relapses, relapsing-remitting MS (RRMS), or whether they are progressing. Progressing patients are further divided on the basis of whether they initially experienced relapses (secondary progressive MS), or whether they deteriorate slowly without evidence of relapses or remissions (primary progressive MS). One question is whether the patients with primary progressive MS (PPMS) differ from the patients with secondary progressive MS, or whether they represent different aspects of a clinical pathologic spectrum. This group has shown that patients with RRMS have myelin-reactive T cells that are less dependent upon costimulation than myelin-reactive T cells from normal controls. The goal is to test the hypothesis that myelin-reactive T cells in patients with PPMS can be distinguished from naive myelin-reactive T cells by a lack of dependence upon costimulation for activation, and that costimulatory requirements for these myelin-reactive T cells change during the course of disease. Glatiramer acetate (Cop-1, Copaxone) has previously been shown to reduce the number of relapses in RRMS and is now being tested for efficacy in patients with PPMS. It is unclear how Copaxone exerts its therapeutic effect. This study will determine whether Glatiramer alters cytokine secretions of myelin-reactive T cells and the T-cell repertoire in PPMS.

  *5R01A147133-03 Award Amount: $140,000 Clinical*

- Title: *Penn Autoimmunity Center of Excellence* NIAID
  P.I.: A.M. Rostami, M.D., Ph.D.
  University of Pennsylvania, Philadelphia, PA

  A Center of Excellence for Autoimmunity at the University of Pennsylvania School of Medicine will be established. It will consist of four projects (three clinical and one basic) and two cores. The clinical component of the center consists of three clinical trials: 1) a Phase I/II trial on the use of antibody to Interleukin-12 (IL-12) for the treatment of multiple sclerosis (MS); 2) a Phase I/II trial on the use of IL-12 in the treatment of inflammatory bowel disease; and 3) the use of anti-CD20 antibody for the treatment of systemic lupus erythematosus (SLE). The basic science component is focused on the elucidation of the basic mechanisms of autoimmunity and immunomodulation related to the clinical trials. Investigators will study the role of IL-12 in the pathogenesis and therapy of MS and its animal counterpart, experimental autoimmune encephalomyelitis. Also, they will focus on the mechanisms of anti-B-cell therapy in SLE and its murine model. An immunology core and an administrative core will be supported under this initiative.

  *5U19AI146358-02 Award Amount: $75,000 Clinical and basic*

▶ Title: *T-cell Reconstitution after Stem Cell Autograft* NIAID
P.I.: Jan Storek, M.D., Ph.D.
Fred Hutchinson Cancer Research Center, Seattle, WA

The goal is to evaluate how the T-cell repertoire is re-established in patients with autoimmune diseases who have undergone lymphocytopenia from high-dose chemotherapy/radiation plus anti-thymocyte globulin, followed by reconstitution with autologous transplantation of hemopoietic (CD34+) precursors. The hypothesis is that in young individuals, a substantial number of regenerating T cells originate from hemopoietic progenitors, whereas in older individuals the vast majority of T cells originate from the expansion of pre-existing T cells. The techniques used will be spectra typing, sequencing of the T-cell receptor genes withing a single spectra typing band, and quantifying T cells that contain T-cell receptor-rearrangement circles.

*5R01A146108-02 Award Amount: $60,000 Clinical*

▶ Title: *How Does Blockage of CD40/CD40L Prevent Autoimmunity?* NIAID
P.I.: Matthias Von Herrath, M.D.
Scripps Research Institute, La Jolla, CA

This grant consists of two pilot projects, three projects, and two cores. Investigators will use three different models of autoimmune diseases to analyze effector functions of dendritic cells, lymphocytes, and regulatory antigen-presenting cells. The program focuses on the blockade of a single pathway and it's study in several different autoimmune scenarios. The program utilizes some novel techniques and is studying the detailed mechanism by which CD40L blockade effectively prevents the development of autoimmunity.

*1U19AI50924-01 Award Amount: $100,000 Basic, animal models*

- Title: *Gene Mapping in Women with Systemic Lupus Erythematosus* NIAMS
  P.I.: Timothy W. Behrens, M.D.
  University of Minnesota, Minneapolis, MN

  This study plans to map and eventually identify the susceptibility genes for human systemic lupus erythematosus (SLE). Over 250 SLE sib-pair and multiplex families, as well as 130 trio (affected SLE patient with both parents) families have been recruited. Genome-wide marker screens have been performed in these Minnesota pedigrees, and several chromosomal regions that appear likely to harbor SLE susceptibility genes have been identified. Dense microsatellite marker mapping has been initiated in several chromosomal regions that show the most convincing evidence for linkage in our family collection (1q41, 6p21 (HLA), 16q21, 20q, and 20p). More recently, analyzing several candidates genes in these regions have begun. This collection of SLE families is one of the largest in the world, and the investigators are well poised to move this project forward in the next funding period. In the next 5 years, the investigators propose to continue collecting additional SLE sib-pair and trio families, with a goal of recruiting 125 sib-pair families and 300 trios. In addition, a group of 200 age-, sex- and ethnicity-matched control individuals for case/control association studies with the accumulated marker data will be collected. The location of the susceptibility loci within the HLA region, using the recombinant ancestral haplotype approach, and then attempt to identify the sequence variations within the HLA that confer risk for SLE, will be further refined. Fine mapping in the non-HLA chromosomal regions that show linkage to the lupus phenotype will be continued. Within the time frame of the next 5 years, the investigators hope to begin identifying the disease-associated sequence polymorphisms that confer risk for human SLE. The identification of the lupus genes will be critically important for furthering our understanding of this disease, and for rationally targeting new therapies.

  *2R01AR43274-06 Award Amount: $245,818 Clinical*

- Title: *Studies of Collagen Gene Regulation in Two Murine Models* NIAMS
  P.I.: Stephen H. Clark, Ph.D.
  University of Connecticut, Farmington, CT

  This research project will utilize two mouse mutations that are models for scleroderma – tight skin (Tsk) and tight skin2 (Tsk2). Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark of the human disease. The long-range objective of this research is to utilize the two mutations, combined with several lines of transgenic mice as experimental tools, to dissect molecular mechanisms of disease pathogenesis.

  *1R01AR48082-01 Award Amount: $200,000 Basic, animal models*

▶ Title: *Immune Mechanisms of Anti-CD40L Trial in Systemic Lupus Erythematosus* NIAMS
P.I.: Syamal Datta, M.D.
Northwestern University, Evanston, IL

CD40L is hyper-expressed by lupus B cells for abnormally prolonged periods, thus sustaining the production of pathogenic autoantibodies. A brief therapy of three injections of anti-CD40L in 1 week into lupus mice prevents the development of nephritis for more than a year. This clinical trial provides an opportunity to study the effects of anti-CD40L on the human immune system *in vivo*, particularly on the cells participating in the chronic ongoing autoimmune response in lupus patients. This study will examine the status of autoimmune T and B cells that are involved in the production of pathogenic anti-nuclear autoantibodies before, during, and after therapy.

*5R01AR046309-02 Award Amount: $50,000 Clinical*

▶ Title: *C-Jun N-terminal Kinase and Joint Destruction in Rheumatoid Arthritis* NIAMS
P.I.: Gary S. Firestein, M.D.
University of California–San Diego, School of Medicine, La Jolla, CA

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis marked by synovial hyperplasia with local invasion of bone and cartilage. Accumulating evidence suggests that RA fibroblast-like synoviocytes (FLS), which form the leading destructive front of rheumatoid synovium, possess unique characteristics and contribute to cartilage degradation. Recently, it has been demonstrated that RA FLS activate the c-Jun N-terminal kinase (JNK) pathway efficiently and that this kinase is phosphorylated in RA synovium. To explore the potential relationship between JNK activation and joint damage in RA, the investigators will evaluate the signal transduction and transcription factor pathways involved in matrix metalloproteinase gene regulation, cartilage invasion, and joint destruction. In particular, the investigators will determine the contribution of the mitogen-activated protein kinase family. Preliminary experiments suggest that JNK is a key regulatory element in the machinery involved in joint destruction. In addition, IL-1-induced JNK phosphorylation is increased in RA and this pathway appears to regulate collagenase gene expression. The hypothesis that JNK is a target for development of chondroprotective agents in arthritis using two unique tools is proposed: 1) SP600125, the first small molecule selective JNK inhibitor; and 2) JNK knockout mice. First, the role of JNK in synoviocyte metalloproteinase production, cytokine expression, and invasion into cartilage will be determined. Second, the upstream signal transduction pathways that regulate JNK in RA FLS will be determined. Finally, the role of JNK in animal models of arthritis will be determined. These data will support the hypothesis that JNK plays a role in the FLS biology and is a potential target for chondroprotective therapy.

*1R01AR47825-01 Award Amount: $100,000 Clinical*

▶ Title: *Cellular and Genetic Basis of Systemic Lupus Erythematosus* NIAMS
P.I.: Shu-Man M. Fu, M.D.
University of Virginia, Charlottesville, VA

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organs with considerable morbidity and mortality. The disorder is characterized by multiple autoantibody production, including antinuclear antibodies (ANA) and anti-ds DNA antibodies with immune complex formation leading to intense inflammation and end-organ damage. Immune complex-mediated glomerulonephritis (GN) is a major manifestation of this disorder. Both genetic and environmental factors play important roles in its pathogenesis. Our laboratory has focused on the origin(s) of the autoantibodies detected in SLE and the genetic factors important in the generation of ANA and anti-dsDNA antibodies and lupus nephritis. Recently, a new model of SLE NZM2328 has been characterized. In this strain, there is female bias for ANA and chronic GN. In a backcross (NZM2328 X C57L/J F1) X NZM2328 analysis, a genetic interval has been identified on chromosome 1 in NZM2328 to control the development of chronic GN. An interval on chromosome 4 was shown to be linked to the production of ANA and anti-dsDNA antibodies. By a marker-assisted method, two congenics – NZM2328.C57Lc1 and NZM2328.C57L.c4 – were generated by moving the genetic segments of interest from chromosomes 1 and 4, respectively, from C57L/J to NZM2328. In NZM2328.C57Lc1 little ANA, anti-dsDNA or chronic GN were seen. In contrast, the NZM2328.C57Lc4 chronic GN was detected despite marked reductions in ANA and anti-dsDNA, dissociating ANA and anti-dsDNA production from lupus nephritis. It appeared that the genetic segment on chromosome 1 controls lupus nephritis and regulates ANA and anti-dsDNA production. These genetic loci have been named Lnc1, the lupus nephritis controlling gene 1 and Adn1, the anti-dsDNA and ANA production gene 1. For this proposal, Lnc1 is assumed to be different from Adn1. This application is focused on the elucidation of the cellular and immunochemical basis for autoantibody production and the generation of GN and to identify the genes, Lnc1 and Adn1. Four species aims proposed are: 1) to characterize further NZM2328 and its two congenic lines, NZM2328.C57Lc1 and NZM2328.C57Lc4; 2) to determine the specificities of immunoglobulins eluted from diseased kidneys from NZM2328.Lc4, clarifying the basis for the dissociation of anti-dsDNA antibody and ANA production from severe proteinuria and chronic GN; 3) to determine the cellular basis of severe proteinuria, chronic GN, and autoantibody production by adoptive cell transfer analysis; and 4) to generate intra c1 congenic recombinant stains from the parental strain NZM2328.C57Lc1, which contain smaller genetic intervals of chromosome 1 derived from C57L/J to determine the minimal C57L/J genetic segment(s) to suppress anti-dsDNA antibody and ANA production, and/or severe proteinuria and chronic GN. Thus, this study will refine the genetics for this interval so that the genes, Lnc1 and Adn1, may be identified relevant to the phenotypic expression by positional cloning. The results from these experiments will provide further understanding of the pathogenesis of SLE. This information should lead to orthologous gene(s) identification in the SLE patients and provide potential targets for more specific and novel therapeutic interventions.

*1R01AR47988-01 Award Amount: $185,000 Basic*

▶ Title: *Fine Specificity of Scleroderma Autoantibodies* NIAMS
P.I.: Judith James, M.D.
Oklahoma Medical Research Foundation, Oklahoma City, OK

This application addresses the important problem of the significance of autoantibodies in scleroderma patients. The project proposes to identify the initial epitope on nRNP and topoisomerase I, which is identified by sera from patients with scleroderma. This will lead to the search for a pathogen in the environment, which could lead to an immune response to the cross-reacting antigen. The possibility of tissue damage due to autoantibodies will also be investigated.

*1R01AR48045-01 Award Amount: $200,000 Translational*

▶ Title: *Registry and Repository of African Americans with Rheumatoid Arthritis* NIAMS
P.I.: Larry Moreland, M.D.
University of Alabama at Birmingham, Birmingham, AL

This 5-year project will be housed at the University of Alabama at Birmingham. It will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (CLEAR) Registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3-years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast United States will gather data which will provide a resource for investigators interested in the genetics of rheumatoid arthritis in African Americans. The CLEAR Registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor-alpha/lymphotoxin-alpha, interleukin (IL)-1, and IL-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3-years disease duration in African Americans. The principal investigator, Dr. Larry Moreland, is a clinical researcher whose primary research interest has been the evaluation of biologic response modifiers (and their mechanisms) which are targeted at the disease process in rheumatoid arthritis.

*1N01AR002247-000 Award Amount: $200,000 Clinical*

▶ Title: *A Model of Sjögren's Syndrome with Anti-Ro/La Antibodies* NIAMS
P.I.: Robert H. Scofield, M.D.
Oklahoma Medical Research Foundation, Oklahoma City, OK

Sjögren's syndrome (SS) is a common rheumatic autoimmune disease which initially affects the salivary and lacrimal glands, but can effect the lungs, kidneys, central nervous system, and vasculature. The etiology and pathological mechanisms are unknown for this disease and therapy is available, but far from ideal. SS is an autoimmune disease as evidenced by the almost universal presence of autoantibodies in the sera of patients. The great majority of patients have antibodies binding one or more components of the Ro/La (or SSA/SSB) ribonucleoprotein particle, which is found in every mammalian cell type examined and whose function is not completely known. There are several animal models of SS, but none of these models have high levels of anti-Ro or anti-La. Thus, while these models may prove useful for studying some aspects of the disease, insights into the origin and pathogenic potential of autoimmunity targeting the Ro ribonucleoprotein cannot be sought or found. The principal investigator has developed a new animal model of SS in which mice are immunized with short peptides (12 to 20 amino acids) derived from the sequence of the 60 kD Ro molecule. In some strains of mice the immune response expands with both B cell and T cell epitope spreading. Initially, the immunogen peptide induces an immune reaction. Then, other epitopes of the 60 kD Ro molecule are targeted as are epitopes on other molecules that are components of the Ro particle, such as 52 kD Ro and La. In the SJL/J mouse strain, pathology develops in the salivary gland that is similar to that found in humans with SS. This proposal will investigate this new model of disease that closely replicates its human counterpart. The nature of the cellular infiltrate will be studied as to its content of T and B lymphocytes and subsets. The cell type critical for development of disease will be determine by transfer experiments. Preliminary data indicate that the phenotype of helper T cells is critical to epitope spreading in this model. The relationships among immune response type, immune diversification after Ro-peptide immunization, and development of pathology will be determined. Immunization will be carried out in mice deficient in various cytokines and with immune deviation strategies in order to determine whether immune deviation will alter development of epitope spreading and disease pathology.

*1R01AR47341-01 Award Amount: $100,000 Basic*

▶ Title: *Combining of N-of-1 Trials to Assess Fibromyalgia Therapies* NIAMS
P.I.: Deborah R. Zucker, M.D.
New England Medical Center, Boston, MA

Fibromyalgia is a common rheumatologic condition and treatment is a challenge. A recent study reported that combination therapy of amitriptyline and fluoxetine resulted in significantly greater improvement in patients' symptoms as compared with either drug alone. This project will use patient-focused N-of-1 trials and combines these trials' results to obtain population estimates of treatment effectiveness. This will extend into community practice to enable comparison of center- and practice-based results. This will also provide a methodological tool to obtain data from community physicians in practice-based settings.

*5R01AR045416-03 Award Amount: $140,000 Clinical*

▶ Title: *Mechanisms of Lupus Induction in L-Canavanine* NIEHS
P.I.: Patricia Fraser, Ph.D.
Center for Blood Research, Boston, MA

The sex difference in estrogen exposure may explain the sex imbalance in systemic lupus erythematosus (SLE) risk. The specific aims of this proposal are to: 1) determine androgen receptor, estrogen receptor, and cytochrome P450 genotypes in SLE subjects and controls by polymerase chain reaction-based methodologies in a large SLE case and control study; and 2) determine the relative importance of genetic markers in aim one with endogenous and exogenous estrogens and with exposure to organochlorines in predicting risk of SLE.

*1R21ES10295-01 Award Amount: $100,000 Clinical*

## *Infectious and Sexually Transmitted Diseases*

▶ Title: *Mid-America Adolescent Sexually Transmitted Diseases Cooperative Research Center* NIAID
P.I.: Donald Orr, M.D.
Riley Hospital, Indianapolis, IN

Sexually transmitted diseases (STD) produce very serious outcomes in women, regardless of race, and often affect their infants as well. In addressing the racial health disparities in the occurrence of STD, NIAID supports Sexually Transmitted Diseases Cooperative Research Centers, which provide a multidisciplinary approach to research in the area of STD by bringing together basic science, clinical and epidemiological research, and behavioral intervention strategies for the prevention and control of STD.

*3U19AI043924-03S1A1 Award Amount: $50,000 Clinical*

## *Maternal-Child Health*

▶ Title: *Nursing Support Intervention for Mothers of Prematures* NINR
P.I.: Diane Holditch-Davis, Ph.D.
University of Wisconsin–Madison, Madison, WI

Premature infants are at risk for developmental problems, and rural, African American prematures are at higher risk for these problems than other prematures. This health discrepancy is probably due to interactions among factors, such as poverty, barriers to service usage, the mothers' emotional distress from the infant's birth and hospitalization, and resultant parenting styles that may be less facilitative of infant development. The purpose of this study is to examine the effectiveness of a culturally congruent intervention providing support to rural, African American mothers of prematures from the time their infants are in intermediate care until they are 18 month of age. During phone calls and home visits, the intervention nurse will help mothers resolve emotional distress due to prematurity and reduce stress related to parenting in the context of work and family, support them in developing relationships with their infants, and help them identify acceptable resources and fit resources to her goals in order to meet complex infant health and developmental needs. The context for the intervention is a therapeutic relationship in which a culturally proficient nurse uses guided discovery to focus on the mother's experiences and concerns and help the mother to identify ways to reduce distress, improve parenting, and tap into strengths available in her family and culture. Mothers receiving the intervention and mothers receiving usual care will be compared to determine whether the intervention affects psychological well being, mother-child relationship quality, length of use of child health and developmental surveillance services, and child development. The investigators expect that improvements in maternal psychological well being will lead to longer use of services, better mother-child relationship quality, and better infant developmental status, particularly lessening the decrease in developmental status that is often seen after 12 months. The cost effectiveness of the intervention will also be determined. Two hundred and twelve rural, African American mothers and their high-risk prematures will be recruited when the babies are in intermediate care and followed until they are 24 months corrected age. The mothers will be randomly assigned to control and intervention groups. The intervention will consist of an in-person contact in the hospital followed by a home visit 1 to 2 weeks after discharge and at 5, 10, and 15 months. Phone contacts will be made weekly during the first month, bimonthly for 2 months, and then monthly. Maternal psychological well being will be measured using depressive symptoms, anxiety, post-traumatic stress symptoms, parenting stress, and minor daily stress. The quality of the infant's social environment will be measured using a 1-hour naturalistic observation of mother-infant interaction, the HOME Inventory, and two measures of maternal perception of the child. Length of use of services will be measured by the Child Services Survey and immunization status, a proxy for adequacy of well-child care, and confirmed from medical records. Child development will be measured by the Bayley II and a language assessment.

*1R01NR05263-01A1 Award Amount: $100,000 Clinical*

## *Menopause*

▶ Title: *Predicting Onset Age and Length of Menopausal Transition* NIA
P.I.: Daniel M. Keenan, Ph.D.
University of Virginia, Charlottesville, VA

Because of the greater life expectancy of today, menopause and its physiological consequences are having an enormous impact on the well being of the older female. The present research is concerned with identifying, elucidating, and quantifying the ovarian and neuroendocrine mechanisms underlying menopause. In particular, to establish that there is a specific sequential pattern of five phases that occurs during the menopausal transition, and to construct statistical predictors of the onset age and duration of the menopausal transition. Moreover, such a predictor will also allow for the estimation of a given subject's "hormonal-reproductive age," not chronological age, which has enormous implications for the infertility consequences of aging. For example, based upon certain endocrine reproductive measurements taken from say a given 40-year-old female, methods will be constructed by which to predict her age of perimenopause onset and its length and, at same time, to state whether she is hormonally that of a 40 year old, or more like a 45 or 35 year old. The ability to predict the age and length of the menopausal transition is clinically important because early menopause has associated with it increased risk of cardiovascular disease and osteoporosis, whereas late menopause has associated with it an increased risk of breast cancer and endometrial cancer. This research consists of three components. First, five prospective and cross-sectional clinical studies specifically designed for the above aims will be conducted at the University of Virginia GCRC, using pre-, peri-, and postmenopausal subjects. Second, a biomathematical model for the aging hypothalamic-pituitary-ovarian axis will be developed which includes its several feedback and feedforward interactions, the dynamical onset and shutdown of the LH surge and ovulation, as well as its eventual cessation. Third, based upon the preceding two, hypotheses concerning the five phases will be tested, and predictors of onset age and duration constructed.

*1K01AG19164-01 Award Amount: $100,558 Clinical*

▶ Title: *Study of Women's Health Across Nation II (SWAN II)* NIA
P.I.: Dr. Sonai McKinlay, Coordinating Center, Multiple sites
and investigators plus a lab
New England Research Institute, Watertown, MA

SWAN consists of both cross-sectional and longitudinal studies on the natural history of menopause and a characterization of endocrinology and physiology of premenopause. Five ethnic groups are included – Caucasian, African American, Hispanic, Chinese, and Japanese. There are seven sites across the country – Boston, Pittsburgh, Chicago, Michigan, University of California–Los Angeles, University of California–Davis, and New Jersey. For the cross-sectional study, there are approximately 16,000 women enrolled, ranging in age from 40 to 55 years, to determine the age of menopause. The longitudinal study has approximately 3,150 women (450 at each site), between the ages of 42 to 52, to determine menopause-specific physiological changes and their predictors and the impact of menopause on subsequent disease. Measurements are being made of the major reproductive axis hormones (LH, FSH, estradiol, progesterone, and testosterone), adrenal markers of aging (DHEAs), other endocrine markers (TSH, sex hormone-binding globulin), and new ovarian markers which have the potential to define the menopausal transition and the postmenopause.

*2U01AG12553-08 Award Amount: $250,000 Clinical*

- Title: *Centers for Dietary Supplements Research: Botanicals* NCCAM
  P.I.: Norman Farnsworth, Ph.D.
  University of Illinois at Chicago, Chicago, IL

  This multidisciplinary team of investigators will focus on the study of the safety and efficacy of botanicals used to treat women for menopause. Studies will address mechanisms of action; identification of active compounds; and characterization of metabolism, bioavailability, and pharmacokinetics of active species in these botanicals. The research component will consist of the following: 1) a pharmacognosy project to carry out standardization of botanical dietary supplements and structure elucidation of active compounds; 2) isolate active compounds for structure elucidation, and then to determine the mechanism(s) of action of botanicals; 3) study the metabolism, absorption and toxicity of active compounds in botanicals including immunotoxicity; and 4) carry out phase I and II clinical trials of black cohosh (*Cimicifugai racemosa)* and red clover (*Trifolium pratense*).

  *5P50AT00155-03 Award Amount: $100,000 Clinical and basic*

- Title: *Menopausal Transition, Mental Health, and Ethnicity* NIMH
  P.I.: Joyce Bromberger, Ph.D.
  University of Pittsburgh, Pittsburgh, PA

  This is an ancillary study of the Study of Women's Health Across the Nation (SWAN) in Pittsburgh. Our current sample consists of 412 African American and Caucasian women; aged 42 to 52 at the start of the study in 1996, who are beginning or will soon begin the menopausal transition. Women are interviewed annually with the Structured Clinical Interview for DSM-IV Axis I Disorders. The specific aims are: 1) to assess whether women will be more likely to develop a new (recurrent) syndromal or subsyndromal depression during the perimenopausal transition than before or after; 2) to determine if a history of major depression is a risk factor for the following during the transition, a) syndromal or subsyndromal depression, b) increased levels of perceived stress, somatic, and psychological symptoms, or c) decreased quality of life or functioning; and 3) to compare rates of new (recurrent) syndromal or subsyndromal depression across the transition for African American and Caucasian women. The longitudinal nature of the SWAN biological and psychosocial data (e.g., medical morbidity, stressful events, lifestyle behaviors) will allow us to evaluate these as antecedents, correlates, and consequences of depression during the course of the study. By continuing to collect systematically psychiatric data in our cohort, in conjunction with the continued collection of Core SWAN data, we have unique opportunity to expand knowledge of women's mental health in midlife and beyond.

  *2R01MH59689-03A1 Award Amount: $100,000 Clinical*

▶ Title: *Menopausal Depression: Chronobiologic Basis* NIMH
P.I.: Barbara L. Parry, M.D.
University of California–San Diego, La Jolla, CA

The specific focus of this project will be to examine the effects of estradiol and progesterone administration on circadian rhythms in humans. The subjects will be healthy postmenopausal women. The investigators will test the hypothesis that estrogen advances the phase and enhances the amplitude and synchrony (the stability of timing relationships) of biological rhythms as measured by melatonin, sleep, and activity, whereas progesterone antagonizes these effects. This proposal represents an extension of the investigators' previous work that examined the effects of endogenous changes in estradiol and progesterone during the menstrual cycle on measures of mood and circadian rhythmicity. This work led to the development of new hypotheses and treatment strategies. The current proposal will allow investigation of these hypotheses further, but in a more controlled design. The investigators anticipate gaining important information on possible mechanisms mediating the effects of reproductive hormones on mood and behavior, and deriving relevant clinical treatment guidelines for menopausal women.

*5R01MH059919-02 Award Amount: $100,000 Clinical*

## *Mental Health*

▶ Title: *Black Rural and Urban Caregivers Mental Health Functioning* NIA
P.I.: Lethia Chadia, Ph.D.
Washington University, St. Louis, MO

This study will assess the mental health and social functioning of rural and urban African American women who provide unpaid care to an elder (65 years and older) by using a cross-sectional research design and random sample of elders. This study will identify the type and quality of caregivers' formal and informal service use. Data will be obtained through personal interviews.

*5R01AG15962-03 Award Amount: $150,000 Clinical*

▶ Title: *Relationship of Morbidity and Mortality between Spouses* NIA
P.I.: Nicholas Christakis, Ph.D.
University of Chicago, Chicago, IL

Employing the perspective and methods of the demography of again, the relationship between the morbidity and mortality of spouses will be examined. Questions about how the morbidity and mortality of one spouse, and the timing and nature of that morbidity and mortality, affects the morbidity, mortality, and timing and nature of morbidity and mortality in the other spouse will be asked. For example, is the hazard of death in one spouse (the "proband") increased by illness or death in the other spouse? If so, how does the proband's hazard of illness or death change over time after the onset of illness or death in the spouse? And how do these effects vary according to the type of severity or duration of the spouse's morbidity? Do particular illnesses in spouses place probands at particularly high risk of developing illness or dying themselves? What role do sociodemographic factors play in all these effects? To address these questions most effectively, a new panel data set with demographic, socioeconomic, and health information about one million elderly married couples, followed up to 10 years, will be created. Using a variety of event history and fixed effects methods, four main analyses will be conducted: 1) how morbidity in one spouse influences mortality in the other will be evaluated. Individuals married to unhealthy spouses will have worse mortality than those married to healthy spouses, and that the longer the spouse is ill, the greater the effect is the working hypotheses. Certain types of spousal morbidity (e.g., those that most compromise activity levels) will be worse for probands is also hypothesized; 2) the widower effect (i.e., the increased tendency of the bereaved to die), with adjustment for the health of both spouses prior to widowhood, will be evaluated; its temporal shape examined in detail; and its dependence on socioeconomic factors assessed; 3) the principal investigator will evaluate how morbidity in one spouse influences morbidity in the other. Are healthy spouses better able than unhealthy spouses to provide health benefits in marriage?; and 4) the impact of widowhood on the morbidity, and not just mortality, of bereaved spouses will be evaluated. This work advances the demography of aging by: closely examining how an individual's morbidity and mortality are affected by the presence or absence of spousal support; focusing on cause-of-death-specific aspects of demographic phenomena; examining theoretically interesting sub-populations along gender, race, socioeconomic, and health status lines; and shedding light on the mechanisms of inter-spousal health effects. This work also has policy implications in that it: supports more accurate projections of the health burdens in the elderly; facilitates targeting of support services to the growing numbers of widowed elderly; and addresses important populations, such as minorities, the poor, the oldest old, those with dementia, and care givers.

*1R01AG17548-01A2 Award Amount: $380,000 Basic*

▶ Title: *Depression Self Management and Women with Disabilities* NICHD
P.I.: Rosemary Hughes, Ph.D.
Baylor College of Medicine, Houston, TX

Depression is a common secondary condition associated with a primary disability. Disproportionately high among women compared to men, depression appears to be even more prevalent among women with disabilities. Although the risk for depression among all persons with disabilities appears to be higher than that among people in general, women with disabilities may be at even greater risk compared to their male counterparts, yet the literature fails to report on a therapeutic modality that is responsive to the unique needs of depressed women with functional limitations. The purpose of this project is to develop and test an innovative, targeted, and theory-driven group intervention designed to ameliorate depression in women with physical disabilities. It is hypothesized that: 1) women with disabilities, who participate in a depression self management group intervention, will report lower levels of depression and higher levels of self management of depression, self efficacy, and social connectedness after the intervention and at a 3-month followup, compared to those who participate in a depression education-only intervention; and 2) self management of depression, self efficacy, and social connectedness will mediate the relation of disability to depression outcomes among women with physical disabilities. This study uses a randomized with-groups and between-groups, pre/post-test design with a 3-month followup. The intervention will be implemented at local public and private chronic care clinics with 154 women with physical disabilities who will randomly be assigned to participate in either the self-management intervention or education-only comparison workshop. The scores of the two groups on measures of self management of depression, self efficacy, social connectedness, and depression will be compared. These assessments will be conducted at three time points – before and after the intervention period, and at a 3-month followup. Formative and summative evaluations, using qualitative and quantitative methodologies, will be conducted. This study is designed to be generalizable for clinical practice in physical medicine and rehabilitation, for mental health services for women with disabilities, and for public health policy governing the delivery of mental health services to people with disabilities.

*1R21HD40980-01 Award Amount: $173,882 Clinical*

- Title: *Gender-specific Risks for Depression in Adolescent Girls* NIMH
  P.I.: Sarah K. Bearman, B.A.
  University of Texas at Austin, Austin, TX

  The proposed project is designed to examine a gender-specific model to explain the increased prevalence of depressive symptoms in adolescent girls, compared to adolescent boys. Combining a longitudinal study which compares risk factors for depression in adolescent girls versus adolescent boys with a randomized prevention study of adolescent girls, this project would contribute significantly to the literature concerning both gender differences in rates of depression and prevention programs for depression in adolescent girls. *Aim 1* is to test whether body imaging and eating disturbances, hypothesized to be gender-specific risk factors, emerge as prospective predictors of depressive symptoms in females, and whether this partially accounts for the relation between gender and depression. *Aim 2* is to test whether a randomized experiment that reduced body dissatisfaction will lead to a subsequent decline of depressive symptoms in adolescent females, and whether manipulating body dissatisfaction will impact dieting and bulimic pathology. The aims for these two studies will be addressed through examination of prospective data from a community sample of adolescents (N=400), and a randomized experiment of a high-risk sample of adolescent females (N=60), respectively.

  *5F31MH12834-02 Award Amount: $25,076 Clinical*

- Title: *Effects on Children of Treating Maternal Depression* NIMH
  P.I.: Anne Riley, Ph.D.
  Johns Hopkins University, Baltimore, MD

  Maternal depression has devastating effects on the mental and physical health of children. This project will study the influence of treating maternal depression on children ages 5 to 11; studing 150 elementary school-aged children whose mothers are depressed (50 Hispanic, 50 African American, and 50 Caucasian) and 50 comparable children whose mothers are not depressed. Their mental health and functioning will be assessed by natural raters in their environments over a 2-year time period that will link child functioning, symptomatology, and psychiatric disorders to mothers' symptomatology, parenting behavior, and family environment.

  *5R01MH058384-04 Award Amount: $50,000 Clinical*

- Title: *Sex Differences in Self Evaluation: Social Factors* NIMH
  P.I.: Eva Pomerantz, Ph.D.
  University of Illinois, Champaign, IL

  Girls are more likely than boys to possess self-evaluative mechanisms that may heighten vulnerability to depressive and anxiety symptoms. It is hypothesized that culturally held gender stereotypes may cause parents to be more controlling in certain behavioral domains with girls than with boys. This pattern of gender socialization is expected to lead girls to be more likely than boys to possess self-evaluative mechanisms that heighten vulnerability to depressive and anxiety symptoms.

  *5R01MH057505-03 Award Amount: $38,684 Clinical*

## *Musculoskeletal Systems*

▶ Title: *Doxycycline Effect on Osteoarthritis Progression* NIAMS
P.I.: Kenneth Brandt, M.D.
Indiana University School of Medicine, Indianapolis, IN

Osteoarthritis (OA) of the knee is the most common cause of chronic disability in this country. This group has shown that prophylactic oral administration of doxycycline (doxy) markedly reduces the severity of cartilage damage in a canine model of OA; even when therapy was initiated after cartilage lesions were established, a protective effect was apparent. Similar results have been noted in guinea pig and rabbit models of OA. The effect is associated with reduction in the levels of collagenase and gelatinase in the OA cartilage. Based on the encouraging data in animal models of OA, a randomized, placebo-controlled 30-month clinical trial will examine the effect of this drug and its ability to prevent the progression of early knee osteoarthritis in women.

*5R01AR43348-05 Award Amount: $200,000 Clinical*

▶ Title: *Glucocorticoids Alter the Birth and Death of Osteoblasts* NIAMS
P.I.: Robert Weinstein, Ph.D
University of Arkansas for Medical Sciences, Little Rock, AR

This study will characterize the effects of chronic glucocorticoid excess on several aspects of bone physiology. Patients with glucocorticoid-induced bone loss will be included. The effect of alendronate (Fosamax) and parathyroid hormone will be tested in mice for efficacy in ameliorating the effect of glucocorticoids.

*5R01AR46191-03 Award Amount: $100,000 Clinical and basic*

▶ Title: *Low-dose Doxycline Effects on Osteopenic Bone Loss* NIDCR
P.I.: Jeffrey B. Payne, D.D.S.
University of Nebraska, Lincoln, NE

This study seeks to demonstrate the clinical efficacy of low-dose doxycycline therapy in reducing bone loss due to periodontitis and estrogen deficiency in a postmenopausal, estrogen-deficient osteopenic population. Success in reducing or arresting bone loss related to periodontitis in an estrogen-deficient osteopenic group would represent important progress in understanding and managing the pathophysiologic mechanisms that are involved in bone loss with this process.

*1R01DE12872-01A2 Award Amount: $363,768 Clinical, translational*

### *Neurology*

- Title: *Estrogen-induced Hippocampal Seizure Susceptibility* NINDS
  P.I.: Catherine Woolley, Ph.D.
  Northwestern University, Evanston, IL

  A significant proportion of women with epilepsy experience increased seizure frequency during phases of the menstrual cycle in which estradiol levels are elevated. This is termed catamenial epilepsy. Animal models of epilepsy also demonstrate that estradiol increases seizure susceptibility. Previous work in the adult female rat has shown that estradiol induces new dendritic spines and axospinous synapses on CA1 pyramidal cells in the hippocampus, a key brain structure in the generation and propagation of seizure activity. Furthermore, estradiol-induced dendritic spines and synapses are correlated with increased excitability of hippocampal neurons and decreased hippocampal seizure threshold. This correlation suggests that estradiol-induced seizure susceptibility in women with catamenial epilepsy may be due, at least in part, to hormone-mediated alterations in hippocampal synaptic connectivity. The studies in this proposal will use the adult female rat to test the hypothesis that estradiol facilitates seizure activity through alteration of hippocampal synaptic structure and physiology.

  *5R29NS037324-04 Award Amount: $35,000 Basic*

### *Nutrition*

- Title: *Food Choline Database Project* NHLBI
  P.I.: John H. Himes, Ph.D.
  University of Minnesota Twin Cities, Minneapolis, MN

  The purpose of this program is to develop a comprehensive and high-quality database on the choline content of foods commonly eaten in the United States. The data will be generated by analyzing nationally representative samples of 400 foods for their content of various forms of choline. Research activities will be managed by the U.S. Department of Agriculture as a dovetailed component of the ongoing National Food and Nutrient Analysis Program, which has already collected the needed food samples. The total direct cost for developing the database is estimated at $400,000 (400 foods at $1,000/food). The food choline database, resulting from this project, will rectify serious gaps in the general knowledge of choline metabolism and requirements, which require calculating individual- and population-level estimates of choline intake.

  *5U24HL61778-04 Award Amount: $50,000 Applied, National database*

▶ Title: *Altered Calcium and Vitamin D Metabolism in Premenstrual Dysphoric Disorder* NIDDK

P.I.: Susan Thys-Jacobs, M.D.
St. Luke's–Roosevelt Hospital Center, New York, NY

Premenstrual dysphoric disorder (PMDD) is widely recognized as a recurrent disorder related to hormone variations of the menstrual cycle. Whereas alterations in calcium homeostasis have long been associated with many affective disturbances, recent evidence has suggested that luteal phase symptomatology may be associated with a perturbation in calcium homeostasis. The purpose of this investigation is to understand, more completely, the extent to which calcium regulation is disturbed in PMDD by utilizing new tools to access calcium and bone turnover. The long-term objective is to elucidate the pathophysiology of PMDD as it relates to the calciotropic hormones and bone markers. The experimental design involves enrolling 70 women with PMDD and 35 controls. Following 2 months of baseline symptom documentation, women with PMDD and controls with be enrolled in a 9-month observational period with frequent hormonal samplings, urinary collections, and daily ratings. Understanding the pathophysiology associated with PMDD may lead to effective therapeutic strategies to prevent the neuropsychiatric disturbances and abnormal calcium regulation that are characteristic of this disorder.

*1R01DK57869-01 Award Amount: $100,000 Clinical*

## *Obesity and Overweight*

▶ Title: *Study of Health Outcomes of Weight Loss* NIDDK

Multiple centers are participating in a randomized, controlled, multicenter clinical trial in obese type 2 diabetic patients. This trial will examine the effects of interventions designed to produce sustained weight loss and a range of health outcomes. The primary outcome is anticipated to be differences in progression of atherosclerosis. This study will examine the effects of the interventions on cardiovascular and cerebrovascular event rates, cardiovascular and all-cause mortality, cardiovascular risk factors, glycemic control, and other outcomes. There will be three arms: 1) *Community Care* – The primary care physician will be given standard-of-care recommendations for treatment of obesity and comorbid conditions, such as diabetes; 2) *Intensive Lifestyle Intervention* – Patients will undergo a long-term behavioral treatment program that includes dietary modification, increased physical activity, and behavioral therapies designed to enhance weight loss and weight maintenance. Obesity-related comorbid conditions will be treated as in group 1; and 3) *Intensive Lifestyle Intervention Plus Weight Loss Medication* – Medication will be added to the intensive lifestyle intervention in an attempt to enhance long-term weight maintenance. Comorbid conditions will be treated as in group 1.

*Award Amount: $100,000 Clinical*

- Title: *A Mentor-based Approach to Long-term Weight Loss* NIDDK
  P.I.: John M. Jackicic, Ph.D.
  University of Kansas Center for Research, Lawrence, KS

  The primary goal of this study is to examine the effect of a mentor-based intervention on long-term weight loss in overweight adult women. The primary analysis will focus on the effect of this intervention on long-term weight loss in women receiving a mentor-based intervention, with additional analysis focusing on the effect of this intervention on long-term weight loss in women functioning as mentors in this study. The investigators hypothesize that a mentor-based intervention will improve long-term weight loss in both mentors and mentor-recipients compared to individuals receiving a standard non-mentored-based, weight-loss intervention. It is believed that a mentor-based intervention will lead to improvements in the long-term treatment of obesity.

  *5R01DK058002-03 Award Amount: $20,000 Clinical*

- Title: *Internet-aided Prevention of Pregnancy-induced Obesity* NIDDK
  P.I.: Jennifer Lovejoy, Ph.D.
  Pennington Biomedical Research Center, Baton Rouge, LA

  This application targets the prevention of pregnancy-associated obesity in African American women. The overall goal of this proposal is to evaluate the effectiveness of traditional vs. Internet-aided behavior modification for weight management in postpartum African American women. The Internet-based intervention will be used in face-to-face group sessions to allow for more extensive behavioral feedback. The research will address the primary hypothesis that the use of the Internet-aided behavioral intervention will be more effective than traditional behavioral intervention programs in preventing excess postpartum weight retention.

  *5R01DK57446-02 Award Amount: $20,000 Clinical*

- Title: *Primary Care Office Management of Obesity* NIDDK
  P.I.: Pamela Davis Martin, Ph.D.
  Pennington Biomedical Research Center, Baton Rouge, LA

  This randomized, two-arm treatment study will use culturally sensitive educational materials by trained primary care physicians. It will compare physician-directed education (standard care group) to another group who receive customized education plus patient-centered messages by primary care physicians. It will attempt to determine whether a physician-delivered, patient-centered intervention is more effective than standard care in regard to prevention of weight gain and achievement of weight loss at 6 months. It will also examine whether the groups differ in regard to weight maintenance at 12- and 18-month followups. It is hypothesized that patients in the patient-centered group will demonstrate less weight gain, more weight loss at 6 months, greater maintenance of weight loss at 12 and 18 months, as well as dietary and physical activity improvement throughout the observation period, than patients receiving standard care.

  *5R01DK57476-03 Award Amount: $20,000 Clinical*

▶ Title: *Weight Gain in Pregnancy: Staying the Range* NIDDK
P.I.: Christine Olson, Ph.D.
Cornell University, Ithaca, NY

The proposed project focuses on primary prevention of obesity in women by slowing the accumulation of weight in the childbearing years. The long-term goal of the proposed study is to decrease the amount of weight retained in the postpartum period by lower income, rural white women who enter pregnancy with normal or high body mass indices. This goal will be addressed by encouraging women to gain an amount of weight during pregnancy that is within the appropriate ranges recommended by the Institute of Medicine (IOM). The project specifically aims to decrease, by 50 percent, the proportion of women who gain above the upper limit of the appropriate IOM range. The project will be implemented in a primary health care setting. The study has a prospective cohort design with an historical control group.

*5R01DK57439-02 Award Amount: $20,000 Clinical*

▶ Title: *Weight Control in Peri- and Early Postmenopausal Women* NIDDK
P.I.: Susan Racette, Ph.D.
Washington University, St. Louis, MO

The primary aim of this study is to assess the effectiveness of a modest lifestyle intervention program on preventing gains in body weight, whole body fat mass, and abdominal adipose tissue during a 2-year period in perimenopausal and early postmenopausal women who are at risk for obesity. The second aim is to determine the effects of the intervention on daily physical activity, which will be calculated from total daily energy expenditure and resting metabolic rate, as determined by the doubly labeled water method and indirect calorimetry, respectively. A randomized, controlled trial will be used to evaluate the intervention in female employees of a large Midwestern medical center.

*1R01DK5746-01 Award Amount: $20,000 Clinical*

▶ Title: *Clinical and Experimental Study of Human Obesity* NIDDK
P.I.: Albert Stunkard, M.D.
University of Pennsylvania, Philadelphia, PA

This project is a longitudinal study of 78 children, from 3 to 5 years of age, from either obese or non-obese mothers. The goal is to examine a group of variables related to food intake and energy expenditure, along with measures of body size or composition, utilizing not only weight and length but measures of skinfold thickness and percent fat by dual energy x-ray absorptiometry and body water, and isotope dilution measures. The study has already found that the two independent measures of energy intake at 3 months of age predict body size and composition at 1 year of age and discounted the belief that a low total energy expenditure and maternal obesity predict body size and composition at 1 year of age. This study will continue to search for risk factors for obesity in the early childhood years.

*5R01DK56251-05 Award Amount: $100,000 Clinical*

## *Pain*

- Title: *Low Back Pain – A Multicenter Randomized Trial* NIAMS
  P.I.: James Weinstein, D.O.
  Dartmouth Medical School, Hanover, NH

  Low back pain is considered one of the most widely experienced health problems. Rates of spinal surgery have increased sharply over time and 15-fold geographic variation in rates of these surgeries has been documented. There is little evidence proving the effectiveness and efficacy of these surgical therapies over non-operative management. This study will use the resource of the National Spine Network to conduct multicentered, randomized, controlled trials for three common diagnostic groups – lumbar intervertebral disc herniation, spinal stenosis, and spinal stenosis secondary to degenerative spondylolithesis. The trials will compare the most commonly used standard surgical treatments to the most commonly used standard non-operative treatments. The primary endpoints will be changes in general health-related quality of life, as measured by the SF-36 health status questionnaire, and spine-related disability, as measured by the Oswestry Low Back Pain questionnaire. Secondary endpoints will include patient satisfaction with treatment, resource utilization of estimation of cost, and utility for current health for estimation of quality-adjusted life years.

  *5U01AR045444-03 Award Amount: $100,000 Clinical*

- Title: *Pain Management in Temporomandibular Joint Disorders* NIDCR
  P.I.: Jennifer Haythornthwaite, Ph.D.
  Johns Hopkins University, Baltimore, MD

  The primary goal of the proposed project is to test the efficacy of psychological interventions, a pharmacological intervention, and the combination of these interventions in reducing pain and improving function in persons with temporomandibular disorders (TMD). Since psychological interventions are costly and require expertise that is frequently unavailable in primary care settings, the proposed project will also examine the efficacy of a minimal contact/self help psychological intervention based on cognitive-behavioral therapy for pain management. In addition to examining the separate and combined effects of psychological and pharmacological interventions for TMD pain, the proposed study will examine whether the minimal contact cognitive-behavioral intervention can accomplish comparable reductions in pain and improvements in function relative to the therapist-administered treatment.

  *1R01DE13906-01A1 Award Amount: $263,058 Behavioral*

▶ Title: *Trigeminal Pain Mechanisms and Control* NIDCR
P.I.: Jon D. Levine, Ph.D.
University of California at San Francisco, San Francisco, CA

The chemotherapeutic agent paclitaxel (Taxol) is widely used for the treatment of many different types of carcinomas. At present, the dose of paclitaxel that can be tolerated by patients is limited primarily by the development of a painful peripheral neuropathy characterized by parenthesis, myalgia, and arthralgia. Similar dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, including vincristine. Therefore, amelioration of the neuropathic pain might not only reduce the suffering of patients who receive paclitaxel or vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies.

*2P01DE08973-11A1 Award Amount: $151,174 Basic*

▶ Title: *Uterine Pain – Mechanisms and Modulation* NINDS
P.I.: Ursula Wesselmann, M.D.
Johns Hopkins University, Baltimore, MD

These studies will provide fundamental new information about the neuroanatomical and neurophysiological mechanisms of pelvic and uterine pain. An experimental model of uterine pain will be used to obtain information about the spinal pathways that process nociceptive afferent input from the uterus; assess the effects of peripheral opioid application on the spinal processing of nociceptive inputs from the uterus; and determine the influence of the estrous cycle on spinal cord processing of noxious uterine stimulation.

*5R01NS036553-04 Award Amount: $100,000 Basic*

## *Pharmacology*

▶ Title: *Gender and Risk of Drug-induced Cardiac Arrhythmias* NHLBI
P.I.: Ray Woosley, M.D., Ph.D.
Georgetown University, Washington, DC

This study will test the hypothesis that gender-specific differences in cardiac ion current densities are responsible for the observed gender differences in QT interval length and the greater sensitivity of females to drugs that cause QT lengthening. They will use the rabbit model system to identify gender-related differences in cardiac electrophysiological characteristics (action potential and whole cell patch clamp recordings at baseline and after quinidine or d-sortalol) and identify the ionic basis for these differences in rabbit ventricular muscle. They will also evaluate the potential roles for sex steroid hormones in the regulation of specific ion channels that display gender differences at baseline or in response to drugs.

*5R01HL58743-02 Award Amount: $50,000 Clinical*

- Title: *Endogenous Regulators of Drug Metabolism* NIGMS
  P.I.: Bernard H. Shapiro, Ph.D.
  University of Pennsylvania, Philadelphia, PA

  The broad objective of this proposal is to investigate the mechanisms by which growth hormone (GH) regulates the sexually dimorphic expression of hepatic isoforms of cytochrome P450 (CYP), which impacts on concerns regarding the gender effectiveness of therapeutic agents. Having identified the basic elements in the masculine "episodic" and feminine "continuous" plasma GH profiles that selectively "signal" the express of eight constitutive sex-dependent rat CYPs, we now propose to examine the mechanisms by which the hepatocyte discriminates between the numerous GH signals and transduces their messages to the nucleus. The investigators hypothesize that each extracellular signal in the circulating GH profiles activate a different signal transduction pathway responsible for the induction or suppression of each isoform. The investigators propose to identify the different signal transduction pathways mediating GH regulation of CYPs by both infusing GH-devoid rats and exposing primary rat hepatocytes to individual GH signals known to regulate expression of each CYP isoform. Similar experiments will be conducted to identify GH-dependent CYP isoforms in human hepatocytes, and the signal transduction pathways mediating their action. Expression levels of hepatic CYPs are gender-dependent in the adult rat (as well as in every other species examined), and regardless of the treatment, males cannot be induced to express the full female pattern of hepatic CYPs, nor can females be treated to express normal male patterns. The investigators propose to study whether the sexually dimorphic CYP isoforms are permanently imprinted by determining the degree of CYP sex reversal in gender-crossed (male to female and female to male) hepatocyte transplants. Follow-up studies will examine gender-based imprinting differences in the signal transduction responses to GH signals.

  *2R01GM45758-09 Award Amount: $317,000 Basic*

## *Physical Activity*

▶ Title: *African American Women's Response to Physical Activity* NINR
P.I.: Beth A. Staffileno, DNSC
Rush–Presbyterian St. Luke's Medical Center, Chicago, IL

The immediate goal of this 3-year proposal is to strengthen the candidate's research knowledge and skills and provide an opportunity to synthesize these in the investigations of physical activity and other outcomes as they relate to cardiovascular disease control and prevention in women, especially those of ethnic minorities. The overall goal is to produce an independent investigator whose career commitment is to the production and dissemination of science that will make an impact on the health of minority women. To reach this goal, the candidate will pursue a three-phase program, based on a Research Essentials Model – a review by the trainee and her co-mentors produced nine training objectives. These objectives provide for progression from knowledge acquisition to skill development to synthesis. Rush University is an environment conducive to multidisciplinary biomedical and clinical research projects. Two mentors, with expertise in patient-oriented outcomes and cardiovascular research (from the colleges of nursing and medicine, respectively), will oversee the candidate's training and execution of the research project. In addition, three senior researchers and content experts, in the areas of recruitment and retention in women and minority populations and patient-oriented outcomes, will serve as consultant faculty. This proposed research synthesis study uses a randomized, controlled design to investigate the impact of short bouts of accumulated physical activity on blood pressure (BP) and health-related quality of life in African American women, a high-risk group for hypertension. This study will not only quantify the impact of exercise prescription on BP and quality of life, but also, for the first time, investigate the role of endothelial function and hemodynamic correlates of BP change in this high-risk population. Given the well documented high prevalence of obesity in African American women, the low levels of physical activity and fitness in these same women, and the link between physical activity, fitness, and obesity with elevated BP, hypertension-prone and mildly hypertensive African American women are logical targets for a physical activity intervention. Findings from this project, as well as the knowledge and skills developed as part of the training experience, will enable the candidate to propose an R01-level investigation (as the principal investigator, in multidisciplinary patient-oriented research).

*1K23NR00168-01A1 Award Amount: $98,993 Clinical*

### *Pulmonology*

- Title: *Lymphangioleiomyomatosis Patient Registry* NHLBI
  P.I.: Gerald Beck, Ph.D.
  Cleveland Clinic Foundation, Cleveland, OH

  Lymphangioleiomyomatosis (LAM) is a rare but fatal pulmonary disease of unknown etiology that strikes women, primarily in their reproductive years. The goal of this project is to establish a registry of individuals with LAM by forming a consortium of six clinical centers and referring physicians who treat patients with LAM. The cohort of identified individuals with LAM will be used to characterize the clinical features of subjects and provide information on the natural course of the disease. The registry will include clinical data and tissue samples which will be used to study the course of the disease and assess interventions. Data and tissue samples will also be banked for future studies.

  *5U01HL58440-05 Award Amount: $100,000 Clinical*

### *Reproductive Health and Developmental Biology*

- Title: *Evidence Report – Use of Uterine Artery Embolization Procedures and Related Surgical Procedures for Treatment of Conditions That Can Lead to Hysterectomy* AHRQ

  ORWH and the Agency for Healthcare Research and Quality (AHRQ) will develop an evidence report on uterine artery embolization procedures and related surgical procedures for treatment of conditions that can lead to hysterectomy. The NIH/ORWH will work with AHRQ to provide guidance, as appropriate to the Evidence-based Practice Centers (EPCs) conducting this review. The EPCs review all relevant scientific literature on assigned clinical care topics and produce evidence reports.

  *Award Amount: $200,000 Collaborative federal agency review*

▶ Title: *Aging of Brain: Effects of Prenatal Nutrition* NIA
P.I.: Jan Blusztajn, Ph.D.
Boston University, Boston, MA

The goal of this study is to determine the mechanisms by which the availability of choline and folic acid during the prenatal period modifies brain structure and function in development, adulthood, and old age. The proposed studies will: 1) determine the molecular mechanisms involved in the brain reorganization that is governed by choline and folate availability by studying signal transduction pathways and developmental patterns of gene expression in brain; 2) measure synaptic function and plasticity in hippocampus of rats exposed to varying levels of choline or folate *in utero*; 3) examine age-related changes in conditioned stimulus processing (attention) as a function of the prenatal availability of choline and folate; 4) determine if supplementation with folate in early development leads to lifelong changes in spatial memory, brain anatomy, and neurochemistry; and 5) investigate whether choline supplementation, either prenatally or across the life span, ameliorates behavioral, anatomical, and biochemical deficits seen in mice lacking the apolipoprotiein E.

*2PO1AG09525-08 Award Amount: $100,000 Basic*

▶ Title: *Development and Differentiation in Reproductive Axis Cooperative Reproductive Sciences Research at Minority Iinstitutions RFA* NICHD
P.I.: *Director*–David R. Mann, Ph.D., Morehouse School of Medicine, Atlanta, GA
*Co-director/Partner*–Tony M. Plant, Ph.D., University of Pittsburgh, Pittsburgh, PA
Specialized Cooperative Centers Programs in Reproductive Research, Pittsburgh, PA

The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new, and/or the enhancement of ongoing, basic science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health.

*154HD-41749-01 Award Amount: $250,000 Basic science, translational, clinical*

The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core. Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant.

*Grant No. 1 – 1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann.*

*Grant No. 2 – 1U54HD41749-010002 (Role of Prohibitin in Follicular Development), Winston E. Thompson.*

*Grant No. 3 – 1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran.*

*Grant No. 4 – 1U54HD41749-010004 (SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.*

▶ Title: *Fragile X Mental Retardation Gene Premutation* NICHD
P.I.: Pamela L. Mellon, Ph.D.
University of California–San Diego, La Jolla, CA

Fragile X syndrome (FRX) is one of the most frequent forms of congenital mental retardation in humans, usually resulting from lack of expression of the Fragile X mental retardation gene (FMR1). Interestingly, unaffected carriers, or so-called FRX premutation carriers, show an increased prevalence of premature ovarian failure (POF) which is generally defined as cessation of reproductive function by age 40. While it is estimated that 1 percent of women worldwide experience POF, the prevalence of POF in FRX premutation carriers has been reported to be 16 percent. On a more basic science level, the FMR1 gene is expressed in many tissues, but its function is unknown. In both male and female gonads, the gene is expressed in the germ cells. For the ovary, expression of the FMR1 gene in oogonia and oocytes could have profound implications for the regulation of oocyte number and ovarian follicular reserve, which clearly can impact the cessation of reproductive function. Three aims are proposed to: 1) characterize the cell-specific FMR1 gene expression changes in normal human and mouse ovaries through their respective reproductive cycles; 2) define the physiology of hypothalamic-pituitary-ovarian function in human female FRX premutation carriers; and 3) create a repository of genetic material and extensive phenotypic information about women with POF that could eventually be used to test other candidate genes for POF.

*5U54HD12303-22 Award Amount: $113,000 Translational*

▶ Title: *Neuroimmunology and Cytokine Alterations in Vulvodynia* NICHD
P.I.: Barbara D. Reed, Ph.D.
University of Michigan at Ann Arbor, Ann Arbor, MI

Hundreds of thousands of women in the United States suffer from vulvodynia, a chronic burning vulvar pain of unknown cause. Millions of health-care dollars are spent annually for this disorder, in the United States alone, not only on management, but also on the large proportion of cases that are misdiagnosed and inadequately treated. This pain, associated with allodynia and hyperpathia, has a strong genetic predelection, with African American women rarely being affected. The broad, long-term objectives of this proposal are to assess the differences in specific neuroimmunological characteristics between women with vulvodynia and asymptomatic controls. The specific aims include evaluation of: 1) the individual cytokine/neurokine production response to stimulation of peripheral blood; 2) local changes in nerve fiber, mast cell, Substance P, and serotonin density in vulvar tissue; 3) the interactions of the systemic and local immunologic systems assessed in 1) and 2); and 4) the multivariable assessment of these laboratory factors, with historical risk factors for vulvodynia, to explore potential pathophysiologic mechanisms accounting for the historical risk factors identified. The research design involves a case-control evaluation of 100 women with vulvodynia, 100 controls matched for ethnicity, and 100 African American control women, using questionnaires, physical examinations, clinical laboratory data, cytokine/neurokine levels in stimulated peripheral blood, and neuroimmunhistological assessment of vulvar, biopsy specimens for nerve fiber density, mast cells, Substance P, and serotonin. Results from this study will lead to improved understanding of neuroimmunologic alterations in women with vulvodynia which will direct future therapeutic strategies for this disorder.

*5R01HD040112-02 Award Amount: $180,954 Clinical*

▶ Title: *Mechanism of Vulvodynia* NICHD
P.I.: Ursula Wesselmann, Ph.D.
John Hopkins University, Baltimore, MD

The long-range objective of this research is to elucidate the pathophysiological mechanisms of vulvodynia, a chronic pain syndrome of the vaginal and vulvar area, in order to develop improved treatment strategies for alleviating chronic pain in these women, targeted at the underlying pathophysiological mechanism. We propose two approaches to gain better understanding of the pathophysiological mechanisms of vulvodynia: (1) we will develop an animal model in the rat, that will allow us to study the spinal cord pathways involved in the processing of noxious input from the vagina; and 2) we propose to characterize pain in patients with vulvodynia in detail. Out hypothesis is that patients with vulvodynia can be differentiated into distinct groups based on their pain characteristics, and that treatment of pain in vulvodynia will be more effective, if based on recognition of the underlying neurophysiological mechanisms.

*1R01HD039699-01A1 Award Amount: $19,046 Clinical*

▶ Title: *Maternal Peridontitis and Adverse Pregnancy Outcome* NIDCR
P.I.: Waranuch Pitiphat, M.S.
Harvard School of Dental Medicine, Boston, MA

This study will evaluate whether periodontitis is a risk factor for adverse pregnancy outcomes, by adding an oral component to the ongoing Project Viva, a prospective study of 6,000 pregnant women, to evaluate this association. Maternal infection during pregnancy has been demonstrated to play an important role in etiology of preterm delivery. Periodontal infection can serve as a reservoir of gram-negative anaerobic organisms and their products, and proinflammatory mediators which could target the placental membranes via systemic circulation thus leading to preterm delivery or fetal growth restriction. The primary aim of this study is to examine the effect of maternal periodontitis on length of gestation and fetal growth. The secondary aim is to explore the association between periodontitis and serum levels of TNF-alpha. The proposed prospective nested case-control study will request pre-existing radiographs from Viva participants.

*1R03DE14004-01A1 Award Amount: $25,000 Case-control study*

▶ Title: *Treating Premenstrual Syndrome and Premenstrual Dysphoric Disorder: Research Versus Clinical Reality* NIMH

P.I.: Kimberly Yonkers, M.D.
Yale University School of Medicine, New Haven, CT

Moderate to severe premenstrual disturbances afflict 15 to 20 percent of women. After years of treatment research that was notable for inconsistent findings, researchers have identified agents that effectively treat women suffering from these conditions. An appealing treatment modality for ameliorating symptoms in women with premenstrual dysphoric disorder (PMDD) is the use of SRIs, only during the luteal phase of the menstrual cycle, an approach supported by several randomized clinical trials. Medication administered by this way limits both drug exposure and side effects to the symptomatic phase of the cycle and is often preferred by patients. Given positive efficacy studies for luteal-phase dosing, it is likely that the Food and Drug Administration will approve the use of this modality for the treatment of moderate to severe premenstrual conditions, such as PMDD. Yet, this is a treatment modality that has only been evaluated in controlled clinical trials, and features that may have enhanced positive study results (monitoring ovulation, compliance counseling by vigilant study staff, and direction regarding when to initiate medication) are noticeably absent in routine clinical practice. Furthermore, evidence suggests that patients in clinical trials, who were able to comply with luteal-phase dosing, are not representative of women commonly seen in clinical practice, and thus the feasibility of luteal-phase dosing is unclear. The specific aims of this application are to: 1) evaluate whether women in a primary care ob-gyn practice, with moderate to severe PMS, will be willing and able to adhere to psychotropic medication treatment that is limited to the luteal phase of the menstrual cycle; 2) determine whether specific patient characteristics (suffering from moderate to severe PMS that does not meet criteria for PMDD versus suffering PMDD; having another co-occurring psychiatric or general medical condition that is not limited to the luteal phase of the cycle versus not having other disorders) influence response to intermittent SRI treatment; 3) evaluate whether a retrospective scale, administered in conjunction with a psychiatric screening scale, can identify women with moderate to severe premenstrual changes; 4) compare and select outcome measures that are most able to show improvement in premenstrual symptoms after treatment with an SRI; and 5) collect symptom data on treatment as usual in order to estimate the effect size required for a subsequent study.

*1R21MH62379-01A1 Award Amount: $100,000 Clinical*

## *Violence*

▶ Title: *NAS Panel on Risk and Prevalence of Elder Abuse and Neglect* NIA

The purpose of this initiative is to request NAS/NRC to organize a Panel on Risk and Prevalence of Elder Abuse and Neglect. The panel meetings will integrate expert knowledge in the field and provide advice on developing the methodology and design for a national probability sample on abuse and neglect. It will also suggest instrumentation for measuring highly sensitive and stigmatized behaviors and provide cross fertilization for studies of child abuse, HIV, violence against women, and criminal behavior. NAS/NRC's Committee on National Statistics will be asked to provide expertise in the design of surveys to measure low-prevalence phenomena in such populations as older, institutionalized women. A panel will help develop options for the research design, specify appropriate populations for sample inclusion (e.g., men, women, the institutionalized, racial and ethnic categories), and design instrumentation that can be used to detect incidents of elder abuse and neglect reliably and validly. The panel will evaluate the potential for pilot studies needed to develop instruments that can detect abusive behavior. The panel will also discuss issues related to confidentiality and data sharing. In addition, the panel will be asked to make recommendations regarding the scope of a national research effort on elder abuse and neglect, which will include institutionalized victims of abuse and neglect and issues related to data collection on victims suffering from dementia.

*Award Amount: $75,000*

▶ Title: *Hispanic Battered Women's Experiences of Health Care* NINR
P.I.: Ursula A. Kelly, M.S.N.
Boston College, Chestnut Hill, MA

The purpose of this descriptive exploratory qualitative study is to improve health care providers' understanding of the health care experiences of Hispanic battered women. The specific aim of the study is to identify aspects of health care interactions with primary care providers (PCPs) that Hispanic battered women perceived as helpful, supportive, or positive, or that made a difference in the women's experience of living with the abuse. This research will provide patient-centered information that will lead to improved health care interventions for this population, increased patient satisfaction with health care, and enhanced patient-provider relationships. Domestic abuse is a significant health problem which PCPs are well positioned to address. There is a lack of understanding of this problem and the needs of victims of abuse, from the patients' perspective, particularly Hispanic women. This study will use feminist methodology to elicit and articulate Hispanic battered women's experiences of health care, the meaning they give to those experiences, and the health care responses they find helpful. Data will be collected through interviews with Hispanic women, who are survivors of domestic abuse, and will be analyzed via content analysis. The resulting description of the women's experiences will enhance PCPs understanding of effective health care interventions for Hispanic survivors of domestic abuse.

*1F31NR07686-01 Award Amount: $26,150 Clinical*

▶ Title: *Biophysical and Immunologic Responses to Battering* NINR
P.I.: Anne B. Woods, M.P.H.
Johns Hopkins University, Baltimore, MD

Intimate partner violence (IPV) has significant long-term effects on women's health. In spite of persistent findings of increased infections, assessment of immune system function among battered women is one of the weakest areas of current research; and mental and physical health effects are typically investigated as separate, distinct outcomes. Conceptualizing the response to abuse within a stress response framework that links mental health effects on hypothalamic-pituitary-adrenal (HPA) axis regulation with Th1/Th2 cell modulation may help to explain the impact of IPV on abused women's immune function. The major purposes of this predictive correlational study are to: 1) identify the prevalence of intimate partner violence among women who utilize health care services at a clinic for the uninsured in Baltimore, MD; 2) to identify the relationship of depressive, post-traumatic stress disorder (PTSD), and comorbid depressive symptoms with immune function; and 3) to identify predictors of immune system alterations among a sample of abused women. All women who present for care at the Shepherd's Clinic will complete a brief health questionnaire, including the Abuse Assessment Screen. Eligible women who screen positive for IPV, along with a comparable, non-abused control group, will be invited to participate in an interview to collect quantitative data on partner abuse, depressive and PTSD symptoms, and health problems. Medical chart review will confirm past immune system disorders. Serum levels of Th1 (interferon) and Th2 (interleukin-10) cytokines, which are mediated through cortisol, will assess modulation of immune system function. Descriptive statistics, Chi-square, ANOVA and ANCOVA techniques will be used to determine the relationship of mental health disorders and immune system function. Multiple logistic regression will investigate predictors of Th1/Th2 cell modulations. This proposed study will contribute information on the effects of intimate partner violence and mental health symptoms on immune function.

*1F31NR07600-01 Award Amount: $26,150 Clinical*

# FY 2002 ORWH RESEARCH INITIATIVES

## *Aging*

▶ Title: *Aging of Brain: Effects of Prenatal Nutrition* NIA
P.I.: Jan Blusztajn, Ph.D.
Boston University, Boston, MA

The goal of this study is to determine the mechanisms by which the availability of choline and folic acid during the prenatal period modifies brain structure and function in development, adulthood, and old age. The proposed studies will: 1) determine the molecular mechanisms involved in the brain reorganization that is governed by choline and folate availability by studying signal transduction pathways and developmental patterns of gene expression in brain; 2) measure synaptic function and plasticity in hippocampus of rats exposed to varying levels of choline or folate *in utero*; 3) examine age-related changes in conditioned stimulus processing (attention) as a function of the prenatal availability of choline and folate; 4) determine if supplementation with folate in early development leads to lifelong changes in spatial memory, brain anatomy and neurochemistry; and 5) investigate whether choline supplementation, either prenatally or across the life span, ameliorates behavioral, anatomical, and biochemical deficits seen in mice lacking apolipoprotiein E.

*2P01AG09525-11 Award Amount: $100,000 Basic*

▶ Title: *A Fall Prevention Program for High-risk Elderly Women* NINR
P.I.: Jean F. Wyman, Ph.D., R.N.
University of Minnesota, Minneapolis, MN

The long-term objective of this study is to develop cost-effective, community-based strategies for the prevention of falls in high-risk elderly women. Specific aims are: 1) test the efficacy of a fall prevention program for high-risk elderly women on fall rates over 1 and 2 years; 2) determine the effects of the fall prevention program on postural competence, functional performance, and a variety of other outcome measures; and 3) identify demographic, clinical, personal, functional, and postural competence variables that predict long-term exercise adherence for participants in the fall prevention program. The participants will be 250 community-dwelling women, aged 70 and over, who are mentally intact, ambulatory, with postural instability – and at least one other fall risk factor – not currently involved in regular exercise, and medically stable with physician approval for independent exercise participation. This study will provide information on the efficacy and cost of simple interventions designed to prevent falls and fall-related injuries, reduce preclinical disability, maintain long-term exercise adherence, and improve quality of life for older women.

*5R01NR005107-03 Award Amount: $150,000 Clinical*

### *Alcohol and Other Substance Abuse*

- Title: *Biobehavioral Trajectories to Alcohol Abuse: A Pilot Study* NIAAA
  P.I.: Roberta Palmour, Ph.D.
  McGill University, Montreal, Quebec Canada

  Adolescent alcohol abuse has now reached epidemic proportions, carrying with it a toll of lost opportunity, suffering, and death. Many studies document the correlation between early alcohol use and later alcohol dependence, and a widespread belief that delaying the onset of alcohol consumption until the end of adolescence will reduce the risk of pathological drinking. An alternate interpretation is that those who drink early are those who are especially vulnerable, either through biology or circumstance. There are major implications of these conflicting explanations for treatment, for research, and for public policy. To disaggregate the influence of specific biobehavioral and sociocultural variables in any appropriate cross section of the human population is exceedingly difficult. A pilot study of the feasibility of addressing this question experimentally by capitalizing upon an animal model of spontaneous alcohol abuse is proposed. *C. aethiops*, a non-endangered African primate, is highly homologous with man, lives in social groups, has a distinct adolescent period in its ontogeny, and contains individuals who differ from one another with respect to alcohol consumption and to behavioral traits (sociability, excitability, etc.). In an 18-month cross-sectional study, 96 male and female vervet monkeys will be housed in groups balanced by sex, level of baseline alcohol consumption, and temperamental behavioral profile. The manipulated factor will be exposure to ethanol and to drinking or non-drinking role models. The principal outcome measure (9 and 18 months later) will be quantity and pattern of ethanol consumption; weekly social behavioral measures will also be collected in standard primatological fashion. Evaluation of the independent or joint effects of gender, behavioral trait status and initial propensity to drink, and of exposure to ethanol or drinking role models will utilize multivariate regression methods. In a second phase, the utility of specific pharmacological interventions in modifying outcome will be evaluated. The exploratory aspect of this approach is the extent to which it might suggest methods to improve decomposition of the relevant factors in human samples.

  *1R21AA013647-01 Award Amount: $100,000 Basic*

- Title: *Alcohol, HIV-risk Behaviors, and Sexual Victimization* NIAAA
  P.I.: Maria Testa, Ph.D.
  Research Institute on Addictions, Buffalo, NY

  This application suggests that childhood sexual abuse and risk-prone personality (high sensation-seeking, high negative affect, low assertiveness) lead women to engage in risky behaviors (heavy alcohol and drug use, and high levels of sexual activity and exposure to risky settings, such as bars) which in turn increase the likelihood of experiencing both sexual victimization and HIV/STD infections. There will be a three-wave, cross-legged panel design using a representative sample of 1,000 unmarried women, ages 18 to 30, recruited from random digit dialing.

  *5R01AA12013-05 Award Amount: $50,000 Clinical*

▶ Title: *Gender and Sex Differences in Stimulant Action* NIDA
P.I.: Cynthia M. Kuhn, Ph.D.
Duke University Medical Center, Durham, NC

Women comprise about one-third of cocaine addicts. They start using cocaine earlier in life, are more sensitive to some cocaine effects and progress to dependence more rapidly. Rodents show some similarities to this pattern: cocaine elicits greater increases in cocain-stimulated locomotion, females work harder for cocaine reinforcement and extracellular dopamine rises more than in male rats. Our preliminary findings suggest that developmental exposures to gonadal steroids contributes to sex difference in cocaine action. The purpose of this proposal is to investigate the basis for the organizational effect of gonadal steroids on forbrain dopamine systems and the behavioral response to psychomotor stimulants mediated by these systems. The investigators will test the hypothesis that sex differences in cocaine effects reflect anatomical or functional differences in dopamine neurons established during ontogeny. To determine when steroid effects are exerted, male and female rats will be gonadectomized on postnatal day 2, prepubertally on day 25 or in adulthood, and cocaine-stimulated locomotion and electrically stimulated dopamine overflow will be determined on postnatal day 70. To evaluate which steroids mediates these effects, rat pups will be treated with vehicle, testosterone or estrogen antagonists ICI82780 (females), and aromatase inhibitor or androgen antagonist flutamide (males) during the early postnatal window or during puberty and the same dependent measures will be assessed. Finally, to evaluate how organizational effects of steroids are manifested, the number of dopamine neurons, density of innervation, dopamine content and electrically stimulated dopamine release in nucleus accumbens and caudate nucleus will be determined following the same treatments. These studies should provide insight into potential biologic mechanisms that influence gender differences in disease related to dopamine neuron function in humans including Parkinson's disease and psychostimulant addiction.

*2R01DA009079-08A1 Award Amount: $296,133 Basic*

- Title: *Timing of Social Service Events on Women's Recovery from Drug Addiction* NIDA
  P.I.: Cathleen A. Lewandowksi, Ph.D.
  Wichita State University, School of Social Work, Wichita, KS

  The objective of this exploratory study is to develop and understand the impact of a multiple agency, service delivery environment on women's drug treatment outcomes. This exploratory study has three specific aims: to assess the impact of a multiple agency, service delivery environment on women's drug treatment outcomes; to describe the characteristics of women in recovery who receive services simultaneously or sequentially from multiple agencies; and to describe the multiple agency service delivery pattern over a 1-year period. The main goal of this study is to lay the groundwork for future studies where more specific hypotheses can be tested. The research design is a longitudinal panel design, where services and drug recovery outcomes for women are examined, using both retrospective data and data collected over a 15-month data collection period. The following drug treatment outcomes will be examined: drug-free at end of study, drug recovery days, completion of treatment phases, employment and school, and reunification with biological children. Research will be conducted at a women's residential drug treatment program in Wichita, Kansas. Women who are admitted to the facility for drug treatment during a 9-month window (135) will be invited to participate. Primary data will be collected using structured interviews and Life History Calendars. These data collection instruments will be pilot tested prior to the study's implementation. The initial structured interview will collect retrospective data on critical incidents occurring in women's lives to that point. Life History Calendars will be used to collect more detailed information on service delivery patterns during the initial 3 months of treatment, and to pinpoint the dates of critical events occurring the 3 months prior to treatment. Secondary data will be collected from the agency's database and case records. Univariate and bivariate statistics will be used to describe characteristics of this population and to examine women's perceptions of the multiple agency service environments. Multivariate data analysis will proceed using event history analysis to examine associations between key variables. Both continuous and discrete time survival analysis will be used to investigate drug treatment outcomes. As the study is exploratory, differences in outcome cannot be necessarily attributed to treatment differences. Instead, interpretation of findings will suggest directions for subsequent studies.

  *1R03DA014360-01A1 Award Amount: $73,000 Basic*

- Title: *Women with Schizophrenia and Co-occurring Substance Use Disorders* NIDA
  P.I.: Jean Gearon, Ph.D.
  University of Maryland, Baltimore, MD

  The primary goals of this project are: 1) to determine if women with schizophrenia and co-occurring substance use disorders are more vulnerable to HIV (e.g., engage in more high-risk behaviors) and violent victimization than either women with major depression and co-occurring substance use disorders, or women with substance use disorders only and no history of serious and persistent mental illness; 2) to determine if women with schizophrenia, who abuse substances, experience more violent victimization than women with major depression and co-occurring substance use disorders, or women with substance abuse disorders alone and no history of serious and persistent mental illness; and 3) to examine the causal sequencing between cognitive functioning, social competency, negative symptoms, and HIV risk and victimization.

  *5R29DA011199-05 Award Amount: $20,000 Clinical*

▶ Title: *Sexual Identity and Drinking: Risk and Protect Factors* NIAAA
P.I.: Tonda L. Hughes, Ph.D.
University of Illinois at Chicago, Chicago, IL

This study will use an existing survey instrument to examine and compare risk and protective factors for heavy drinking and alcohol-related problems in lesbians and heterosexual women. The study will include data from 600 women, 18 years of age or older.

*5K01AA00266-04 Award Amount: $44,007 Clinical*

## *Cancer*

▶ Title: *Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines* NCI
P.I.: Douglas R. Lowy, M.D.
National Cancer Institute, Bethesda, MD

This project will perform the early phase clinical trials of two HPV16-based papillomavirus vaccines. L1 is a major structural papillomaviral protein that can self assemble into virus-like particles (VLPs). It is thought that L1 VLP will only protect by preventing primary infection. To add another level of protection, a chimeric VLP was developed by adding the L2 minor capsid protein to the L1. After preclinical vaccine results, an early-phase human trial of L1 HPV16 VLP vaccine is being tested. There are four groups of 12 normal volunteers, 18 to 29 years old. In each group, ten volunteers received the vaccine and two received a placebo in a double-blind fashion.

*1Z01BC09052 Award Amount: $600,000 Clinical*

▶ Title: *Mitotic Checkpoint and Genomic Stability in Ovarian Cancer* FIC
P.I.: Dong-Yan Jin, M.D., Ph.D.
University of Hong Kong

Ovarian cancer is a major cause of cancer death in women worldwide, but the molecular mechanisms of its pathogenesis are not known. The applicant has found that mitotic checkpoint defects are common in ovarian cancer cell lines. The proposed studies are designed to investigate the molecular basis of mitotic checkpoint in mammalian cells and its relevance to genomic instability in ovarian cancers. The hypothesis is that mitotic checkpoint genes are defective in ovarian cancers leading to genetic instability and, thus, contribute to the pathogenesis of this cancer.

*1R01TW006186-01 Award Amount: $17,500 Basic*

- Title: *Tumor Progression and Apoptosis in Mouse Mammary Gland* FIC
  P.I.: Edith C. Kordon, Ph.D.
  Instituto de Investigaciones Hematologicas (IHEMA), Argentina

  The project addresses two main goals: discovering new pathways involved in mammary tumor progression, particularly those related to the loss of hormone-dependency; and determine the events that initiate the cascades that trigger programmed mammary cell death during mammary gland involution. Understanding what determines the neoplastic-cell lack of response to the regulatory controls for cell proliferation and death is the main goal for experimental oncology. In the case of mammary cells, one of the main controls for proliferation and differentiation resides in the action of pregnancy-related hormones. Determine new genes and pathways that release the mammary epithelial cells from such a control is a fundamental issue in the fight against breast cancer.

  *1R01TW006212-01 Award Amount: $17,500 Basic*

- Title: *Acrogranin Function in the Ovary* FIC
  P.I.: Laura Diaz-Cueto, M.D., Ph.D.
  Coordinacion de Investigacion en Salud IMSS

  Ovarian carcinoma is the fifth most common cause of cancer among women in the United States, with more than 23,000 new cases diagnosed and approximately 14,000 deaths each year. In Mexico, ovarian cancer is the seventh cause of cancer among women. Recent studies have demonstrated that a new family of growth factors (epithelin, granulins, and acrogranin [the precursor]) have regulatory activities on preimplantation mouse embryo, normal epithelial and tumoral cells in rodents and human, following interesting signal transduction pathways, and are overexpressed in some kind of human cerebral tumors, renal cell epithelial carcinomas.

  *1R01TW006189-01 Award Amount: $17,500 Translational*

- Title: *Ethnicity-based Proteomic Biomarkers in Breast Cancer* NCI
  P.I.: Helena R. Chang, M.D.
  University of California, Los Angeles, CA

  African American women with breast cancer are more likely found at advanced stage and, therefore, have a worse survival. While the poor outcome observed in African American women with breast cancer may be multifactorial, the aggressiveness of their disease may have a biological base. A significant tumor shrinkage, induced by preoperative chemotherapy, may be used as a surrogate marker to predict patient's survival outcome. This study will search for novel specific proteins in breast cancer that predict tumor responses to preoperative chemotherapy. The chemical identities of these proteins will be determined by mass spectrometry/proteomics. In addition, whether the "drug-resistant" biomarkers are more common in African American women will be systematically compared with Caucasian American women. Finally, the prognostic value of the biomarkers will be compared with the conventional parameters, such as patients' demographic and tumor features, in a multivariant analysis to determine their independent predicative value and interaction of various factors.

  *1R01CA093736-01A1 Award Amount: $100,000 Basic*

## *Cardiovascular Disease*

▶ Title: *Why is Cardiac Risk Increased in Rheumatoid Arthritis?* NIAMS
P.I.: Daniel H. Solomon, M.D., M.P.H.
Brigham and Women's Hospital, Boston, MA

While rheumatoid arthritis (RA) is primarily considered a condition affecting the joints and impairing function, past data suggest that cardiac disease represents the number one cause of mortality in RA. However, the adjusted rates of cardiovascular death and myocardial infarction in RA are poorly characterized. Additionally, whether the increased cardiovascular risk is because of the medications used for RA or the underlying disease severity is unknown. The proposed research has two major aims: 1) to quantify the rates of cardiovascular death and myocardinal infarction in patients with RA, after controlling for known cardiovascular risk factors; and 2) to determine the contribution of RA medication exposure and disease severity to cardiovascular disease rates. Prior work on this issue has largely been conducted in referral populations and attempts to control for known cardiovascular risk factors have been poor. This issue will be studied in a large Medicare/Medicaid database that the investigators have extensive experience working with. This database contains information on 2 million patients, followed for 10 years, and includes diagnosis and procedures for all physicians and inpatient visits. In addition, prescription data from a large pharmacy benefits program has been integrated into this database, allowing for a complete characterization of an individual patient's medication exposure. While any one diagnosis of RA may not be accurate in such a database, the project entails a validation sub-study to develop an algorithm for selecting patients with a high probability of having RA. The proposed project will be an important advance in this area because of the large number of patients with RA to be included (over 5,000), the community-based nature of their care, the ability to control for known cardiovascular risk factors, the extensive medication information allowing for us to explore key hypotheses regarding corticosteroid exposure, and the attempt to simultaneously control for disease severity.

*1R03AR048264-01 Award Amount: $100,000 Clinical*

- Title: *Cardiovascular Risk in Former Gestational Diabetic Women* NINR
  P.I.: Kathleen B. King, Ph.D.
  University of Rochester, Rochester, NY

  The association between diabetes and risk for cardiovascular disease is well established. Women with a history of gestational diabetes mellitus (GDM) are at increased risk of developing type 2 diabetes later in life, and limited but suggestive evidence demonstrates that these women also are more likely to have an unfavorable risk factor profile for coronary heart disease (CHD). The primary aim of this project is to examine the prevalence of risk factors for CHD in women with a history of GDM, compared to women without a history of GDM. The investigators will test whether women with a history of GDM: 1) have a higher calculated 10-year relative risk for CHD; 2) have more adverse levels of individual risk factors for CHD; and 3) are more likely to develop CHD risk factors at a younger age, compared to women who did not have GDM, controlling for body size. The secondary aim of this project is to evaluate women's perceptions of their future risk of developing both CHD and diabetes, and whether perception of risk is related to the actual risk. Eighty women with a history of GDM (cases), and 80 women without a history of GDM (controls), who were 30 years of age or older when they gave birth and are now 5- to 10-years postpartum, will be recruited. Cases and controls will be matched for age, ethnicity, and body mass index (BMI) within 1 year of the index pregnancy. Data will be collected during an outpatient admission to the NIH-funded General Clinical Research Center. The primary outcomes will calculate relative risk of CHD, serum lipids, blood pressure, and insulin sensitivity. The secondary outcomes will be perception of risk for diabetes and CHD. Body size will be control by matching on pre-pregnancy BMI, as well as controlling for current BMI, and central obesity. Demographic and clinical variables, in particular variables known to be related to CHD and/or distributed differently among cases and controls, will be considered for inclusion as control variables prior to hypothesis testing. Regression and logistic regression analysis will be used to test for differences between women, with and without GDM, on the study outcomes. Correlational analysis will be used to determine the relationship between perception and actual risk.
  *1R01NR007659-01A1 Award Amount: $100,000 Clinical*

## *Diabetes*

▶ Title: *The Post-Diabetes Prevention Program Followup Study* NIDDK
P.I.: Sarah Fowler, Ph.D.
George Washington University, Washington, DC

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. DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of 3.4 years (range 2.4 to 5.4) with a total of 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 percent risk 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 research 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 percent minorities, is the largest IGT population ever studied. Moreover, the sub-cohort that has developed diabetes (n=700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of 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 cardiovascular disease (CVD), CVD risk factors, and atherosclerosis in new onset type 2 diabetes and IGT; and 4) examine topics 1 through 3 in minority populations, men vs. women, and in older subjects in DPP.

*2U01DK048489-10 Award Amount: $300,000 Clinical*

▶ Title: *Diabetes Prevention Program Primary Prevention Program Data Coordinating Center* NIDDK
P.I.: Sarah Fowler, Ph.D.
George Washington University, Washington, DC

The Diabetes Prevention Program is a multicentered, randomized trial designed to determine whether type 2 diabetes can be prevented or delayed in a population of high-risk individuals. Included in the high-risk population are women with a history of gestational diabetes mellitus (GDM) and individuals with impaired glucose tolerance. There are 3,234 participants enrolled in the three-arm study with two active treatment groups (metformin and lifestyle) compared to placebo controls. Of the total recruited, 68 percent were women – 13 percent of these had a history of GDM, and nearly 50 percent were from minority populations.

*5U01DK048489-08 Award Amount: $67,500 Clinical*

- Title: *Diabetes Prevention Program Primary Prevention Trial* NIDDK
  P.I.: David Marrero, Ph.D.
  Indiana University–Perdue, University at Indianapolis, Indianapolis, IN

  The primary goal of the proposed project is to determine, via a collaborative multicenter trial, whether interventions can: a) prevent persons with impaired glucose tolerance (IGT) or a history of gestational diabetes mellitus (GDM) from developing non-insulin-dependent diabetes mellitus (NIDDM); and b) prevent the worsening of glucose tolerance in people with newly diagnosed NIDDM. Because of the ethnic diversity of the study populations, a secondary goal is to design the interventions to be sensitive to varying social, ethnic, and cultural values. With the use of the Regenstrief Medical Record System, we have identified three potential high-risk populations: 1) 6,721 persons with a prior history of diabetes with random blood glucose values of 108 to 160 mg/dl and concomitant risk factors for NIDDM, of whom 54 percent are African American; 2) 3,688 patients with NIDDM in whom we will contact their first-degree relatives; and 3) between 530 to 600 women with a history of GDM projected to be available by enrollment, 34 percent of whom are African American. We plan to evaluate, using a randomized control group comparison design, the relative effectiveness of the proposed interventions in reducing conversion to NIDDM in persons with IGT, and deterioration of glucose tolerance in newly diagnosed NIDDMs as primary end points and macrovascular risk factors, coronary events, and overall mortality as secondary end points.

  *5U01DK048406-09 Award Amount: $67,500 Clinical*

- Title: *Diabetes Prevention Program* NIDDK
  P.I.: Harry Shamoon, M.D.
  Yeshiva University, New York, NY

  By selecting populations at higher than average risk for the ultimate development of NIDDM, the Diabetes Center at the Albert Einstein College of Medicine will test the following hypothesis: The reduction in risk of developing NIDDM in persons at high risk for the development of diabetes will be dependent on treatment which affects insulin resistance, islet B-cell dysfunction, and/or hepatic glucose production. Interventions which include diet, exercise sulfonylurea drugs, and metformin in a factorial design can address this hypothesis. The Albert Einstein Center has a large, identified population of individuals from racial and ethnic minority groups in the Bronx and Westchester Counties who receive their medical care in Einstein-affiliated programs; an identified and well-characterized population of women who had gestational diabetes diagnosed between 1988 and the present, and an annual accrual of an additional cohort of women with gestational diabetes; members of the treatment team with specific competence in diabetes in Hispanic and in African American individuals; expertise in related areas, such as hypertension control, cardiovascular risk reduction, and behavioral techniques intended to achieve therapeutic goals.

  *5U01DK048349-09 Award Amount: $21,000 Clinical*

▶ Title: *NIDDM Primary Prevention Trial* NIDDK
P.I.: Neil White, M.D.
Washington University, St. Louis, MO

The proposed intervention is centered on an intensive, multidisciplinary program to promote long-term weight loss and increase physical activity among 200 volunteers who work in or live near the Washington University Medical Center in St. Louis. The proposed intervention is designed to minimize physical discomfort and lifestyle disruption; to emphasize gradual, moderate changes in the foods usually eaten; to maximize continued adherence over 5 years; and to be acceptable to both white and African American volunteers. In order to sustain this weight loss long term, it is proposed to have the intensively managed patients seen regularly by trained members of a multidisciplinary team that will consist of an exercise technician, a nutritionist, a nurse, and a social worker trained in behavioral medicine. Volunteers randomized to the control group will be seen quarterly and provided with state-of-the-art educational and motivational materials that will include recommendations for weight loss, increase physical activity, and a prudent diet low in saturated fats and cholesterol.

*5U01DK048400-09 Award Amount: $22,000 Clinical*

▶ Title: *Diabetes Prevention Program* NIDDK
P.I.: Janet A. Tobian, M.D.
University of Chicago, Chicago, IL

This grant is a multicenter trial in which subjects would be screened for inclusion and exclusion criteria. A primary prevention subgroup will consist of subjects with impaired glucose tolerance (IGT) by National Diabetes Data Group (NDDG) criteria with a fasting plasma glucose (FPG) equal to or more than 110 mg/dl. A secondary intervention subgroup will consist of individuals with NIDDM by NDDG criteria and a FPG 140 mg/dl. The subjects will be randomized in a 2 x 2 factorial design to: 1) intensive program of diet, exercise, and stress reduction versus standard dietary and exercise advice, as well as 2) therapy with either glipizide or placebo. We propose that the diet and exercise intervention be modeled after the PATHWAYS program (diet, exercise, and stress management) which has been validated as an effective method of weight reduction in inner-city African American women. Individuals will be followed to test whether these interventions can: 1) prevent the worsening of glucose tolerance in these subjects over 5 years; and 2) reduce cardiovascular morbidity and mortality.

*5U01DK048381-09 Award Amount: $22,000 Clinical*

## *Endocrinology*

▶ Title: *Plasticity of Hypothalamic Neurons: Estrogen Effects* NINDS
P.I.: Oline K. Ronnekleiv, Ph.D.
Oregon Health Science University, Portland, OR

The long-term objective of this research is to explore the biphasic effects of 17-beta-esttradiol (E2) on synaptic transmission that results in inhibition and subsequent activation of gonadotropin-releasing hormone (GnRH) neurons. Preoptic (POA) GABA neurons, that synapse on GnRH neurons, are critical for mediating these effects of E2. The working hypothesis is that estrogen modulates the expression and function of ion channels and receptors in hypothalamic GABA neurons, which are involved in negative and positive feedback of GnRH release. The first experiments will explore the effects of estrogen on calcium T-channel activity in hypothalamic GABA neurons during negative and positive feedback. Tissues will be prepared from ovariectomized oil- and E2-treated animals. The mRNA expression of T-channel subunits will be measured using ribonuclease protection assay (RPA) and *in situ* hybridization. This expression will be correlated with T-channel activity in individual neurons using whole-cell patch recording and single-cell RT-PCR. Also, the effects of estrogen on the coupling of the GABA-B receptor in inhibition of I(t) will be measured using whole-cell recording. The second experiment will explore the effects of E2 on the expression of Katp channels in POA GABA neurons. The relative mRNA expression of the Katp subunits (Kir 6.2 nd SUR 1, 2) will be measured in the POA following estrogen-using RPA and *in situ* hybridization. The responses to Katp channel openers, and the effects of baclofen, will be measured in GABA neurons using whole-cell recording, and the expression of Katp transcripts identified using RT-PCR. The third experiments will explore how E2 alters the coupling of the alphal-adrenergic and glutamate metabotropic receptors to SK channels in hypothalamic GABA neurons. The effects of estrogen on the SK current in GABA neurons will be measured using whole-cell recording and single-cell RT-PCR. Also, the cellular pathways underlying the effects of E2 on the alphal-adrenergic inhibition of the SK current will be explored using whole-cell recording during negative and compared to positive feedback. Finally, the coupling of the glutamate metabotropic (mGluR1, GluR5) receptors to inhibition of SK channels in POA GABA neurons will be explored using whole-cell recording, and the relative mRNA expression of mGluR1, GluR5 in GABA neurons determined using RT-PCR. These studies will provide important new information about the mechanisms by which E2 alters the excitability of POA GABA neurons during negative and positive feedback and, in general, how estrogen modulates GABAergic synaptic activity in the mammalian brain.

*2R01NS035944-05A1 Award Amount: $100,000 Basic*

## *Eye Disease*

▶ Title: *Incidence of Late Macular Degeneration in Older Women* NEI
P.I.: Anne L. Coleman, M.D.
University of California–Los Angeles, Los Angeles, CA

Age-related macular degeneration (ARM) is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and the progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors, such as diabetes mellitus and prior cataract surgery, with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the trajectory of visual decline in older women over a 14-year period. Secondarily, it aims to determine the impact of late ARM on vision-targeted, health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5,482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision with automated perimetry, intraocular pressure, and uncorrected refractive error. These women also had a refraction and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5 percent of these women have photographically validated late ARM, 41.5 percent have early ARM, and 54 percent have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEI-VFQ. In addition, visual acuity and contrast sensitivity will be re-measured. Fundus photographs of both eyes through dilated pupils will be obtained. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-related Maculopathy Grading System in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30 percent of the eyes with ARM, and 10 percent of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

*1U10EY13626-01A1 Award Amount: $230,000 Epidemiologic, case-control*

▶ Title: *Visual Dysfunction and Quality of Life in Multiple Sclerosis* NEI
P.I.: Laura J. Balcer, M.D.
University of Pennsylvania, Philadelphia, PA

Visual impairment is a leading cause of symptoms in patients with multiple sclerosis (MS). The extent to which vision has been affected by new therapies for MS is not known, and has been difficult to assess using traditional measures of neurologic impairment. The visual profile of MS has not been examined, and the relation of visual function to overall neurologic impairment in patients with MS has not been determined in a large, heterogeneous cohort. This proposal will accomplish the following specific aims: 1) define the visual profile of MS in a large cohort (400 patients), and determine which measures best identify visual dysfunction in patients with MS; and 2) determine the relation of visual function to vision- and disease-specific HRQOL in patients with MS.

*1R01EY13273-02 Award Amount: $125,000 Cohort Study*

### *Gastroenterology*

▶ Title: *Cognitive Therapy as a Treatment for Irritable Bowel Syndrome* NIDDK
P.I.: Edward Blanchard, Ph.D.
State University of New York, Albany, NY

Recent research suggests that cognitive therapy (CT) is highly effective (70 to 80 percent clinically improved) in the short-term (3 months) as a treatment for irritable bowel syndrome. This application seeks to replicate and extend previous small-scale studies by conducting a controlled clinical trial of CT vs. a self-help support group as an attention placebo control and followup of the treated patients for at least 12 months.

*5R01DK54211-04 Award Amount: $100,000 Clinical*

▶ Title: *Biofeedback for Fecal Incontinence and Constipation* NIDDK
P.I.: William E. Whitehead, Ph.D.
University of North Carolina, Chapel Hill, NC

Among constipation patients, half are reported to have pelvic floor dyssynergia, a condition marked by an inability to relax pelvis floor muscles during evacuation. Biofeedback has been recommended for the treatment of both conditions because uncontrolled studies over the past 10 to 25 years suggest that these treatments are as effective as medical or surgical management and involve no risk. However, placebo-controlled trials are lacking in this area. The aims of the proposed research are: 1) to compare biofeedback to alternative therapies for which patients have a similar expectation of benefit; 2) to identify which patients are most likely to benefit; and 3) to assess the impact of treatment on quality of life. Two long-term, prospective, single-blind studies will be conducted. *Study I* will compare biofeedback for the treatment of fecal incontinence to a standard therapy, Kegel exercises. *Study II* will compare biofeedback for pelvic floor dyssynergia to a skeletal muscle relaxant drug (diazepam) and to placebo medication. These studies will help to establish the efficacy of biofeedback on the treatment of defecatory disorders.

*3R01DK57048-03 Award Amount: $75,000 Clinical*

## *Genitourinary*

▶ Title: *Balkan Nephropathy: Environmental and Clinical Epidemiology* FIC
P.I.: Palmen S. Dimitrov, M.D.
National Center of Hygiene, Medical Ecology & Nutrition, Bulgaria

This project is designed to identify the earliest stages of Balkan endemic nephropathy (BEN) by following up offspring of BEN cases and controls drawn from a previous study of this disorder in Bulgaria. BEN is a chronic kidney disease of unknown etiology, although it shows both familial and geographic aggregation. The strong familial aggregation seen in this disorder does raise the possibility of genetic components to this disease. Although its causes are not well understood and its geographical range is thought to be limited, it is a significant cause of morbidity and mortality in rural Bulgarian populations. This disease could reveal important physiologic components common to other kidney diseases, as well.

*1R01TW006192-01 Award Amount: $17,500 Epidemiologic, case control*

## *HIV/AIDS*

▶ Title: *Haiti Comprehensive AIDS and Tuberculosis Research Training (PA02-022) Phase I – ICOHRTA – AIDS and TB Grant Programs* FIC
P.I.: Jean W. Pape, M.D.
GHESKIO Centers, Port au Prince, Haiti

This proposal is for the GHESKIO Centers in Port au Prince, Haiti to prepare for the ICOHRTA-AIDS/TB program. The GHESKIO Centers is a Haitian non-governmental research and training organization working in close partnership with the Haitian Government on HIV and inter-related diseases, such as tuberculosis and sexually transmitted infections. The research base for the ICOHRTA-AIDS/TB program in Haiti will be: 1) HIV prevention clinical trials of HIV vaccines and vaginal microbicides through the NIH HVTN and HPTN; 2) therapeutic clinical trials for adults and children of highly active antiretroviral therapy regimens and tuberculosis regimens; and 3) operational and health science research in support of an expansion of GHESKIO service activities to 25 departmental health centers in Haiti. This expansion is being supported by the Haitian MOH, the United States Agency for International Development, and the Mission of French Cooperation.

*1R21TW006151-01 Award Amount: $20,000 Clinical, training and capacity building*

▶ Title: *Natal-Columbia Clinical AIDS and Tuberculosis Training Program* FIC
*(PA02-022) Phase I – ICOHRTA – AIDS and Tuberculosis Grant Programs*
P.I.: Salim S. Abdool Karim, M.D., Ph.D.
University of Natal, South Africa

South Africa is currently experiencing one of the worst HIV epidemics in the world and tuberculosis is the most common opportunistic infection associated with advancing HIV disease and AIDS. The recent, substantial increase in numbers of people co-infected with HIV and tuberculosis is exacerbating the existing tuberculosis crisis in South Africa. Building on longstanding collaborative relationships, a collaborative program in clinical, operational, and health services research and training will be developed to fill an important training gap in the local response to the HIV and tuberculosis epidemics in South Africa. The continuum of training concept that has evolved through Fogarty AITRP for HIV and tuberculosis basic science, public health, behavioral and ethics research training where Fellows do coursework in the United States and conduct their research in South Africa will be applied to this proposed training program for building clinical, operational, and health services research capacity.

*1R21TW006111-01 Award Amount: $20,000 Clinical, training, capacity building*

▶ Title: *AIDS and Tuberculosis Training Opportunities Program (ATTOP)* FIC
*(PA02-022) Phase I – ICOHRTA – AIDS and Tuberculosis Grant Programs*
P.I.: Peter N. Mugyenyi, DCH, MRCP
Joint Clinical Research Center, Uganda
Keywords: HIV/AIDS, tuberculosis

Although the seroprevalence of HIV has declined in Uganda over the past 10 years, the HIV epidemic in Uganda is far from controlled. In the face of the HIV epidemic, tuberculosis rates are high and associated with significant mortality. With the advent of antiretroviral therapy, prevention strategies alone are no longer sufficient to meet the current needs in Uganda. One key step in the rebuilding of the Ugandan public health infrastructure resulted from a unique collaboration between the Ugandan Ministry of Health, the Ministry of Defense, and Makerere University to form the Joint Clinical Research Center (JCRC). JCRC is a research and health care facility devoted entirely to HIV and leads the way in opening Africa to antiretroviral therapy. The goal of this proposal is to develop a comprehensive training program that will build the Ugandan capacity to translate basic and clinical research findings into public health policy and interventions. The training program will build on a growing number of clinical research projects on HIV and tuberculosis and extend the findings of these studies to the public health and policy arena.

*1R21TW006117-01 Award Amount: $10,000 Clinical, training, capacity building*

▶ Title: *AIDS and Tuberculosis Research Training Program for Botswana* FIC
*(PA02-022) Phase I – ICOHRTA – AIDS and Tuberculosis Grant Programs*
P.I.: Sheila D. Tlou, Ph.D.
University of Botswana, Gaborone, Botswana

With an HIV prevalence rate of 38.5 percent among adults aged 15 to 49, the most economically productive age group, and a shortage of health care providers equipped to provide AIDS care, Botswana is experiencing an economic and public health crisis. In addition, despite a successful tuberculosis (TB) prevention program, particularly regarding the prevention of TB among those who are HIV positive, TB is responsible for 20 percent of all hospital admissions and 20 percent of adult deaths in Botswana. While the spread of these diseases offer a challenging future for the country, Botswana is committed to supporting research and interventions aimed at halting these epidemics and caring for those affected. As Botswana undertakes efforts to advance comprehensive responses to the AIDS epidemic – such as providing antiretroviral therapy and establishing new education and outreach programs – developing means by which scientific and operational research capacity increases is critical. Data gathered from such efforts will have important implications for improving care, creating effective prevention methods, and designing better public health programs and policies. Therefore, the development of training programs for those who are to be engaged in clinical, operational, and health services research must be carefully developed so as to build upon Botswana's expertise and to offer new opportunities for those in need of additional information and training. Through this proposal, we will develop a comprehensive research training plan for HIV, AIDS, and TB in Botswana that meets the specific needs of the country and region, ensures long-term sustainability, and fosters collaboration with other organizations and individuals working within the country.

*1R21TW006101-01 Award Amount: $20,000 Clinical, training, capacity building*

▶ Title: *Planning for Chinese HIV Prevention Training Program* FIC
*(PA02-022) Phase I – ICOHRTA – AIDS and Tuberculosis Grant Programs*
P.I.: Zunyou Wu, M.D., Ph.D.
National Center for AIDS Prevention and Control, China

The Chinese Center for Disease Control and Prevention (China-CDC) will plan a comprehensive training program for HIV/AIDS prevention and treatment for China (China-ICOHRT A). The objectives of the 1-year planning proposal are: 1) to identify priorities for China in training of health professionals and personnel on AIDS and tuberculosis by consulting officials from the Ministry of Health, public health officers, researchers, and clinicians from provincial and local health agencies and institutes in China; 2) to assess resources available for research training by visiting the collaborating American institutions with the results of the earlier needs assessment to appropriately explore the resources at each institution; and 3) to develop a comprehensive training program based on priority and resources assessments. An assessment of China's needs and its own research resources will be carried out for producing a report and prioritizing the current needs of AIDS/HIV control and prevention in China.

*1R21TW006094-01 Award Amount: $10,000 Training, capacity building*

▶ Title: *Typology of Street Prostitutes: HIV Risk and Well Being* NIDA
P.I.: Celia Williamson, Ph.D.
University of Toledo, Toledo, OH

The overall aim of the proposed qualitative, grounded-theory research project is to identify the types of prostitutes involved in street-level prostitution. This will be accomplished over a 2-year period by attending to the specific aims of the project which are: 1) to examine and verify the existence of various behavioral types of street-level prostitutes; 2) to examine the moderating and mediating factors associated with well being and risk; 3) to examine how the type affects women's involvement with four common risk factors associated with street-level prostitution, namely HIV, violence, drug abuse, and emotional and physical well being; 4) to examine the lifestyle of each type of female street-level prostitute; and 5) to determine the factors that contribute to women initially becoming a particular type of street-level prostitute or shifting to another type within the range of street-level prostitution. This study is a validation study to verify what was found in a preliminary qualitative study of 21 women from the midwest. A typology of street-level prostitutes, namely, conventional pimp controlled, renegade, and outlaw prostitutes were found in the preliminary study. The proposed study will take place in the midwestern state of Ohio. Forty-five women will be involved including: 15 conventional pimp controlled; 15 renegade; and 15 outlaw prostitutes. Of those 45, 15 will be interviewed in jail, 15 in social service programming, and 15 actively working. The study will fill an important gap in that a more complete knowledge base will be developed to provide important scientific data for planning future research on women's involvement in street-level prostitution. This study is in preparation for a larger multiyear R01 study that will seek to determine the common pathways from entrance to exit for the categories of women involved in street-level prostitution. The present proposal will also offer important practical insights on service-related barriers and provide helping professionals with the information needed to develop programming that is tailored to the needs of street-level prostitutes, in order to slow the speed of HIV and other prostitute-related risk factors.

*1R03DA014999-01A1 Award Amount: $71,000 Clinical*

▶ Title: *HIV-related Oral Disease among Women in Harare* FIC
P.I.: John S. Greenspan, BDS, Ph.D.
University of California, San Francisco, CA

This research has focused on HIV-infected populations in the United States. However, the investigators are proposing, as part of the present FIRCA application, to expand the study of the role and significance of oral manifestations of HIV infection to a setting that, thus far, has been understudied: sub-Saharan Africa. Because biologic assays to measure HIV disease progression are rarely accessible in sub-Saharan African countries due to prohibitive cost, other less expensive means of monitoring disease progression are needed. In U.S. populations, visual inspection of the mouth and diagnosis of selected oral mucosal lesions have been found to be good predictors of HIV disease progression. If the predictive role of oral examination can be confirmed in sub-Saharan Africa, this would provide an important new tool for clinicians and public health specialists in this setting with respect to initiation of certain prophylactic drug regimens, such as tuberculosis or pneumocystis pneumonia prophylaxis, or antiretrovirals. In collaboration with an investigator who is conducting a cross-sectional study among HIV-infected and -noninfected women in Zimbabwe to estimate oral mucosal disease prevalence in relation to HIV serostatus in this population, this investigator is proposing to conduct a longitudinal study by expanding this ongoing cross-sectional study among Zimbabwean women. The objectives are: 1) to estimate oral mucosal disease incidence in relation to a known immunologic marker of HIV disease progression (CD4 lymphocyte count); and 2) assess the sensitivity and specificity of detecting oral mucosal lesions by visual inspection of the mouth by trained nurses in a family planning and gynecology clinic in the sub-Saharan African setting. To address these objectives, the investigator will conduct followup oral examinations at 6-month intervals on 225 HIV-positive participants who are being recruited into a cross-sectional study from an ongoing parent cohort study. Each participant would be seen at 6-month intervals over a 3-year period as a part of the proposed study.

*1R03TW006054-01 Award Amount: $34,523 Clinical*

## *Immunity and Autoimmunity*

▶ Title: *Sex-based Differences in Antiviral Immunity and Systemic Lupus Erythematosus* NIAID
P.I.: Sally R. Sarawar, Ph.D.
LaJolla Institute, Ontario, CA

Systemic lupus erythematosus (SLE) is a prevalent autoimmune disease with a significantly higher incidence in females than in males. Studies on the etiology of SLE indicate that both genetic and environmental factors influence disease penetrance. A strong correlation between SLE and previous infection with Epstein Barr virus (EBV), but not with other viruses, has been reported. However, some studies have failed to find evidence of a viral etiology for SLE. This may be due to the high prevalence of EBV infection, unknown host/virus parameters, and the fact that multiple genetic loci control susceptibility to SLE. New Zealand mice are susceptible to SLE, and genetic loci that control disease susceptibility in these mice have been identified. C57/BL6 congenic mouse strains carrying one or more of three of the susceptibility loci, designated SLE 1, 2, and 3, have been generated. It has been shown that the presence of at least two loci is necessary for high disease penetrance. We propose that a mouse viral homologue of EBV could substitute for the presence of a second locus, and could trigger disease in mice congenic for a single locus. We also suggest that this effect may differ in males and females, due, in part, to the more vigorous response to infection in the latter. We have a mouse model of gammaherpesvirus infection, which closely resembles EBV infection in humans and, like EBV, is able to induce non-specific B-cell activation and autoantibody production, but does not induce overt autoimmune disease in C57BL/6 mice. In the present study, we will determine whether there are sex-based differences in the immune response to MHV-68 infection. We will determine whether infection of susceptible mice, bearing one or more SLE susceptibility locus, with MHV-68 can induce or exacerbate autoimmune disease and whether this effect differs in male and female mice. We will also determine whether there are genes whose expression is similarly modified by the presence of disease loci and the viral infection, and whether their expression correlates with the induction of autoimmune disease.

*1R21AI51862-01 Award Amount: $50,000 Basic*

▶ Title: *Mechanism Regulating Neutrophil Activation in Pregnancy* NIAID
P.I.: Howard R. Petty, Ph.D.
Wayne State University, Detroit, MI

This grant will identify and characterize differences in the innate and adaptive immune response between genders, with a specific call for interdisciplinary clinical and basic research studies that may be important in the understanding and treatment of autoimmune diseases. Neutrophils are key cells in the development of homeostatic, as well as pathologic inflammatory responses. These cells play a central role in the generation of tissue damage in autoimmune diseases (i.e., rheumatoid arthritis) as well as in infectious diseases, including sepsis. The studies outlined in this application are designed to study the differences in neutrophil function in non-pregnant women, pregnant women, and men. The study finding may offer a unique opportunity for the identification of endogenous mechanisms affecting women's health. Studying neutrophil biology during pregnancy will result in a mechanistic understanding of factors responsible for clinical improvement in certain autoimmune diseases during pregnancy, and will also lead to the development of novel therapeutic approaches to control inflammation and autoimmunity.

*1R01AI51789-01 Award Amount: $50,000 Translational*

▶ Title: *Sex-based Differences in the Immune Response* NIAID
P.I.: Betty Diamond, M.D.
Albert Einstein College of Medicine, Bronx, NY

The grant will undertake studies to investigate the effects of estradiol on the negative selection of naive autoreactive B cells in BALB/c and C57B1/6 mice. The goal of the study is to understand what genes and pathways are involved in estrogen-mediated B cell survival and activation, and to understand what underlies an estrogen-mediated breakdown in humoral self-tolerance. The three specific aims are: 1) investigating the estradiol-induced alterations in marginal zone (MZ) B cell phenotype, function, and gene expression, and finally addresses B-cell repertoire selection; 2) addressing the role of estradiol in the generation of MZ B cells and the role of intracellular tyrosine kinase, Pyk-2, in the phenotype formation of these cells, and focuses on how estradiol rescues MZ B cells, and some potentially autoreactive B cells, in Pyk-2-deficient mice; and 3) characterizing estradiol-induced signaling pathways that may alter B-cell repertoire selection in BALB/c versus C 57B1/6 mice, and will identify the cell type responsible for differential responsiveness to estradiol. The work should provide informative data about the survival of cells that may initiate an autoimmune response, and the role of sexual dimorphism in this phenomenon.

*1R01AI51767-01 Award Amount: $50,000 Basic*

▶ Title: *Genetics of Rheumatoid Arthritis* NIAMS
P.I.: Peter Gregersen, M.D.
North Shore–Long Island Jewish Research Institute, Bronx, NY

The objective of this contract is the continuation of the North American Rheumatoid Arthritis Consortium along with a centralized repository of data, cells, and DNA of well-characterized rheumatoid arthritis (RA) pairs/pedigrees to advance the discovery of specific genes involved in the susceptibility and severity of RA. The contractor will conduct research and generate resources based on the most current information about the likely chromosomal locations of these genes, as well as current knowledge about the underlying biology and pathophysiology of RA. The resources will generally consist of clinical information and biological materials on well-defined patient populations, as well as databases containing data on clinical phenotype, genotypes, and other biomarkers. In order to maximize the utility of this resource, these databases and biological repositories will be designed to allow for future addition of new information, including clinical followup, genotyping, and new biomarker data.

*N01AR22263 Award Amount: $250,000 Genetics consortium*

- Title: *Cognitive Dysfunction Neuropsychiatric Systemic Lupus Erythematosus* NIAMS
  P.I.: Michael D. Lockshin, M.D.
  BVC–Hospital for Special Surgery, New York, NY

  Neuropsychiatric systemic lupus erythematosus (SLE) consists of 19 defined neuropsychiatric syndromes, of which cognitive dysfunction is one of the most disabling and least understood. Cognitive dysfunction occurs in more than 25 percent of SLE patients. In some patients cognitive dysfunction is due to stroke, but in others its cause is unknown. Autoantibody-induced neuronal cytotoxicity is a possible cause for cognitive dysfunction, and autoantibody to the NMDA receptor may play a role in cognitive dysfunction. This project will characterize cognitive dysfunction in patients in whom lupus disease activity, damage, atherosclerosis, and antiphospholipid antibody are quantified; to determine the association of anti-NMIDA (glutamate) receptor and antiphospholipid antibodies to cognitive dysfunction, to test whether magnetic resonance spectroscopy detects lesions that underlie cognitive dysfunction, and to delineate the relationship of MRS abnormalities to anti-NMDA receptor antibody, lupus disease activity, atherosclerosis, and antiphospholipid antibody.

  *1R01AR049165-01 Award Amount: $100,000 Clinical*

- Title: *Brain Connections* NIAMS
  P.I.: Michelle A. Petri, M.D.
  John Hopkins University, Baltimore, MD

  Neuropsychiatric manifestations of systemic lupus erythematosus (NPSLE) are both common and an important source of morbidity. Of the case definitions for NPSLE syndromes that have recently been developed, cognitive dysfunction appears to be the most prevalent. Little is known about the influence of comorbidities or ethnicity and race on disease outcomes or the underlying biological basis for this important NPSLE syndrome. Perhaps, most importantly, no rational therapeutic approach for the treatment of SLE-related cognitive dysfunction currently exists and is unlikely to be developed without a better understanding of disease mechanisms. One hundred newly diagnosed patients with SLE, from ten sites, will be studied for the development of cognitive dysfunction, determined using both repeatable computerized and traditional neuropsychological tests. We will evaluate the relationship of structural and functional brain imaging (using anatomic magnetic resonance imaging and resting FDG-PET), several relevant biomarkers (antiphospholipid antibodies, cytokines, and adhesion molecules) and comorbidities (race and ethnicity, depression, fibromyalgia, and corticosteroid use) to cognitive dysfunction, and the impact of cognitive dysfunction on quality of life. Factors distinguishing transient or reversible versus irreversible cognitive dysfunction will be determined using a repeated measures analysis approach. The ability to study the relationship between changes in cognitive functioning and these other variables in a group of newly diagnosed SLE patients is crucial to the successful discovery of early pathologic changes that could be potentially amenable to disease-reversing therapies.

  *1R01AR49125-01 Award Amount: $40,000 Clinical*

▶ Title: *Identifying Genes for Neuropsychiatric Lupus* NIAMS
P.I.: Nilamadhab Mishra, M.D.
Wake Forest University, Winston-Salem, NC

In brief, this project will examine the genes responsible for neurologic disturbances in murine models of systemic lupus erythematosus (SLE) by microarray analysis. SLE is a chronic, idiopathic autoimmune disease characterized by episodic flares and progression of disease, substantial morbidity, and mortality. It is a multisystem rheumatic disease with a wide variety of associated clinical, neurological, and psychiatric syndromes, including cognitive, behavioral, affective, and/or motor manifestations that may effect up to 75 percent of SLE patients. Both morbidity and mortality remain high because of lack of understanding of the underlying mechanisms related to abnormal central nervous system function. Although the genes responsible for neurological disturbances in SLE are not finely dissected out, preliminary studies in mouse models of lupus suggests aberrant cytokine genes expression in hippocampus and cerebellum are responsible for the neurological deficit.

*1R21AR49153-01 Award Amount: $20,000 Basic*

▶ Title: *Antibodies to NR2 in Systemic Lupus Erythematosus* NIAMS
P.I.: Betty Diamond, M.D.
Yeshiva University, New York, NY

Cognitive impairment occurs in a large percent of lupus patients. We have recently demonstrated that a subset of anti-DNA antibodies in patients with systemic lupus erythematosus (SLE) binds to a defined linear epitope on the NR2 NMDA receptor. These antibodies can be found in the cerebrospinal fluid (CSF), as well as in serum. This project will explore further the antigenicity of the NR2 receptor in SLE and the functional consequences of anti-receptor antibodies. The serum from lupus patients will be studied to determine whether there are antibodies to other epitopes that function as a receptor agonists or antagonists, and whether there is T cell recognition of NR2 epitopes. Also, rodent models will be studied to determine whether serum antibody can penetrate an intact blood-brain-barrier, what concentrations of antibody that must be present in the CSF to cause disease, and whether there are selectively vulnerable populations of neurons. The overall goal of this collaborative interactive program is to develop the scientific foundation for prevention therapies for cognitive decline in SLE.

*1R01AR49126-01 Award Amount: $40,000 Clinical*

▶ Title: *Brain Cell Death in MRL Mice: Targets and Mechanisms* NIAMS
P.I.: Boris Sakic, Ph.D.
McMaster University, Ontario, Canada

This research will elucidate pathogenic mechanisms of neuropsychiatric systemic lupus erythematosus by studying neuroimmunologic disease in autoimmune MIRL-Ipr mice. Lymphoid cell infiltration into the choroid plexus, neuronal atrophy, cerebrospinal fluid (CSF) neurotoxicity, and an anxiety/depessive behavioral state in MRL-Ipr mice suggest that cytotoxic cells and metabolites in the CSF accelerate apoptosis in limbic regions, thus accounting for altered performance in tasks reflective of emotional reactivity and motivation. The project aims to examine: 1) whether DNA fragmentation involves neurons, glial, and/or endothelial cells (will be achieved by combining immunofluorescence with TUNEL staining); 2) whether population of periventricular brain stem cells is susceptible to neurotoxic effects of CSF (will be achieved by culturing neurospheres and assessing the effects of incubation with CSF from MRL-Ipr mice); 3) whether brain cell death involves apoptotic pathways (will be achieved by examining nuclear morphology with electron microscopy, by detecting DNA laddering with chemilumnescent method, and caspase activation with immunohistochemistry); and 4) whether immunosuppression prevents neurodegeneration and CSF neurotoxocity.

*1R21AR49163-01 Award Amount: $100,000 Basic*

▶ Title: *Tau Lymphocyte Dysfunction in Lupus Erythematosus* NIAMS
P.I.: Gary M. Kammer, M.D.
Wake Forest University, Winston-Salem, NC

Systematic lupus erythematosus (SLE) is an autoimmune disorder of indeterminate etiology characterized by impaired T cell effector functions. The investigators have demonstrated impaired protein kinase A-catalyzed protein phosphorylation due to deficient type I protein kinase A (PKA-I) isozyme activity. Deficient isozyme activity predominantly reflects markedly reduced or absent type I regulatory beta (RIß) subunit protein. This research will investigate the hypothesis that deficient PKA-I isozyme activity is an integral signaling disorder that results in impaired $CD4^+$- and $CD8^+$-mediated helper and cytotoxic functions, respectively, which can be partially reconstituted by restoring physiologic PKA-I activity. The objective is to investigate the molecular basis of how defective signaling via the PKA-I isozyme contributes to these abnormal T-cell functions. The specific aims are: 1) to investigate the mechanisms regulating RIß protein and transcript turnover in T cells; 2) to determine whether deficient PKA-I activity exists in each of the principal subsets of SLE T cell for a specific SLE T-cell subset; 2a) to demonstrate that deficient isozyme activity is associated with downregulation of surface $CD59^+$ expression; 3) to examine the role of the $RIß_2C_2$ holoenzyme in T cell effector functions in SLE and normal T cells; 3a) to transiently transfect autologous RIß $_C$DNA into $CD4^+$ and $CD8^+$ T cells from SLE subjects to determine whether reconstitution of RIß protein and physiologic PKA-I activity restores T-cell effector functions; 3b) to determine whether transient transfection of a RIß and/or RIß dominant-negative mutant impairs T-cell effector functions; 4) to perform SLE multiplex family studies to determine; 4a) the prevalence of RIß protein deficiency; and 4b) whether deficient PKA-I activity due to reduced or absent RIß protein is a heritable disorder in families of lupus probands. The significance of this research is its potential to explain how defective signaling circuitry within the T cell can lead to the aberrant T-cell effector functions that result in lupus immunopathogenesis.

*2R01AR039501-12 Award Amount: $100,000 Basic*

▶ Title: *Rheumatic Disease Sera: Probes of Disease Mechanism* NIAMS
P.I.: Livia Casciola-Rosen, Ph.D.
Johns Hopkins University, Baltimore, MD

Lack of specific therapies for systemic autoimmune rheumatic disease contributes to the high human burden from these diseases in the population. Development of effective and specific therapies requires the definition of pathways important in disease pathogenesis. Human autoantibodies, from patients with these diseases, constitute powerful probes of such pathways. The long-term goals of this proposal are to define the molecular mechanisms responsible for specific targeting of autoantigens in systemic autoimmune diseases, and thereby provide insights into the critical pathways of disease initiation and propagation. The majority of autoantigens targeted across the spectrum of systemic autoimmune diseases are unified by their clustering in the surface blebs of apoptotic cells, and their susceptibility to efficient cleavage by granzyme B during cytotoxic lymphocyte granule-induced apoptosis. The generation of unique fragments by granzyme B is a unique feature of autoantigens, implicating the ctotoxic lymphocyte granule pathway in the selection of molecules for a high titer autoantibody response. Since the cytotoxic lymphocyte granule pathway is widely active *in vivo* the absence of autoimmunity, additional undefined elements likely play critical roles in autoimmune disease pathogenesis. The pathology in systemic autoimmune diseases is characteristically patchy, with inflamed and damaged areas immediately adjacent to apparently normal tissue. The investigators have recently observed that numerous autoantigens (which are granzyme B substrates) undergo mitosis-specific phosphorylation leading to an SDS-stable conformational change. The investigators propose that cycling cells, within inflamed tissue, are differentially antigenic relative to the quiescent cells in the adjacent healthy tissue, and the pathogenic immune response in systemic autoimmunity is directed exclusively against the cycling subset of cells. This hypothesis will be pursued by (i) defining the unique biochemistry and cell biology of cytotoxic lymphocyte-induced cell death of cells at different stages of the cell cycle, (ii) studying cell cycle status and autoantigen fragmentation *in vivo* to determine whether there is evidence of preferential cytolysis of proliferating target cells in tissues from patients and animals with systemic autoimmune diseases, and (iii) defining the role of the granzyme B pathway and cell cycle status in initiation and propagation of systemic autoimmunity *in vivo*, using mice with defects in cell cycle regulation and the granzyme B pathway.

*2R01AR044684-05A1 Award Amount: $100,000 Basic*

- Title: *TGF-beta Receptor Signaling in Scleroderma* NIAMS
  P.I.: Maria Trojanowska, Ph.D.
  Medical University of South Carolina, Charleston, SC

  Organ fibrosis, a major pathological manifestation of scleroderma (SSc), is the result of excessive position of collagen I and other extracellular matrix (ECM) proteins. Despite the significant progress that has been made towards unraveling the physiological and pathological mechanisms involved in regulation of collagen genes, a full understanding of these processes is still lacking. In particular, very little is currently known about the molecular mechanism responsible for constitutive upregulation of ECM proteins by SSc fibroblasts. Such knowledge is critical for the development of suitable targets for therapeutic intervention. Previously, the investigators proposed to test the hypothesis that autocrine TGF-ß signaling, through overexpression of TGF-ß receptors, is at least partially responsible for the SSc phenotype. To test this hypothesis, they blocked GF-ß signaling by overexpressing a kinase-deficient TGF-ß receptor II. Contrary to expectations, SSc fibroblasts were mainly unresponsive to this treatment with regard to collagen production. However, this treatment resulted in a significant downregulation of the ECM production in healthy skin fibroblasts. These results led to a revision of their hypothesis and promoted them to investigate alternate mechanisms that may be responsible in the SSc phenotype. To investigate TGF-ß independent pathways, they have focused on connective tissue growth factor (CTGF) and IGF binding protein 5 (IGFBP5). The current research proposal is based on the novel observations indicating that CTGF induction of ECM in human fibroblasts is dependent on insulin signaling, and that IGFBP5 also stimulates collagen production by fibroblasts. The following specific aims are proposed to test the hypothesis that interactions between TGF-ß, CTGF, and insulin/IGF pathways are involved in the regulation of the SSc phenotype: 1) they will continue to examine the role of the components of the TGF-ß signaling pathway in the manifestation of the SSc phenotype; 2) they will determine the role of the CTGF-mediated pathway in ECM production SSc fibroblasts. The mechanism of CTGF stimulation of the COL1A2 promoter and characterize the components of the insulin/IGF signaling pathway that contribute to CTGF-ß induction of collagen; 3) they will determine the mechanism of IGFBP5 stimulation of collagen production by SSc and healthy fibroblasts. They will analyze expression patterns of IGFBPs in SSc and healthy fibroblasts and utilize purified IGFBP proteins and corresponding cDNAs to probe their role in collagen regulation by SSc and healthy fibroblasts; and 4) they will examine the *in vivo* expression of the TGF-ß receptor subunits, CTGF and IGF/IGFBPs, in SSc skin.

  *2R01AR044882-05 Award Amount: $100,000 Basic*

▶ Title: *Autoimmunity Center of Excellence* NIAID
P.I.: Leonard Chess, M.D.
Columbia University College of Physicians & Surgeons, New York, NY

This center will establish an interdisciplinary basic and clinical research program to focus on the evaluation of novel therapeutic approaches to five autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, and scleroderma. The investigators hypothesize that there are four principal events involved in the immunopathogenesis of these diseases: 1) predisposing genes establish a T-cell repertoire capable of recognizing self peptides intrinsic to the autoimmune process; 2) previously tolerant autoreactive CD4+ T-cell clones become activated and expand to change the T-cell repertoire to reflect autoreactive effector T cells; 3) regulatory mechanisms, including the activation of TH1 and TH2 CD4+ T-cell subsets as well as those involving CD8 T cells fail, through processes such as clonal deletion or changes in the cytokine milieu; and 4) pathogenic autoantibodies develop through cognitive T cell-B cell interactions which effect tissue injury. In these diseases one would predict that reducing the clonal expansion of relevant autoreactive T cell by blockade of T-cell receptor signaling or interruption of the CD40 ligand-dependent pathway could downmodulate disease activity. Also, interruption of the inflammatory effector functions of T cell mediated by TNF or CD40L would similarly reduce disease potential. These hypotheses will be tested during the natural history of disease and during specific immune interventions.

*5U19AI46132-04 Award Amount: $75,000 Clinical*

▶ Title: *Virginia Mason/University of Colorado Health Sciences Center Autoimmune Center* NIAID
P.I.: George S. Eisenbarth, M.D.
University of Colorado, Denver, CO

This grant consists of three research projects. The overall objective of this application is to derive markers of autoimmune disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in genetic, immunologic, and environmental determinants that lead to disease. *Project 1* will use tetramers to analyze the peripheral antigen-specific T-cell profile in IDDM. *Project 2* will identify three cohorts of individuals at increased risk for rheumatoid arthritis and attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. The third project will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

*1U19AI50864-03 Award Amount: $200,000 Translational*

- Title: *Autoimmunity: Treatment by Co-stimulatory Signal Blockade* NIAID
  P.I.: Samia J. Khoury, M.D.
  Brigham and Women's Hospital, Boston, MA

  A Center of Excellence for Autoimmunity will be established at the Brigham and Women's Hospital. Projects supported under this initiative will focus on the study of therapy of autoimmune diseases by blocking co-stimulatory signals. Investigators will focus on the CD40-CD40L pathway. The human diseases of major focus are multiple sclerosis, inflammatory bowel disease, 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. Four projects are supported. The overall goals of *Project 1* are to study, in a pilot trial, the efficacy and safety of anti-CD40L therapy in multiple sclerosis. The goals of *Project 2* are to study, in a pilot trial, the efficacy and safety of anti-CD40L therapy in inflammatory bowel disease. *Project 3* will focus on the immunologic changes associated with anti-CD40L therapy in patients with multiple sclerosis and inflammatory bowel disease. *Project 4* will study the immune mechanisms of psoriasis. Data obtained from the pilot studies will be useful in designing Phase M clinical trials, and immunologic investigations will help to identify surrogate markers for disease activity.

  *5U19AI46130-04 Award Amount: $75,000 Clinical*

- Title: *Denver Autoimmunity Center of Excellence* NIAID
  P.I.: Brian L. Kotzin, M.D.
  University of Colorado Health Sciences Center, Denver, CO

  A Center of Excellence for Autoimmunity will be established at the University of Colorado Health Sciences Center. The center builds on a strong research and clinical base in type 1 diabetes, celiac disease, systemic lupus, rheumatoid arthritis, multiple sclerosis, autoimmune skin disease, autoimmune pulmonary disease, and other autoimmune disorders. Under this initiative, two clinical trials will be conducted. *Clinical Project 1* will evaluate subcutaneous insulin vaccination to prevent the appearance anti-islet autoantibodies in infants at high risk for the development of autoantibodies and disease. *Clinical Project 2* will test humanized anti-C5 mAbs in patients with active lupus nephritis. Three basic components will be studied: 1) to define the T-cell specificities and distribution of insulin and islet antigen-reactive T-cells in murine models and patients with type 1 diabetes; 2) to determine the effects of inhibition of IL-18 and complement on cytokine production and disease in collagen-induced arthritis and rheumatoid synovion; and 3) to define the non-MHC genetic contributions to different clinical subtypes of autoimmune polyendocrine syndrome II. These basic projects will provide important information to design future clinical trials, to monitor the effectiveness of immunologic therapies, and/or provide surrogate markers to correlate with immunologic therapies in autoimmune diseases.

  *5U19AI46374-04 Award Amount: $75,000 Clinical and basic*

▶ Title: *Penn Autoimmunity Center of Excellence* NIAID
P.I.: A.M. Rostami, M.D., Ph.D.
University of Pennsylvania, Hershey, PA

A Center of Excellence for Autoimmunity at the University of Pennsylvania School of Medicine will be established. It will consist of four projects (three clinical and one basic) and two cores. The clinical component of the center consists of three clinical trials: 1) a Phase I/II trial on the use of antibody to Interleukin-12 (IL-12) for the treatment of multiple sclerosis (MS); 2) a Phase I/II trial on the use of IL-12 in the treatment of inflammatory bowel disease; and 3) the use of anti-CD20 antibody for the treatment of systemic lupus erythematosus (SLE). The basic science component is focused on the elucidation of the basic mechanisms of autoimmunity and immunomodulation related to the clinical trials. Investigators will study the role of IL-12 in the pathogenesis and therapy of MS and its animal counterpart, experimental autoimmune encephalomyelitis. Also, they will focus on the mechanisms of anti-B-cell therapy in SLE and its murine model. An immunology core and an administrative core will be supported under this initiative.

*5U19AI146358-04 Award Amount: $75,000 Clinical and basic*

▶ Title: *T-cell Reconstitution after Stem Cell Autograft* NIAID
P.I.: Jan Storek, M.D., Ph.D.
Fred Hutchinson Cancer Research Center, Seattle, WA

The goal is to evaluate how the T-cell repertoire is re-established in patients with autoimmune diseases who have undergone lymphocytopenia from high-dose chemotherapy/radiation plus anti-thymocyte globulin, followed by reconstitution with autologous transplantation of hemopoietic (CD34+) precursors. The hypothesis is that in young individuals, a substantial number of regenerating T cells originate from hemopoietic progenitors, whereas in older individuals the vast majority of T cells originate from the expansion of pre-existing T cells. The techniques used will be spectra typing, sequencing of the T-cell receptor genes withing a single spectra typing band, and quantifying T cells that contain T-cell receptor-rearrangement circles.

*5R01A146108-04 Award Amount: $60,000 Clinical*

▶ Title: *How Does Blockage of CD40/CD40L Prevent Autoimmunity?* NIAID
P.I.: Matthias Von Herrath, M.D.
Scripps Research Institute, La Jolla, CA

This grant consists of two pilot projects, three projects, and two cores. Investigators will use three different models of autoimmune diseases to analyze effector functions of dendritic cells, lymphocytes, and regulatory antigen-presenting cells. The program focuses on the blockade of a single pathway and it's study in several different autoimmune scenarios. The program utilizes some novel techniques and is studying the detailed mechanism by which CD40L blockade effectively prevents the development of autoimmunity.

*1U19AI51973-02 Award Amount: $100,000 Basic, animal models*

- Title: *Mechanism of Copaxone Therapy in Multiple Sclerosis* NIAID
  P.I.: Michael Racke, M.D.
  University of Texas Southwestern Medical Center at Dallas, Dallas, TX

  Multiple sclerosis (MS) patients are categorized on the basis of whether they have clearly defined relapses, relapsing-remitting MS (RRMS), or whether they are progressing. Progressing patients are further divided on the basis of whether they initially experienced relapses (secondary progressive MS), or whether they deteriorate slowly without evidence of relapses or remissions (primary progressive MS). One question is whether the patients with primary progressive MS (PPMS) differ from the patients with secondary progressive MS, or whether they represent different aspects of a clinical pathologic spectrum. This group has shown that patients with RRMS have myelin-reactive T cells that are less dependent upon costimulation than myelin-reactive T cells from normal controls. The goal is to test the hypothesis that myelin-reactive T cells in patients with PPMS can be distinguished from naive myelin-reactive T cells by a lack of dependence upon costimulation for activation and that costimulatory requirements for these myelin-reactive T cells change during the course of disease. Glatiramer acetate (Cop-1, Copaxone) has previously been shown to reduce the number of relapses in RRMS and is now being tested for efficacy in patients with PPMS. It is unclear how Copaxone exerts its therapeutic effect. This study will determine whether Glatiramer alters cytokine secretions of myelin-reactive T cells and the T-cell repertoire in PPMS.

  *5R01A147133-04 Award Amount: $140,000 Clinical*

- Title: *EBNA-1 in Lupus* NIAID
  P.I.: John B. Harley, M.D.
  Oklahoma Medical Research Foundation, Oklahoma City, OK

  The environmental factors associated with systemic lupus erythematosus (SLE) include Epstein-Barr virus (EBV). Once infected, EBV is well known to persist in all human hosts for life. Novel approaches to the detection of this pathogen and to the assessment of the host response to this pathogen are warranted. Among the most interesting viral products is Epstein-Barr virus nuclear antigen-1 (EBNA-1), which contains a peptide sequence that inhibits antigen presentation and class 1 HLA-dependent cytotoxic T cell responses. Preliminary data show that EBNA-1 also contains sequences that appear to be differentially bound by SLE, as opposed to normal sera. SLE will be studied from the perspectives of the anti-EBNA-1 humoral immune response, of EBNA-1 expression in B cells, and of EBNA-1 sequence variants.

  *2R01AI31584-09 Award Amount: $200,000 Basic*

▶ Title: *Sex Hormone Regulation of Innate Immunity in Women and Men* NIAID
P.I.: Charles R. Wira, Ph.D.
Dartmouth Medical School, Lebanon, OH

This program will evaluate the hypothesis that sex hormones regulate the innate, and potentially the adaptive, immune responses. This project, which includes an abundance of preliminary data, utilizes cutting-edge technologies to investigate the role of epithelial cells of the female reproductive tract (FRT), which form the front line of defense against sexually transmitted diseases. The principle investigator previously demonstrated that sex hormones influence antigen presentation and immunoglobulin levels in uterine secretions. A unique approach with exceptionally strong initial data to investigate the effects of estradiol on natural killer cells in the FRT is incorporated. The two other projects are more preliminary and descriptive. These projects will study the effect of sex hormones on the function of polymorphonuclear neutrophils and the maturation of dendritic cells in the FRT. Since little is known about the effects of hormones on these cells in the FRT, this is the state of the science. This synergetic program will lead to a greater understanding of the mechanisms by which sex hormones affect the innate immune system and the response to pathogens. Novel approaches to prevention of infectious diseases of the FRT could be developed with increased knowledge.

*1P01AI051877-01 Award Amount: $300,000 Basic*

▶ Title: *Investigating Interleukin-6 Experimental Myasthenia Gravis* NIAID
P.I.: Premkumar Christadoss, M.D.
University of Texas Medical Branch, Galveston, TX

Studies suggest a pivotal role for interleukin-6 (IL-6), tumor neurosis factor (TNF), and IL-18 in development of experimental autoimmune myasthenia gravis (EAMG), because a dramatic suppression of clinical EAMG was observed in IL-6, TNF receptor p55 p75, or IL-18 gene KO mice in the B6 background. The precise cellular and molecular mechanisms by which IL-6, TNF, and IL-18 contribute to EAMG pathogenesis are not known. The central hypothesis is that IL-6 contributes to EAMG pathogenesis by activating acetylcholine receptor (AChR)-specific T and B cells and germinal center (GC) formation, promoting secondary anti-AChR IgG antibodies and activation of the C3 component of complement. The immunopathological and clinical effects will be evaluated by *in vivo* IL-6 administration in B6 and IL-6 KO mice during primary and/or secondary immunizations with AChR. Clinical and immunopathological signs of EAMG will be induced in B6 mice by *in vivo* administration of IL-6 after priming with AChR. AChR-primed LNC will be exposed to IL-6 and its effect on anti-AChR IgM and IgG isotopes will be evaluated. Also, we will examine whether IL-6 and TNF act in concert or regulate one another in mediating EAMG. B7-1 gene-deficient or B7-1 molecule-blocked mice, and B6 mice will be immunized with AChR, and the effect evaluated of B7-1 deficiency for blocking in EAMG development and production of Il-6 and TNF. To prevent EAMG, antibody to IL-6 will be administered with primary and/or secondary immunizations with AChR. To ameliorate established clinical EAMG, antibody to IL-6 will be administered after clinical signs are established. Finally, combination of immunotheraphy will be performed with high-dose AChR T cell epitope tolerance and IL-6 neutralization in B6 mice. If IL-6 is involved in activating pathogenic AChR-specific B cells, forming GC, and upregulating and activating C3, and if *in vivo* blocking of IL-6 function induces remission of established clinical EAMG, then IL-6 antagonist could be used in MG therapy. To avoid non-specific immunosuppression by IL-6 antagonists, high-dose AChR T cell epitope tolerance could be given as maintenance therapy after the first course of combination immunotheraphy.

*1R01AI049995-01A1 Award Amount: $294,570 Basic*

▶ Title: *Mechanisms of T Cell-induced APC Cytotoxicity in Lupus* NIAMS
P.I.: Mariana J. Kaplan, M.D.
University of Michigan, Ann Arbor, MI

The application proposes funding with the specific intent of developing an independent research program by the principal investigator. The applicant has been pursuing basic science research in the areas of T cell immunology and pathogenesis of systemic erythematosus lupus (SLE) for the past 4 years. The proposal is a natural extension of the applicant's current research on monocyte/macrophage (Mø) apoptosis. Apoptosis-inducing molecules mediate the autologous monocyte/Mø killing caused by $CD4^+$ lupus T cells. Target cell killing by this mechanism can lead to the generation of autoantibodies. The specific aim is to determine the pathways involved in monocyte/Mø apoptosis induced by SLE $CD4^+$ T cells. The applicant will test whether it is possible to inhibit the development of autoimmunity in an SLE animal model, by blocking the apoptotic pathways involved in monocyte/Mø killing by autoreactive $CD4^+$ T cells. The role of the macrophage apoptosis in triggering or augmenting autoimmunity will also be investigated.

*Methods:* 1) Measurement of cell surface expression of death-receptor ligands on SLE and control T cells by flow cytometry. 2) With cytotoxicity assays, determine whether these apoptotic pathways are functional in SLE moncyte/Mø and whether blocking these can inhibit the autologous moncyte/Mø killing by SLE T cells. 3) Given the redundancy of the pathways involved in Mø cytotoxicity, the applicant will test, *in vitro*, if inhibiting the death signals downstream of the death receptors (FADD, caspases, FLIP) is sufficient to inhibit monocyte/Mø apoptosis induced by these ligands. 4) *In vivo* studies will try to characterize whether the blockade on monocyte/macrophage death-receptor ligands, by monoclonal antibodies or fusion proteins, can inhibit the development of murine SLE, and whether the elimination of tissue macrophages *per se* (with clodronate liposomes *in vivo*) is sufficient to induce autoimmunity in an animal model. The results of the studies proposed might identify potential mechanisms involved in the generation of autoantigens in SLE. These could lead to the development of novel therapeutic interventions designed to reverse these abnormalities and abrogate or block the onset and severity of this disease. The sponsor and the institution are committed to contributing protected time, career development, and resources to the applicant.

*1K08AR048235-01 Award Amount: $100,000 Basic*

▶ Title: *Studies of Collagen Gene Regulation in Two Murine Models* NIAMS
P.I.: Stephen H. Clark, Ph.D.
University of Connecticut, Farmington, CT

This research project will utilize two mouse mutations that are models for scleroderma – tight skin (Tsk) and tight skin2 (Tsk2). Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark of the human disease. The long-range objective of this research is to utilize the two mutations, combined with several lines of transgenic mice as experimental tools, to dissect molecular mechanisms of disease pathogenesis.

*1R01AR48082-02 Award Amount: $200,000 Basic, animal models*

▶ Title: *Fine Specificity of Scleroderma Autoantibodies* NIAMS
P.I.: Judith James, M.D.
Oklahoma Medical Research Foundation, Oklahoma City, OK

This application addresses the important problem of the significance of autoantibodies in scleroderma patients. The project proposes to identify the initial epitope on nRNP and topoisomerase I, which is identified by sera from patients with scleroderma. This will lead to the search for a pathogen in the environment, which could lead to an immune response to the cross-reacting antigen. The possibility of tissue damage due to autoantibodies will also be investigated.

*1R01AR48045-02 Award Amount: $200,000 Translational*

▶ Title: *Registry and Repository of African Americans with Rheumatoid Arthritis* NIAMS
P.I.: Larry Moreland, M.D.
University of Alabama at Birmingham, Birmingham, AL

This 5-year project will be housed at the University of Alabama at Birmingham. It will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (CLEAR) Registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3-years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast United States will gather data which will provide a resource for investigators interested in the genetics of rheumatoid arthritis in African Americans. The CLEAR Registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor-alpha/lymphotoxin-alpha, interleukin-1, and interleukin-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3-years disease duration in African Americans. The principal investigator, Dr. Larry Moreland, is a clinical researcher whose primary research interest has been the evaluation of biologic response modifiers (and their mechanisms) which are targeted at the disease process in rheumatoid arthritis.

*1N01AR002247-000 Award Amount: $200,000 Clinical*

### *Infectious and Sexually Transmitted Diseases*

- Title: *Sex in Viral Myocarditis* NIAID
  P.I.: Sally A. Huber, Ph.D.
  University of Vermont, Burlington, VT

  Myocarditis is an inflammatory disease of the myocardium. Approximately 65 percent of cases follow recent enterovirus infections and occur in males. As in humans, CVB3 infections cause severe myocarditis in male, but not virgin female mice. Androgens (progesterone and testosterone) increase virus receptor expression on cardiac myocytes, while 17-beta-estradiol treatment does not. Since lymphocytes also express CVB3 receptors, we hypothesize that hormones might modulate lymphocyte expression of these molecules as well. Cytokine release differs between male and female lymphocytes with male cells producing interferon (IFN) gamma and female cells producing interleukin-10. We hypothesize that viruses, which have repetitive symmetry of the virus capsid, cross-link important cell surface molecules on lymphocytes and cause rapid non-antigen-specific lymphocyte activation. These studies may provide new insights as to how viruses affect developing host defense responses and how hormones can modulate this initial response.

  *1R21AI51850-01 Award Amount: $50,000 Translational*

- Title: *Mid-America Adolescent Sexually Transmitted Diseases Cooperative Research Center* NIAID
  P.I.: Donald Orr, M.D.
  Riley Hospital, Indianapolis, IN

  Sexually transmitted diseases (STD) produce very serious outcomes in women, regardless of race, and often affect their infants as well. In addressing the racial health disparities in the occurrence of STD, NIAID supports Sexually Transmitted Diseases Cooperative Research Centers, which provide a multidisciplinary approach to research in the area of STD by bringing together basic science, clinical and epidemiological research, and behavioral intervention strategies for the prevention and control of STD.

  *5U19AI43924-05 Award Amount: $50,000 Clinical*

## *Menopause*

▶ Title: *Study of Women's Health Across Nation II (SWAN II)* NIA
P.I.: Dr. Sonai Mathews, Coordinating Center, Multiple sites and investigators plus a lab
New England Research Institute, Watertown, MA

SWAN consists of both cross-sectional and longitudinal studies on the natural history of menopause and a characterization of endocrinology and physiology of premenopause. Five ethnic groups are included – Caucasian, African American, Hispanic, Chinese, and Japanese. There are seven sites across the country – Boston, Pittsburgh, Chicago, Michigan, University of California–Los Angeles, University of California–Davis, and New Jersey. For the cross-sectional study, there are approximately 16,000 women enrolled, ranging in age from 40 to 55 years, to determine the age of menopause. The longitudinal study has approximately 3,150 women (450 at each site), between the ages of 42 to 52, to determine menopause-specific physiological changes and their predictors and the impact of menopause on subsequent disease. Measurements are being made of the major reproductive axis hormones (LH, FSH, estradiol, progesterone, and testosterone), adrenal markers of aging (DHEAs), other endocrine markers (TSH, sex hormone-binding globulin), and new ovarian markers which have the potential to define the menopausal transition and the postmenopause.

*5U01AG12546-09 Award Amount: $250,000 Clinical*

▶ Title: *Centers for Dietary Supplements Research: Botanicals* NCCAM
P.I.: Norman Farnsworth, Ph.D.
University of Illinois at Chicago, Chicago, IL

This multidisciplinary team of investigators will focus on the study of the safety and efficacy of botanicals used to treat women for menopause. Studies will address mechanisms of action; identification of active compounds; and characterization of metabolism, bioavailability, and pharmacokinetics of active species in these botanicals. The research component will consist of the following: 1) a pharmacognosy project to carry out standardization of botanical dietary supplements and structure elucidation of active compounds; 2) isolate active compounds for structure elucidation, and then to determine the mechanism(s) of action of botanicals; 3) study the metabolism, absorption and toxicity of active compounds in botanicals including immunotoxicity; and 4) carry out phase I and II clinical trials of black cohosh (*Cimicifugai racemosa)* and red clover (*Trifolium pratense*).

*5P50AT00155-04 Award Amount: $100,000 Clinical and basic*

- Title: *Menopausal Depression: Chronobiologic Basis* NIMH
  P.I.: Barbara L. Parry, M.D.
  University of California–San Diego, La Jolla, CA

  The specific focus of this project will be to examine the effects of estradiol and progesterone administration on circadian rhythms in humans. The subjects will be healthy postmenopausal women. The investigators will test the hypothesis that estrogen advances the phase and enhances the amplitude and synchrony (the stability of timing relationships) of biological rhythms as measured by melatonin, sleep, and activity, whereas progesterone antagonizes these effects. This proposal represents an extension of the investigators' previous work that examined the effects of endogenous changes in estradiol and progesterone during the menstrual cycle on measures of mood and circadian rhythmicity. This work led to the development of new hypotheses and treatment strategies. The current proposal will allow investigation of these hypotheses further, but in a more controlled design. The investigators anticipate gaining important information on possible mechanisms mediating the effects of reproductive hormones on mood and behavior, and deriving relevant clinical treatment guidelines for menopausal women.

  *5R01MH059919-03 Award Amount: $100,000 Clinical*

### *Mental Health*

- Title: *Improving Antidepressant Adherence in Older Adults* NIMH
  P.I.: Joanne Sirey, Ph.D.
  New York Presbyterian Hospital–Cornell University, New York, NY

  The goal of the research within this Research Scientist Award is to provide further interdisciplinary training and research opportunities to transition the applicant to become an independent investigator in interventions research. The career goal of the applicant is to develop interventions to improve adherence to antidepressant treatment among depressed older adults in primary care. The career development objectives of this application are to learn: 1) the theories underlying behavioral change interventions; 2) the design and evaluation of interventions in late-life depression; 3) assessment of older adults' attitudes and beliefs; and 4) factors that affect treatment adherence across illness. This training will provide the knowledge and skills to assess and to address negative attitudes and beliefs about: 1) depression and the usefulness of treatment efficacy, 2) stigma, and 3) treatment self efficacy. The research proposed will pilot the usefulness of a brief, individualized intervention to improve adherence to selective serotonin reuptake inhibitors antidepressant therapy by older adults prescribed by primary care physicians. The intervention is designed to improve adherence by addressing the negative attitudes and beliefs that are obstacles to adherence for adults with late-life depression. Although the intervention is not a therapy to reduce depression; but because depression itself can contribute to negative attitudes and beliefs, one of the goals of the intervention is to buffer the effect of depression on adherence. The intervention targets obstacles to adherence and if proven useful, would be a manualized and feasible way to reduce the personal and public health costs of undertreatment of late-life depression in older adults seen in primary care.

  *1K23MH066381-01 Award Amount: $100,000 Clinical*

▶ Title: *Effects on Children of Treating Maternal Depression* NIMH
P.I.: Anne Riley, Ph.D.
Johns Hopkins University, Baltimore, MD

Maternal depression has devastating effects on the mental and physical health of children. This project will study the influence of treating maternal depression on children ages 5 to 11; studying 150 elementary school-aged children whose mothers are depressed (50 Hispanic, 50 African American, and 50 Caucasian) and 50 comparable children whose mothers are not depressed. Their mental health and functioning will be assessed by natural raters in their environments over a 2-year time period that will link child functioning, symptomatology, and psychiatric disorders to mothers' symptomatology, parenting behavior, and family environment.

*5R01MH058384-05 Award Amount: $50,000 Clinical*

▶ Title: *Sex Differences in Self-Evaluation: Social Factors* NIMH
P.I.: Eva Pomerantz, Ph.D.
University of Illinois, Champaign, IL

Girls are more likely than boys to possess self-evaluative mechanisms that may heighten vulnerability to depressive and anxiety symptoms. It is hypothesized that culturally held gender stereotypes may cause parents to be more controlling in certain behavioral domains with girls than with boys. This pattern of gender socialization is expected to lead girls to be more likely than boys to possess self-evaluative mechanisms that heighten vulnerability to depressive and anxiety symptoms.

*5R01MH057505-04 Award Amount: $47,599 Clinical*

▶ Title: *Health Survey of Two-spirited Native Americans* NIMH
P.I.: Karina L. Walters, Ph.D.
University of Washington, Seattle, WA

American Indian and Alaskan Native lesbian, gay, bisexual, transgendered, and two-spirited individuals (two spirits) are a drastically understudied and underserved group, at risk for multiple health and mental health problems. There are no national, quantitative, representative studies of this population on any topic. Building upon solid preliminary data, we will conduct structured survey interviews with 400 two spirits drawn from six sites across the United States. With these interview data, we will test a theoretical model of stress and coping specific to this population. Sub-aims are: 1) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, mental health indicators); 2) test the direct associations between trauma and health outcomes; 3) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and 4) examine the mediating role of substance use on the trauma-HIV sexual-risk behavior and trauma-mental health relationships. The results will contribute toward the refinement of a sample strategy useful in studying other hidden and stigmatized populations. Through the course of this project, we aim to develop the research infrastructure at the six community agencies comprising our participant recruitment sites in order to facilitate future goals of designing and evaluating interventions to address the urgent needs of two spirits.

*1R01MH65871-01 Award Amount: $175,000 Clinical*

### *Musculoskeletal Systems*

- Title: *Osteoarthritis Initiative* NIAMS

  The Osteoarthritis Initiative *(*OAI) is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5 to 7 years, OAI will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The consortium includes public funding from the National Institutes of Health and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. OAI will provide approximately $8 million yearly, for as many as six clinical research centers, to establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

  *Award Amount: $800,000 Public-Private partnership*

- Title: *New Methods for Monitoring Treatment for Osteoporosis* NIAMS
  P.I.: Richard Brand, Ph.D.
  University of California, San Francisco, CA

  The overall goal of this project is to develop improved monitoring methods for evaluating the success of a treatment on an individual patient basis using patient-specific estimates of the probability of non-response to treatment, or its complement, the probability of response to treatment. This will provide an empirically grounded and conceptually sound statistical tool for monitoring success of treatment for osteoporosis. This project will extend recently published work in this area, which was focused on the use of a patient's pre- to post-treatment change in total hip bone mineral density (BMD) for judging whether or not the patient has responded to treatment with alendronate. The procedure was calibrated with data from the Fracture Intervention Trial (FIT), a randomized placebo-controlled trial, which evaluated alendronate for treatment of osteoporosis. Clinicians may be overly ready to conclude that treatment with alendronate has failed. For example, when a treated subject has no increase in total hip BMD from baseline, there is only a small probability that a treated patient has actually failed to respond to treatment. Although different from current clinical opinion, this conclusion results from proper consideration of background changes in placebo-treated control subjects as a backdrop for judging the changes in treated subjects. To make this methodology more versatile, extensions to accomplish two important goals will be developed. The first is to handle many different configurations of patient monitoring data that are typically encountered in clinical practice (e.g., repeated BMD measurements, BMD measurements at multiple sites, etc.). The second is to use patient-specific characteristics such as age, race, BMI, and baseline BMD in the calculation of probability of non-response. Application of the methods to FIT data and the Multiple Outcomes of Raloxifene Evaluation data will provide new substantive results that will: 1) contribute to useful clinical guidelines for judging how well a patient is responding to osteoporosis treatment; and 2) provide guidance about cost-efficient patient-monitoring strategy.

  *1R01AR048527-01A1 Award Amount: $100,000 Clinical*

▶ Title: *Glucocorticoids Alter the Birth and Death of Osteoblasts* NIAMS
P.I.: Robert Weinstein, Ph.D.
University of Arkansas for Medical Sciences, Little Rock, AR

This study will characterize the effects of chronic glucocorticoid excess on several aspects of bone physiology. Patients with glucocorticoid-induced bone loss will be included. The effect of alendronate (Fosamax) and parathyroid hormone will be tested in mice for efficacy in ameliorating the effect of glucocorticoids.

*5R01AR 46191-04 Award Amount: $100,000 Clinical and basic*

▶ Title: *Low-dose Doxycline Effects on Osteopenic Bone Loss* NIDCR
P.I.: Jeffrey B. Payne, D.D.S.
University of Nebraska, Lincoln, NE

This study seeks to demonstrate the clinical efficacy of low-dose doxycycline therapy in reducing bone loss due to periodontitis and estrogen deficiency in a postmenopausal, estrogen-deficient osteopenic population. Success in reducing or arresting bone loss related to periodontitis in an estrogen-deficient osteopenic group would represent important progress in understanding and managing the pathophysiologic mechanisms that are involved in bone loss with this process.

*1R01DE12872-02 Award Amount: $308,924 Clinical, translational*

## *Neurology*

▶ Title: *Estrogen-induced Hippocampal Seizure Susceptibility* NINDS
P.I.: Catherine Woolley, Ph.D.
Northwestern University, Evanston, IL

A significant proportion of women with epilepsy experience increased seizure frequency during phases of the menstrual cycle in which estradiol levels are elevated. This is termed catamenial epilepsy. Animal models of epilepsy also demonstrate that estradiol increases seizure susceptibility. Previous work in the adult female rat has shown that estradiol induces new dendritic spines and axospinous synapses on CA1 pyramidal cells in the hippocampus, a key brain structure in the generation and propagation of seizure activity. Furthermore, estradiol-induced dendritic spines and synapses are correlated with increased excitability of hippocampal neurons and decreased hippocampal seizure threshold. This correlation suggests that estradiol-induced seizure susceptibility in women with catamenial epilepsy may be due, at least in part, to hormone-mediated alterations in hippocampal synaptic connectivity. The studies in this proposal will use the adult female rat to test the hypothesis that estradiol facilitates seizure activity through alteration of hippocampal synaptic structure and physiology.

*5R29NS037324-05 Award Amount: $35,000 Basic*

### *Nutrition*

- Title: *Food Choline Database Project* NHLBI
  P.I.: John H. Himes, Ph.D.
  University of Minnesota Twin Cities, Minneapolis, MN

  The purpose of this program is to develop a comprehensive and high-quality database on the choline content of foods commonly eaten in the United States. The data will be generated by analyzing nationally representative samples of 400 foods for their content of various forms of choline. Research activities will be managed by the U.S. Department of Agriculture as a dovetailed component of the ongoing National Food and Nutrient Analysis Program, which has already collected the needed food samples. The total direct cost for developing the database is estimated at $400,000 (400 foods at $1,000/food). The food choline database, resulting from this project, will rectify serious gaps in the general knowledge of choline metabolism and requirements, which require calculating individual- and population-level estimates of choline intake.

  *5U24HL61778-04 Award Amount: $50,000 Applied, National database*

- Title: *Altered Calcium and Vitamin D Metabolism in Premenstrual Dysphoric Disorder* NIDDK
  P.I.: Susan Thys-Jacobs, M.D.
  St. Luke's–Roosevelt Hospital Center, New York, NY

  Premenstrual dysphoric disorder (PMDD) is widely recognized as a recurrent disorder related to hormone variations of the menstrual cycle. Whereas alterations in calcium homeostasis have long been associated with many affective disturbances, recent evidence has suggested that luteal phase symptomatology may be associated with a perturbation in calcium homeostasis. The purpose of this investigation is to understand, more completely, the extent to which calcium regulation is disturbed in PMDD by utilizing new tools to access calcium and bone turnover. The long-term objective is to elucidate the pathophysiology of PMDD as it relates to the calciotropic hormones and bone markers. The experimental design involves enrolling 70 women with PMDD and 35 controls. Following 2 months of baseline symptom documentation, women with PMDD and controls with be enrolled in a 9-month observational period with frequent hormonal samplings, urinary collections, and daily ratings. Understanding the pathophysiology associated with PMDD may lead to effective therapeutic strategies to prevent the neuropsychiatric disturbances and abnormal calcium regulation that are characteristic of this disorder.

  *1R01DK57869-03 Award Amount: $100,000 Clinical*

## *Obesity and Overweight*

▶ Title: *Increasing Physical Activity Levels in Low-income Women* NIDDK
P.I.: Barbara J. Speck, R.N., Ph.D.
University of Louisville, Louisville, KY

This project is aimed at reducing community environmental barriers to physical activity in medically underserved women. The setting for the study is a church-sponsored community center with a nurse-managed clinic that is located in a low-income neighborhood. Pretest data will include psychosocial questionnaire, physiologic (cholesterol, blood pressure), and anthropometric measures. The 6-month intervention will be twofold: 1) provide culturally appropriate educational activities to increase women's comfort level at the community center, and 2) provide multiple culturally appropriate physical activity opportunities utilizing the gymnasium and exercise equipment. The long-term goal is to establish physical activity opportunities for women at this community center that could be adapted at other community centers.

*1R01DK63523-01 Award Amount: $178,750 Clinical*

▶ Title: *Look AHEAD (Action for Health in Diabetes)* NIDDK
Wake Forest University (coordinating center), Winston Salem, NC
Johns Hopkins University, Baylor College of Medicine,
University of Colorado Health, University of Washington, University of Tennessee, St. Lukes–Roosevelt Institute, University of Alabama at Birmington, Miriam Hospital, Pennington Biomedical Research, University of Texas Health Science, University of Minnesota, University of Pittsburgh, Massachusetts General Hospital, University of California Los Angeles, University of Pennsylvania, Southwest American Indian Center (12 clinical centers)

This multicenter randomized clinical trial examines the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. The Look AHEAD trial will enroll 5,000 obese patients with type 2 diabetes over a 2.5 year period. Participants will be randomly assigned to one of two interventions – the Lifestyle Intervention or Diabetes Support and Education – and will be followed for a total period of up to 11.5 years. The primary aim of Look AHEAD is to study the effects of the two interventions on major cardiovascular events: heart attack, stroke, and cardiovascular death. Look AHEAD also will investigate the impact of the interventions on other cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include: diabetes control and complications, fitness, general health, health-related quality of life, and psychological outcomes. The cost and cost effectiveness of the lifestyle intervention, relative to diabetes support and education, will be assessed.

*Award Amount: $100,000 Clinical*

▶ Title: *Clinical and Experimental Study of Human Obesity* NIDDK
P.I.: Albert Stunkard, M.D.
University of Pennsylvania, Philadelphia, PA

This project is a longitudinal study of 78 children, from 3 to 5 years of age, from either obese or non-obese mothers. The goal is to examine a group of variables related to food intake and energy expenditure, along with measures of body size or composition, utilizing not only weight and length but measures of skinfold thickness and percent fat by dual energy x-ray absorptiometry and body water, and isotope dilution measures. The study has already found that the two independent measures of energy intake at 3 months of age predict body size and composition at 1 year of age and discounted the belief that a low total energy expenditure and maternal obesity predict body size and composition at 1 year of age. This study will continue to search for risk factors for obesity in the early childhood years.

*5R01DK56251-06 Award Amount: $100,000 Clinical*

### *Pain*

▶ Title: *Low Back Pain – A Multicenter Randomized Trial* NIAMS
P.I.: James Weinstein, D.O.
Dartmouth Medical School, Hanover, NH

Low back pain is considered one of the most widely experienced health problems. Rates of spinal surgery have increased sharply over time and 15-fold geographic variation in rates of these surgeries has been documented. There is little evidence proving the effectiveness and efficacy of these surgical therapies over non-operative management. This study will use the resource of the National Spine Network to conduct multicentered, randomized, controlled trials for three common diagnostic groups – lumbar intervertebral disc herniation, spinal stenosis, and spinal stenosis secondary to degenerative spondylolithesis. The trials will compare the most commonly used standard surgical treatments to the most commonly used standard non-operative treatments. The primary endpoints will be changes in general health-related quality of life, as measured by the SF-36 health status questionnaire, and spine-related disability, as measured by the Oswestry Low Back Pain questionnaire. Secondary endpoints will include patient satisfaction with treatment, resource utilization of estimation of cost, and utility for current health for estimation of quality-adjusted life years.

*5U01AR045444-04 Award Amount: $100,000 Clinical*

▶ Title: *Sex Differences in Opioid Analgesia* NIDA
P.I.: Anne Z. Murphy, Ph.D.
University of Maryland School of Medicine, Baltimore, MD

Chronic pain afflicts millions of people each year. Opioid-based narcotics are the most prevalent therapeutic treatment for chronic pain management, with morphine being the most commonly prescribed. There are now well-established sex differences in the ability of morphine to alleviate pain; in animal models of acute pain, the effective dose of morphine is approximately five to ten times greater for females in comparison to males. Similar results have been reported in humans. To date, the underlying mechanisms mediating sex differences in opiate sensitivity are not known. The midbrain periaqueductal (PAG) and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. The major hypothesis is that the opiate-sensitive intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and is the major determinant of sex-based differences in opioid analgesia. Previous studies examining the dimorphic effect of opioid administration utilized acute assays of nociception. Studies proposed in *Aim 1* will characterize the sexually dimorphic effect of central morphine administration using a model of chronic inflammatory pain. Preliminary data indicate that the PAG-NRM pathway is sexually dimorphic. Studies proposed in *Aim 2* will use neural tract tracing techniques to delineate the anatomical organization of the PAG-NRM spinal cord circuit in males and females. *Aim 3* will examine the functional organization of this circuit in a model of prolonged inflammatory pain. PAG is enriched in opioid receptors. Studies proposed in *Aim 4* will characterize both the distribution and expression pattern of the opioid receptors. The influence of chronic inflammatory pain and gonadal steroid manipulations will also be examined. These studies will establish that the intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and provide the neural substrate for sex-based differences in opioid analgesia.

*1R01DA016272-01 Award Amount: $293,764 Basic*

▶ Title: *Trigeminal Pain Mechanisms and Control* NIDCR
P.I.: Jon D. Levine, Ph.D.
University of California at San Francisco, San Francisco, CA

The chemotherapeutic agent paclitaxel (Taxol) is widely used for the treatment of many different types of carcinomas. At present, the dose of paclitaxel that can be tolerated by patients is limited primarily by the development of a painful peripheral neuropathy characterized by parenthesis, myalgia, and arthralgia. Similar dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, including vincristine. Therefore, amelioration of the neuropathic pain might not only reduce the suffering of patients who receive paclitaxel or vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies.

*5P01DE08973-12 Award Amount: $155,237 Basic*

- Title: *Pain Management in Temporomandibular Joint Disorders* NIDCR
  P.I.: Jennifer Haythornthwaite, Ph.D.
  Johns Hopkins University, Baltimore, MD

  The primary goal of the proposed project is to test the efficacy of psychological interventions, a pharmacological intervention, and the combination of these interventions in reducing pain and improving function in persons with temporomandibular disorders (TMD). Since psychological interventions are costly and require expertise that is frequently unavailable in primary care settings, the proposed project will also examine the efficacy of a minimal contact/self help psychological intervention based on cognitive-behavioral therapy for pain management. In addition to examining the separate and combined effects of psychological and pharmacological interventions for TMD pain, the proposed study will examine whether the minimal contact cognitive-behavioral intervention can accomplish comparable reductions in pain and improvements in function relative to the therapist-administered treatment.

  *1R01DE13906-02 Award Amount: $312,514 Behavioral*

- Title: *Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants* NIDCR
  P.I.: James R. Fricton, D.D.S., M.S.
  University of Minnesota, MN

  The development of the National Institute of Dental and Craniofacial Research's TMJ Implant Registry and Repository at the University of Minnesota will allow collection of clinical information and biological specimens on patients with TMJ implants throughout the United States. This will stimulate both basic and clinical studies and improve our understanding of the pathobiology of TMJ diseases and disorders. In addition, the availability of retrieved implant materials will help in the design and development of a new generation of implantable materials and advance our understanding and success of treatment of patients with TMJ implants.

  *N01DE22635 Award Amount: $100,000 Registry*

## *Physical Activity*

▶ Title: *Physical Activity in Older Rural Midwestern Women* NINR
P.I.: Donna J. Plonczynski, M.S.N.
University of Illinois–Chicago, Chicago, IL

The purpose of this cross-sectional study is to describe the physical activity behavior (household, work, volunteer, and leisure) determinants of physical activity, and cardiovascular risks (body mass index [BMI] and blood pressure [BP]) in older (65 to 85 years) women with at least one chronic illness, residing in rural communities in the Midwest. The background determinants (demographics, environmental resources, social influence, and current health) and intrapersonal determinants (motivation [intrinsic motivation and barrier self efficacy], cognitive appraisal [illness cognition], and affective health) of physical activity will be explored in relation to physical activity behavior and cardiovascular risks, as guided by a modification of the Model of Physical Activity Behavior. Subjects will include 176 older rural volunteer women who are cognitively intact, self described as able to perform physical activity, English speaking, and who have at least one chronic illness. Recruitment will proceed through flyers, newspaper notices, and key informants in a rural, low-income, Midwest county. The face-to-face questionnaire, administered in their homes or a location of their choosing, will include measures of background and intrapersonal determinants of physical activity. Physical activity will be measured with the Older Adult-Exercise/Physical Activity Inventory. Additionally, BMI will be determined with a weight and height scales, and BP will be measured by an automated Omron 6006 monitor. Model development will proceed by systematically evaluating all the proposed relationships within the MPAB using descriptive statistics, T-tests, ANOVA, logistic correlations, stepwise regression, and chi-square analysis.

*1F31NR008070-01 Award Amount: $26,188 Clinical*

## *Reproductive Health and Developmental Biology*

▶ Title: *Intermediate Outcomes of Hysterectomy and Alternatives* AHRQ
P.I.: Miriam Kuppermann, Ph.D.
University of California–San Francisco, San Francisco, CA

The project expands on our existing prospective longitudinal study of 811 women with non-cancerous uterine conditions for which hysterectomy is a reasonable treatment option: abnormal bleeding, symptomatic uterine leiomyomata, and pelvic pain/endometriosis. The principal aims of the proposed study are: 1) to determine whether and how intermediate-term (4- to 8-year) clinical and quality-of-life outcomes differ by treatment group (hysterectomy, uterus-preserving surgery, or non-surgical treatments) for their uterine conditions; and 2) to develop predictive models of treatment choice and satisfaction from a broad array of domains.

*1R01HS11657-01A1 Award Amount: $250,000 Outcome research*

- Title: *Variation in Cytokine and Matrix Metalloproteinase Genes and Risk of Preterm Premature Rupture of the Membranes* FIC
  P.I.: Pedro E. Ferrand, M.D.
  University of Chile, Santiago, Chile

  Preterm premature rupture of the membranes (PPROM) is a major cause of preterm birth and perinatal morbidity and mortality. It has been hypothesized that pro-inflammatory cytokines are important mediators of PPROM. Cytokines induce expression of matrix metalloproteinases (MMPs) that degrade the extracellular matrix, which gives the membranes their tensile strength. We hypothesize that variation in pro-inflammatory cytokine and MMP genes contributes to the risk of PPROM, and that gene-environment interactions amplify the risk. The long-term goal of this research is to identify genes that make significant contributions to risk of PPROM, and how infection interacts with these genes to increase the risk of the unfavorable obstetrical outcome. The study population will be recruited from the obstetrical services of the Hospital San Borja Arriaran, Santiago, Chile (over 9,000 deliveries per year). The study will be restricted to Hispanic women, their partners, and offspring. If positive results emerge from the association studies, we will examine linkage using the transmission disequilibrium test. Collectively, these studies could provide evidence for the contribution of genetic factors to the risk of preterm birth.

  *1R01TW006197-01 Award Amount: $17,500 Translational*

- Title: *Characterization of Flagellar Proteins Involved in Sperm Motility* FIC
  P.I.: Rossana Sapiro, M.D.
  University of the Republic of Uruguay, Montevideo, Uruguay

  This program will identify flagella proteins involved in sperm motility, and will lend to a greater understanding of mechanisms underlying male infertility and the possible development of new contraceptors. The proteome of human sperm, with motility and ultrastructural defects that mirror those of the SPAG6-deficient mouse, will be examined to screen for humans with SPAG6 deficiency. The knowledge gained from this research will provide a molecular framework for understanding sperm motility defects that cause male infertility, and possibly offer new avenues for contraception through the disruption of purposeful sperm motion.

  *1R01TW006223-01 Award Amount: $17,500 Basic*

▶ Title: *Neuroimmunology and Cytokine Alterations in Vulvodynia* NICHD
P.I.: Barbara D. Reed, Ph.D.
University of Michigan at Ann Arbor, Ann Arbor, MI

Hundreds of thousands of women in the United States suffer from vulvodynia, a chronic burning vulvar pain of unknown cause. Millions of health-care dollars are spent annually for this disorder, in the United States alone, not only on management, but also on the large proportion of cases that are misdiagnosed and inadequately treated. This pain, associated with allodynia and hyperpathia, has a strong genetic predilection, with African American women rarely being affected. The broad, long-term objectives of this proposal are to assess the differences in specific neuroimmunological characteristics between women with vulvodynia and asymptomatic controls. The specific aims include evaluation of: 1) the individual cytokine/neurokine production response to stimulation of peripheral blood; 2) local changes in nerve fiber, mast cell, Substance P, and serotonin density in vulvar tissue; 3) the interactions of the systemic and local immunologic systems assessed in 1) and 2); and 4) the multivariable assessment of these laboratory factors, with historical risk factors for vulvodynia, to explore potential pathophysiologic mechanisms accounting for the historical risk factors identified. The research design involves a case-control evaluation of 100 women with vulvodynia, 100 controls matched for ethnicity, and 100 African American control women, using questionnaires, physical examinations, clinical laboratory data, cytokine/neurokine levels in stimulated peripheral blood, and neuroimmunhistological assessment of vulvar, biopsy specimens for nerve fiber density, mast cells, Substance P, and serotonin. Results from this study will lead to improved understanding of neuroimmunologic alterations in women with vulvodynia which will direct future therapeutic strategies for this disorder.

*5R01HD040112-03 Award Amount: $180,954 Clinical*

▶ Title: *Control of Menstrual Bleeding Disturbances in Women* NICHD
P.I.: Ian Stewart Fraser, M.D.
Sydney Centre for Reproductive Health Research, Ashfield, Australia

This project will evaluate two promising approaches to the treatment of prolonged and frequent episodes of breakthrough bleeding, which sometimes accompany the use of the implantable, progestogen-only implant, Implanon. These erratic episodes of bleeding can be a major reason for discontinuation of use. There is increasing evidence that continuous exposure to progestogens results in a tendency for the endometrium to release active enzymes, called matrix metalloproteinases (MMPs), which can promote premature breakdown of the tissue. Inhibition of the action of these enzymes may stabilize the endometrium and improve the bleeding pattern. A commonly used tetracycline compound, Doxycycline, has strong anti-MMP action, and preliminary evidence in a mouse model of menstruation suggests that it may, indeed, stabilize the endometrium. There is preliminary evidence that a short course of an antiprogesterone (Mifepristone) may also stabilize the endometrium, and it is postulated that a combination of an antiprogesterone with estrogen may be even more effective. Preliminary evidence in mice indicates that estrogen exposure of the endometrium in the absence of progesterone strongly inhibits the formation of new blood vessels, and simultaneous anti-progesterone exposure will mimic this situation.

*1R01HD043192-01 Award Amount: $100,000 Basic*

- Title: *Mechanism of Vulvodynia* NICHD
  P.I.: Ursula Wesselmann, Ph.D.
  John Hopkins University, Baltimore, MD

  The long-range objective of this research is to elucidate the pathophysiological mechanisms of vulvodynia, a chronic pain syndrome of the vaginal and vulvar area, in order to develop improved treatment strategies for alleviating chronic pain in these women, targeted at the underlying pathophysiological mechanism. We propose two approaches to gain better understanding of the pathophysiological mechanisms of vulvodynia: 1) we will develop an animal model in the rat, that will allow us to study the spinal cord pathways involved in the processing of noxious input from the vagina; and 2) we propose to characterize pain in patients with vulvodynia in detail. Out hypothesis is that patients with vulvodynia can be differentiated into distinct groups based on their pain characteristics, and that treatment of pain in vulvodynia will be more effective, if based on recognition of the underlying neurophysiological mechanisms.

  *1R01HD039699-02 Award Amount: $19,046 Clinical*

- Title: *Development and Differentiation in Reproductive Axis Cooperative Reproductive Sciences Research at Minority Institutions RFA* NICHD
  P.I.: *Director*–David R. Mann, Ph.D., Morehouse School of Medicine, Atlanta, Ga
  *Co-director/Partner*–Tony M. Plant, Ph.D., University of Pittsburgh, Specialized Cooperative Centers Programs in Reproductive Research, Pittsburgh, PA

  The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new, and/or the enhancement of ongoing, basic science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health.

  The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core. Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant.

  *Grant No. 1 – 1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann.*

  *Grant No. 2 – 1U54HD41749-010002 (Role of Prohibitin in Follicular Development), Winston E. Thompson.*

  *Grant No. 3 – 1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran.*

  *Grant No. 4 – 1U54HD41749-010004(SP Regulation of Gene Expression in Spermato*genesis), *Kelwyn H. Thomas.*

  *5U54HD41749-02 Award Amount: $250,000 Basic, translational, clinical*

▶ Title: *Fragile X Mental Retardation Gene Premutation* NICHD
P.I.: Pamela L. Mellon, Ph.D.
University of California – San Diego, La Jolla, CA

Fragile X syndrome (FRX) is one of the most frequent forms of congenital mental retardation in humans, usually resulting from lack of expression of the Fragile X mental retardation gene (FMR1). Interestingly, unaffected carriers, or so-called FRX premutation carriers, show an increased prevalence of premature ovarian failure (POF) which is generally defined as cessation of reproductive function by age 40. While it is estimated that 1 percent of women worldwide experience POF, the prevalence of POF in FRX premutation carriers has been reported to be 16 percent. On a more basic science level, the FMR1 gene is expressed in many tissues, but its function is unknown. In both male and female gonads, the gene is expressed in the germ cells. For the ovary, expression of the FMR1 gene in oogonia and oocytes could have profound implications for the regulation of oocyte number and ovarian follicular reserve, which clearly can impact the cessation of reproductive function. Three aims are proposed to: 1) characterize the cell-specific FMR1 gene expression changes in normal human and mouse ovaries through their respective reproductive cycles; 2) define the physiology of hypothalamic-pituitary-ovarian function in human female FRX premutation carriers; and 3) create a repository of genetic material and extensive phenotypic information about women with POF that could eventually be used to test other candidate genes for POF.

*5U54HD12303-23 Award Amount: $113,000 Translational*

▶ Title: *Genotype and Phenotype Correlations in Infertility* NICHD
P.I.: Lawrence Layman, M.D.
Medical College of Georgia, Augusta, GA

Although infertility affects 10 to 15 percent of all individuals attempting to have children, little is known about the molecular basis of human puberty and fertility. The long-term goal of the investigator's laboratory is to elucidate the mechanisms underlying the development of normal puberty and reproductive capability by utilizing patients with infertility who possess gene mutations. Two groups of infertile patients will be studied: those with idiopathic hypogonadism (IHH), and those with normal puberty who have ovulation disorders or sperm abnormalities. Patients with IHH constitute a severe reproductive-deficient phenotype with absent puberty, low serum gonadotropins, and infertility. Most infertility patients have normal puberty, and constitute men with sperm abnormalities (azoospermia, oligospermia, and/or asthenopermia) or women with ovulation disorders. The overlying hypothesis is that identification of the genetic mutations in these groups will lead to better understanding of: 1) which forms of IHH are hereditary; 2) whether FSH is necessary for normal sperm concentration and fertility in men, follicular development beyond the antral stage in women, and for normal androgens in both men and women; and 3) whether gene mutations affect the function of the encoded proteins. These hypotheses will be addressed by the following specific aims: 1) to test candidate genes for linkage and/or mutations in IHH patients; 2) to screen infertility patients for FSH mutations, specifically those with abnormal semen analyses and those with ovulation disorders, likely to possess FSH mutations; and 3) to create the mutants, express them *in vitro*, and determine their effects upon the encoded protein. The elucidation and analysis of gene mutations in infertile patients will be important to determine the genetic basis for some forms of infertility, and to determine the underlying mechanisms of puberty and reproduction.

*1K24HD040287-01A1 Award Amount: $100,000 Clinical*

▶ Title: *Cellular and Molecular Mechanisms of Mammalian Ovulation* NICHD
P.I.: Ok-Kyung Park-Sarge, Ph.D.
University of Kentucky, Lexington, KY

The long-term goal of this research is to elucidate the molecular cascades of LH-induced signals, within preovulatory follicles, leading to ovulation. The LH surge stimulates the synthesis of progesterone and its intracellular receptors, progesterone receptors (PRs), in the granulosa cells of preovulatory follicles. Interaction between progesterone and PRs in an autocrine/paracrine fashion is essential for ovulation. However, the exact mechanism by which ligand-dependent activation of PRs controls ovulation and, thus normal reproductive cyclicity and fecundity, are unknown. To gain insight into the molecular mechanisms underlying PR-mediated ovarian functions, the investigators initiated cloning of PR downstream genes in luteinizing granulosa cells. The two genes that they characterized as PR-downstream are the ligand-receptor system for pituitary adenylate cyclase-activating poypeptide (PACAP) and its receptor type I, $PAC_1$. The temporal and spatial pattern of expression and secretion of the ligand PACAP, along with the cellular localization of the receptor $PAC_1$, in the ovary advocates the potential significance of this ligand-receptor system for ovulatory processes. Pharmacological blockade of ligand-dependent activation of $PAC_1$ appears to interfere with the efficacy of LH and progesterone in bringing about ovulatory processes. Thus, the working hypothesis is that PACAP-induced activation of $PAC_1$ mediates at least, in part, PR function critical for follicular rupture with release of a meiotically mature oocyte. The immediate goal of this research is to determine the functional importance of PACAP within preovulatory follicles, during the periovulatory period, using *in vivo* and *in vitro* approaches. In *Aim 1*, they will test whether PR-induced PACAP is critical for follicular rupture and for expression of ovulation-related genes, including proteolytic enzymes. In addition, they will identify $PAC_1$-downstream genes that may play an important role in follicular rupture. In *Aim 2*, they will determine the initial death and survival pathway(s) that is modulated by PR-induced PACAP in luteinizing granulosa cells. In *Aim 3*, they will test whether PR-induced PACAP regulates the polyadenylation translation capacity of meiotically maturing oocytes. The proposed studies are designed to provide functional endpoint(s) of interaction between PR-induced PACAP and $PAC_1$ in preovulatory follicles during the preovulatory period. Information derived from the results will allow better management of fertility, infertility, and endocrine-based disorders.

*1R01HD041609-01A1 Award Amount: $100,000 Basic*

▶ Title: *A National Training Program in Reproductive Medicine* NICHD
P.I.: Christos Coutifaris, M.D., Ph.D.
University of Pennsylvania, Hershey, PA

Reproductive endocrinology and infertility (REI) is one of the three subspecialty fellowships for advanced training after completion of a residency in obstetrics and gynecology. Formal certification for this advanced training in reproductive medicine is under the aegis of the Division of Reproductive Endocrinology and Infertility of the American Board of Obstetrics and Gynecology, Inc. This board eventually awards certificates of special competence for the practice of reproductive endocrinology and infertility to individuals after completion of an accredited training program and subsequent passing of a written and finally an oral examination. The Society for Reproductive Endocrinology and Infertility, the society of board certified REIs, has as a major mission – the support of programs involved in the selection, training, and networking of fellows. It is within this framework that this research training is proposed. Research is an central feature of fellowship programs. Board-approved training programs are academically rigorous and require a major commitment to research. This is the only formalized time during the training of obstetrician/gynecologists that such a rigorous commitment to an academic research exercise is required. More importantly, this is the only time when physicians in training have the opportunity to develop a lasting interest (and hopefully a passion) for research. This is the sole window through which the pipeline of academic reproductive medicine specialists can be kept open. Until recently, the academic development of fellows in training had been predominantly funded through clinical revenue. Unfortunately, during the past 5 years, financial constraints have prompted the discontinuation of many (29 percent) fellowship programs in REI and a reduction of total fellowship positions (by 50 percent) in the continuing active programs. This is occurring at a time when there is an increase in the available academic positions, and at a time of unprecedented advances in the research aspects of the field. The objective of the present proposal is to seek funding for a required 2-year training period in research for three fellows per year, who are involved in meritorious research as part of their respective approved fellowship programs. It is anticipated that such support will greatly contribute to the early development of physician scientists in the field of reproductive medicine and will better prepare fellows to enter the pipeline of the NIH-funded positions in the Reproductive Scientists Development Program and the Women's Reproductive Health Research Career Development initiative.

*1T32HD040135-01A1 Award Amount: $100,000 Clinical*

▶ Title: *Depo-Provera and Bone Mineral Density in Premenopausal Women* NICHD
P.I.: Kathleen Clark, Ph.D.
University of Iowa, Iowa City, IA

Depot-medroxyprogesterone acetate (DMPAm Depo-Provera™) is a progestin-only injectable contraception preparation that disrupts the hypothalamic-pituitary-ovarian-axis (HPO) and suppresses estradiol concentrations, possibly to levels found in postmenopausal women. This has raised concern regarding the potential adverse effect of estrogen deficiency on peak bone mineral density (BMD) in premenopausal women, increasing their risk of developing osteoporosis following menopause. The ongoing parent project is a longitudinal study evaluating changes in BMD every 3 months for 24 months in 275 women; 160 who receive their first DMPA injection simultaneously with study initiation, and 115 control subjects who are not using any hormonal method of contraception. The study will determine the effect of DMPA on BMD in women, aged 18 to 30, and whether DMPA-related BMD loss would be attenuated by higher calcium intakes. Further, it will describe baseline and post-injection estradiol levels, patterns of irregular bleeding, and weight gain, and determine whether those characteristics can identify woman at greatest risk for DMPA-related BMD loss. At baseline, participants have their BMD, height, weight, and percent body fat measured, as well as blood collected for assay of estradiol concentrations. Enrollees complete a comprehensive interview detailing nutritional, lifestyle, demographic, medical, reproductive, and behavioral factors that may influence BMD. Additionally, all participants are given one 90-day menstrual calendar to complete at home. At each 3-month followup evaluation, BMD and physical measurements are repeated and the nutrition and physical activity components of the interview updated. The menstrual calendar is collected, reviewed, and a new 90-day calendar is provided. This proposal will extend the observation period of the parent study from 24 months per enrollee to a maximum of 42 months per enrollee. This longitudinal design will be continued, maintaining all methods and protocols employed in the parent study. There are few published longitudinal studies of BMD changes in women using DMPA for contraception, and none that extend beyond the 24 months. Thus, there are no studies that adequately characterize the patterns of BMD change over time. Through published cross-sectional studies, two potentially contradictory hypothesis regarding relationship between the length of DMPA use and BMD have been suggested: 1) that BMD will be inversely and linearly related to length of DMPA use, and 2) that BMD will decline initially but level off with continued use. These hypotheses could represent differential risks for DMPA-related bone loss and may influence clinical decisions regarding the acceptable duration of DMPA use. Extending the observational period of this study will be an efficient and cost effective means of more fully understanding DMPA-related bone changes over a period of time that, realistically, reflects the length of DMPA use by a substantial proportion of women choosing DMPA for contraception.

*3R01HD039100-03S1 Award Amount: $183,750 Clinical*

▶ Title: *Maternal Periodontitis and Adverse Pregnancy Outcome* NIDCR
P.I.: Waranuch Pitiphat, M.S.
Harvard School of Dental Medicine, Boston, MA

This study will evaluate whether periodontitis is a risk factor for adverse pregnancy outcomes, by adding an oral component to the ongoing Project Viva, a prospective study of 6,000 pregnant women, to evaluate this association. Maternal infection during pregnancy has been demonstrated to play an important role in etiology of preterm delivery. Periodontal infection can serve as a reservoir of gram-negative anaerobic organisms and their products, and proinflammatory mediators which could target the placental membranes via systemic circulation thus leading to preterm delivery or fetal growth restriction. The primary aim of this study is to examine the effect of maternal periodontitis on length of gestation and fetal growth. The secondary aim is to explore the association between periodontitis and serum levels of TNF-alpha. The proposed prospective nested case-control study will request pre-existing radiographs from Viva participants.

*1R03DE14004-02 Award Amount: $25,000 Case-control study*

### *Violence*

- Title: *Improving Interventions for Drug Abuse–Partner Violence* NIDA
  P.I.: Cynthia Connelly, Ph.D.
  Children's Hospital Research Center, San Diego, CA

  Through the Mentored Career Development Award (K01) program, the applicant will establish an independent program of substance abuse research focused on improving the identification and intervention for substance abuse, intimate partner violence (IPV), and co-occurring affective disorders (AD) in early intervention settings. The applicant's strong background of academic, research, and nurse clinical training in substance abuse, violence, family health, and health services research provides an excellent foundation for this work. The proposed training goals provide additional instruction and mentoring in: 1) the complex linkage between ATOD, IPV, and AD and engagement and treatment strategies for early preventative intervention; 2) longitudinal data analysis and modeling techniques; 3) cultural issues and health disparities that complicate early intervention efforts among diverse populations; and 4) training in the ethical conduct of research. This training will prepare the applicant to pursue a research career in prevention science targeting substance abuse among women of childbearing age. Phase I secondary data analysis will be conducted on longitudinal data provided by two large samples of postpartum women to examine the role of ATOD, IPV, and AD on engagement and participation with an early intervention – home visitation. Subgroup analyses based on age, race, and ethnicity, and combinations of ATOD, IPV, and AD, will be examined. In Phase II, existing protocols for provider education and training in assessment, including instrumentation, interpretation, and triage, will be critically examined in two model programs. Phase III will use findings from Phases I and II, as well as mentoring from experts in specific content areas, to inform the development of strategies and preliminary protocols to strengthen early preventative interventions addressing these specific issues and to pilot test these protocols. Phase III will identify characteristics that impact implementation at the provider, family, and program level and will generate preliminary data to inform research and program development. The data will form the basis for a R01 application to prospectively test the effectiveness of strategies designed to improve provider education and practice related to ATOD, IPV, and AD among women of childbearing age.

  *1K01DA015145-01 Award Amount: $100,000 Clinical*

*APPENDIX B*

# *Office of Research on Women's Health Research Awards*

## ORWH-SUPPORTED SPECIAL PROJECTS, FISCAL YEAR 2001

▶ Title: *Governors' Spouses Initiative to Curb Underage Drinking* **NIAAA**
Award: $100,000
Contact: Suzanne Medgyesi-Mitschang, Ph.D.

Continued funding in FY 2001 for this project supports Phase II of the Governor's Spouse Initiative to Curb Underage Drinking. In FY 2001, highlights include the development of effective state-oriented programs on outreach, education, coordination, and data gathering. Some FY 2001 activities include:

- Prevention guide to assist policy makers, practitioners, community leaders, and concerned citizens in determining the most appropriate approaches to prevention of underage drinking in their states and municipalities;
- Dedicated website to serve as central source of information about all aspects of early onset alcohol use and the initiative;
- National media campaign to make prevention of early onset drinking a national priority;
- Policy briefings for state legislators in the 28 participating states;
- Research Task Force to lead to increased research on alcohol use by older children and young adolescents, minority differences in underage drinking, and effective interventions for youth in various age, gender, geographic, socioeconomic, and population groups; and
- Evaluation of the initiative's success in raising national awareness about the problem of alcohol use by children, aged 9 to 15, and mobilizing efforts to prevent it.

▶ Title: *Preventive Hormone Therapy Decisionmaking on the World Wide Web* NIA
Award: $176,575
Contact: Thomas R. Taylor

The application extends prior work of this research team related to physician practice and patient decisions regarding hormone replacement therapy (HRT). Specifically, the proposed research has two major goals:

- To develop a computerized decision support system that can be distributed over the world wide web designed to assist women in their decisions regarding HRT; and
- To evaluate the impact of the decision support aid on decisions that women make regarding HRT.

- Title: *Reprinting of* Lupus: A Patient Care Guide for Nurses and Other Health Professionals — NIAMS
  Award: $10,000
  Contact: Judith Wortman

  Funding is provided to support the reprinting cost associated with *Lupus: A Patient Care Guide for Nurses and Other Health Professionals*. NIAMS will acknowledge ORWH's support by listing ORWH on the front page of its care guide as one of their sponsors.

- Title: *Health Disparities Based on Sexual Orientation* — DHHS
  Award: $3,000 — Office of HIV/AIDS Policy
  Contact: Christopher Bates

  The funding of this project was used to support the Office of HIV/AIDS Policy, DHHS, in the preparation of the Steering Committee on Health Strategic Plan on Health Disparities Based on Sexual Orientation, and to organize and cross reference the DHHS inventory of programs, policies, and initiatives pertaining to these populations throughout the department.

- Title: *Pilot Study to Assess Older, Minority, Low-income Women's Needs for Healthcare Information and Skill Development In Negotiating with Healthcare Providers for Services* — UMBC
  Award: $24,999
  Contact: Professor Robert Rubinstein

  Funding supported a pilot study on older, multicultural, primarily foreign-born, low-income, community-dwelling women's quest for healthcare access. Results of this study will be presented in a poster session at the annual conference of the American Public Health Association, which meets in Atlanta in October, and at a poster session at the Gerontological Society of America Annual International conference, which is meeting in Chicago in November, 2001.

- Title: *Sister to Sister – Everyone Has A Heart:* Women's Heart Day: Because a Woman's Heart is Different
  Award: N/A
  Contact: Irene Pollin

  The Sister to Sister – Everyone Has A Heart awareness campaign will help fill the gap by putting a spotlight on cardiovascular issues to help change women's health behavior. The campaign will address important awareness issues concerning heart disease in women. The campaign provided a series of free heart disease screening throughout the Washington metropolitan area from February 16-22, 2001. This health fair was designed as a model to develop a nationwide program.

- Title: *Wish.net.org* — WISH-NET
  Award: $16,000
  Contact: Joan Rachlin

  Wish-net.org was developed by Public Responsibility in Medicine and Research. Wish-net is a mentoring site designed to support girls and women of all ages and at all stages who are interested or working in the fields of science and medicine. NIH is taking over this site as of FY 2002.

# ORWH-SUPPORTED SPECIAL PROJECTS, FISCAL YEAR 2002

▶ Title: *Sister to Sister – Everyone Has a Heart Foundation Health Fair* NHLBI
Award: $20,000
Contact: Greg Morosco, Ph.D.

The Sister to Sister – Everyone Has A Heart Foundation was founded to increase awareness about heart disease as the number one killer of women and to encourage healthy lifestyles. It is the only national organization whose focus is on screening women for heart disease. Because of the lack of awareness among women about the seriousness of heart disease, and the belief that women can modify, control, or treat their risk factors for this disease, the foundation's mission is:

- To provide women with opportunities to be screened for early detection and treatment of heart disease, and
- To educate women about prevention measures, including a healthy diet, regular exercise, stress management, and smoking cessation to reduce heart disease risk factors.

The foundation sponsored a second health fair in Washington, DC on February 22, 2002 and will duplicate the campaign in other cities in 2003 and beyond. ORWH provided $20,000 ($8,000 screening kits and $12,000 data analysis) to expand screenings during the February 2002 Woman's Heart Day campaign. This activity supports and reinforces the public outreach efforts and activities of the National Institutes of Health and, in particular, those of the National Heart, Lung, and Blood Institute and ORWH.

▶ Title: *Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health* NIAMS, ORWH
Award: $8.7 million
Contact: Dr. Charisee Lamar

ORWH funded eleven new Specialized Centers of Research (SCORs) on Sex and Gender Factors Affecting Women's Health. Funding for the centers will total approximately $11 million per year for 5 years with cofunding by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Child Health and Human Development, the National Institute of Diabetes and Digestive and Kidney Diseases, The National Institute on Drug Abuse, the National Institute of Mental Health, the National Institute of Environmental Health Sciences, and the Food and Drug Administration. These centers will provide new opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health.

Each SCOR will promote interdisciplinary collaborations and develop a research agenda bridging basic and clinical research on sex and gender factors underlying a priority health issue. The SCOR program will complement other federally supported programs addressing women's health issues. Such programs include the Building Interdisciplinary Research Careers in Women's Health, the Women's Reproductive Health Research Career Development Centers, and numerous NIH Request for Applications (RFAs) and Program Announcements (PAs).

This is the first time ORWH has taken the lead in developing and funding a new research initiative relating to women's health. The multidisciplinary nature of the centers will provide innovative approaches to advancing research on the role of sex- and gender-related health effects. The research scope of the SCORs stems from three sources: the Institute of Medicine report, *Exploring the Biological Contributions to Health Does Sex Matter? An Agenda for Research on Women's Health for the 21st Century*, and from recommendations from the National Institutes of Health institutes and centers. The multidisciplinary nature of these centers will provide opportunities for innovative approaches to research on the role of sex- and gender-related health effects.

Thirty-six applications, containing 184 projects, were received in response to the SCOR RFA: OD-02-002, however, one was withdrawn by the applicant prior to review. Applications were reviewed in two phases due to the number and diversity of the projects. Phase one reviewers provided critiques and scores based on scientific merit of the individual projects.

There was no review meeting for Phase 1. Scores and critiques were made available to Phase 2 reviewers through the internet-assisted review system. Phase two reviewers read the critiques and scores of each application prior to attending the review session. The Phase 2 committee consisted of investigators experienced in running centers funded by NIH institutes. Overall scores were determined by the combination of the two-phase review.

The SCORs were selected on the basis of having at least three highly meritorious interdisciplinary research projects that explore an important issue related to sex and gender health differences, related by a common theme. 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. Research priority areas, including mental health, reproductive health, pain disorders, and urinary tract health, will be addressed by grantees of this new ORWH initiative.

The primary institute program director will review the annual progress reports submitted by the SCORs, and will provide a yearly report on the scientific progress of the grantee. The ORWH SCOR Coordinator will oversee the applications to coordinate policy issues for the overall program. The SCOR Coordinator will make site visits, arrange annual meetings of the investigators, and write reports on the program for the Director of ORWH.

Research priority areas, including mental health, reproductive health, pain disorders, and urinary tract health, will be addressed by the new centers. The following section outlines SCOR themes, center directors, individual projects, and affiliations.

- *Pharmacology of anti-epileptic and psychotropic medications during pregnancy and lactation,*
  Zachary Stowe, M.D., Emory University
- *Role of sex and gender differences in substance abuse relapse,*
  Kathleen Brady, M.D., Ph.D., Medical University of South Carolina
- *Genes, androgens and intrauterine environment in polycystic ovarian syndrome,*
  Andrea Dunaif, M.D., Northwestern University
- *Sex and gender factors in the pathophysiology of irritable bowel syndrome and interstitial cystitis,*
  Emeran Mayer, M.D., University of California–Los Angeles
- *Mechanisms underlying female urinary incontinence,*
  Jeanette Brown, M.D., University of California–San Francisco
- *Sex differences in pain sensitivity,*
  Joel Greenspan, Ph.D., University of Maryland
- *Birth, muscle injury and pelvic floor dysfunction,*
  John DeLancey, M.D., University of Michigan, Ann Arbor
- *Genetic and environmental origins of adverse pregnancy outcomes,*
  Gerald Schatten, Ph.D., University of Pittsburgh
- *Mechanisms by which drug transporters alter maternal and fetal drug exposure during pregnancy,*
  Jashvant Unadkat, Ph.D., University of Washington
- *Molecular and epidemiologic basis of acute and recurrent urinary tract infections in women,*
  Scott Hultgren, Ph.D., Washington University
- *Sex, stress and cocaine addiction,*
  Rajita Sinha, Ph.D., Yale University

▶ Theme: *Pharmacology of Antiepileptic and Psychotropic Medications during Pregnancy and Lactation*
Director: Zachary Stowe, M.D.
Emory University
Grant: P50MH068036

- *Administrative Core,* Zachary Stowe, M.D.
- *Epilepsy and Child Birth: Pharmacokinetics/Pharmacodymanic Modeling of Antiepileptic Drugs*, Page Pennell, M.D.
- *Mood and Anxiety Disorders in Pregnancy and Lactation: Pharmacokinetics/Pharmacodynamic Modeling of Psychotropic Medications,* Zachary Stowe, M.D.
- *Antiepileptic Drugs and Psychotropics in Pregnancy: Rodent Model,* Michael Owens, Ph.D.
- *Pharmacokinetics/Pharmacodynamic/Pharmacogenetic Modeling Core,* Lindsay Devane, Pharm.D.
- *Assay Core,* James Ritchie, Ph.D.

▶ Theme: *Role of Sex and Gender Differences in Substance Abuse Relapse*
Director: Kathleen Brady, M.D., Ph.D.
Medical University of South Carolina
Grant: P50DA016511

- *Administrative Core,* Kathleen Brady, M.D., Ph.D.
- *Sex Differences in an Animal Model of Relapse,* Ronald See, Ph.D.
- *Gender Difference in Response to Cues in Cocaine Dependence,* Kathleen Brady, M.D., Ph.D.
- *Gender, Menstrual Cycle, and Smoking Cue Reactivity,* Himanshu Upadhyaya, M.D.
- *Gender Influence on Preclinical Alcohol Pharmacology,* Lawrence Middaugh, Ph.D.

▶ Theme: *Genes, Androgens, and Intrauterine Environment in Polycystic Ovarian Syndrome*
Director: Andrea Dunaif, M.D.
Northwestern University
Grant: P50HD044405

- *Administrative Core,* Andrea Dunaif, M.D.
- *Gene, Intrauterine Environment, and Polycystic Ovarian Syndrome,* Andrea Dunaif, M.D.
- *Identification of Chromosome 19 Polycystic Ovarian Syndrome Susceptibility Gene,* Margrit Urbanek, Ph.D.
- *Fetal Androgen Induces Ovarian, LH, and B-Cell Defects*, David Abbott, Ph.D.
- *Neuroendocrine Actions of Androgens in Females,* Jon Levine, Ph.D.

▶ Theme: *Sex Differences in Pain Sensitivity*
Director: Joel Greenspan, Ph.D.
University of Maryland
Grant: P50AR049555

- *Administrative Core,* Joel Greenspan, Ph.D.
- *Ionic Mechanisms of Temporomandibular Joint Pain,* Michael Gold, Ph.D.
- *Central Nervous System Mechanisms for Gender Differences in Pain, and Their Relevance to Temporomandibular Disorder Pain,* Joel Greenspan, Ph.D.
- *Sex Differences in Visceral Pain: Influence of Gonadal Steroids,* Anne Murphy, Ph.D.

- Theme: *Sex and Gender Factors in the Pathophysiology of Irritable Bowel Syndrome and Interstitial Cystitis*
  Director: Emeran Mayer, M.D.
  University of California–Los Angeles
  Grant: P50DK064539

  - *Administrative Core,* Emeran Mayer, M.D.
  - *Sex Differences in the Colonic Responses to Stress: Role of Corticotropin-releasing Factor Pathways,* Yvette Tache, Ph.D.
  - *Sex Differences in Neuroendocrine and Immunologic Responses in Irritable Bowel Syndrome,* Lin Chang, M.D.
  - *Sex Differences in Central Stress Circuit Responsiveness in Irritable Bowel Syndrome and Interstitial Cystitis Patients,* Emeran Mayer, M.D.
  - *Sex Differences in Corticotropin-releasing Factor, Noradrenergic Function, and Oxytocin in Cats with Interstitial Cystitis,* Tony Buffington, D.V.M., Ph.D.
  - *Neuroendocrine Measures Core,* Gordon Ohning, M.D., Ph.D.

- Theme: *Mechanisms Underlying Female Urinary Incontinence*
  Director: Jeanette Brown, M.D.
  University of California–San Francisco
  Grant: P50DK064538

  - *Administrative Core,* Jeanette Brown, M.D.
  - *Diabetes: Lower Urinary Tract Dysfunction and Infections,* Jeanette Brown, M.D.
  - *Urinary Incontinence: Reproductive/Hormonal Risk Factors,* David Thom, M.D., Ph.D.
  - *Urinary Incontinence: Molecular Mechanism and Matrix-based Therapy,* Tom Lue, M.D.
  - *Biostatistic Core,* Eric Vittinghoff, Ph.D.

- Theme: *Birth, Muscle Injury, and Pelvic Floor Dysfunction*
  Director: John DeLancey, M.D.
  University of Michigan, Ann Arbor
  Grant: P50HD044406

  - *Administrative, Human Subjects, and Biostatistics Core,* John DeLancey, M.D.
  - *Pelvic Floor Biomechanics and Birth-related Injury,* James Ashton-Miller, Ph.D.
  - *Selection Criteria for Pelvic Muscle Therapy in Stress Urinary Incontinence,* Janis Miller, R.N., Ph.D.
  - *Which Pelvic Floor Defects Cause Stress Incontinence?* John DeLancey, M.D.
  - *Measurement and Imaging Core,* James Ashton-Miller, Ph.D.

▶ Theme: *Genetic and Environmental Origins of Adverse Pregnancy Outcomes*
Director: Gerald Schatten, Ph.D.
University of Pittsburgh
Grant: P50ES012359

- *Adminstrative Core*, Gerald Schatten, Ph.D.
- *Maternal and Fetal Consequences of Tobacco Smoke Exposure,* Julie DeLoia, Ph.D.
- *Epigenetic, Genetic, and Environmental Regulation of Pregnancy in Primates,* Gerald Schatten, Ph.D.
- *Pregnancy Loss: Genomic Imprinting of Skewed X-inactivation,* J. Richard Chaillet, M.D., Ph.D.
- *Imaging Core,* Eric Ahrens, Ph.D.
- *Pregnancy Core,* Laura Hewitson, Ph.D.

▶ Theme: *Mechanisms by which Drug Transporters Alter Maternal and Fetal Drug Exposure during Pregnancy*
Director: Jashvant Unadkat, Ph.D.
University of Washington
Grant: P50HD044404

- *Administrative Core,* Jashvant Unadkat, Ph.D.
- *Changes in Hepatic and Intestinal P-glycoprotein and CYP3A Activity during Pregnancy,* Jashvant Unadkat, Ph.D.
- *The Breast Cancer Resistance Protein in Pregnancy: Activity, Expression, and Regulation,* Qingcheng Mao, Ph.D.
- *Role of OCT3 in Drug Pharmacokinetics during Pregnancy,* Vadivel Ganapathy, Ph.D.

▶ Theme: *Molecular and Epidemiologic Basis of Acute and Recurrent Urinary Tract Infections in Women*
Director: Scott Hultgren, Ph.D.
Washington University
Grant: P50DK064540

- *Administrative Core*, Scott Hultgren, Ph.D.
- *Host-Pathogen Interactions in Acute and Chronic Urinary Tract Infections,* Scott Hultgren, Ph.D.
- *Microbial Reservoirs and Urinary Tract Infections in Women*, Thomas Hooton, M.D.
- *Functional Genomic Studies of Urinary Tract Infections,* Jeffery Gordon, M.D.

▶ Theme: *Sex, Stress, and Cocaine Addiction*
Director: Rajita Sinha, Ph.D.
Yale University
Grant: P50DA016556

- *Scientific and Administrative Core,* Rajita Sinha, Ph.D.
- *Molecular Basis of Sex Differences in Cocaine Addiction,* Jane Taylor, Ph.D., Marina Picciotto, Ph.D.
- *Early Life Stress and Vulnerability to Cocaine Addiction,* Therese Kosten, Ph.D.
- *Sex Differences in Stress-related Cocaine Relapse,* Rajita Sinha, Ph.D.
- *Functional Magnetic Resonance Imaging of Gender and Stress Response in Cocaine Dependence,* Thomas Kosten, M.D.

▶ Title: *Governors' Spouses Initiative to Curb Underage Drinking* NIAAA
Award: $100,000
Contact: Suzanne Medgyesi-Mitschang, Ph.D.

The Office of Research on Women's Health (ORWH) provided $100,000 to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to support the "Governors' Spouses Initiative to Curb Underage Drinking." The Leadership to Keep Children Alcohol Free was established in 1999 by NIAAA and the Robert Wood Johnson Foundation (RWJF) in response to the need for leadership in the prevention of alcohol consumption by children aged 9 to 15. Based on the best alcohol research and led by 33 governors' spouses, this initiative has also been joined by five additional federal funding partners including ORWH, the National Center on Minority Health and Health Disparities, the Office of Juvenile Justice and Delinquency Prevention, the Substance Abuse and Mental Health Services Administration, and the National Highway Traffic Safety Administration, as well as several national organizations with a shared interest in children's health. The goals of this unique collaboration of Governors' spouses, federal partners, and national organizations are:

- To raise public awareness about the serious issue of alcohol use by children, and
- To mobilize prevention efforts across the country.

Overall, the initiative has made great strides on a number of fronts. Professionals in the field report that the initiative has re-energized the field of underage drinking prevention across the country. It is also fostering new collaborations among researchers and practitioners. Its message is also being heeded as state legislatures create study groups (Georgia and North Carolina) and to propose legislation related to curtailing alcohol abuse (Oregon, Ohio, Alaska, Hawaii).

The following are highlights of the initiative's accomplishments to date:

- Number of participating governors spouses has increased to 33 current spouses and three emeritus spouses (Michele Ridge, Sue Ann Thompson, Theresa Racicot). Further recruitment continues with the hope of engaging all 50 states in the initiative, including Puerto Rico.
- Current and former governors' spouses are actively engaged in educating the public, policy makers, and youth in their states and nationally through speaking engagements, Op Ed pieces, production of PSAs and videos, poster contests, policy briefings for state legislators and other public officials, alcohol education and prevention conferences, involving youth in prevention efforts, and facilitating collaboration across state and local agencies.
- The membership of the Executive Working Group increased to 28 national organizations, including several national organizations targeting the concerns of diverse cultural and ethnic groups.
- Three publications in English and Spanish were developed and distributed nationally: 1) *Keep Kids Alcohol Free: Strategies for Action (Mantengamos a los ninos libres de alcohol: Estrategias para entrar en accion)*, 2) *How Does Alcohol Affect the World of a Child? (? De que Manera Afecta el Alcohol el Mundo de un Nino?)*, and 3) *Make a difference: Talk to you Child about Alcohol (Haga La Diferencia: Hable con sus Hijos Sobre el Uso del Alcohol)*.
- A first series of ten, and a second series of seven, one-page summaries of studies with relevance to early alcohol use were developed, entitled "Science, Kids, and Alcohol: Research Briefs." Topics covered include the effect of alcohol dependence on brain activity, youth drinking patterns by sex, race and ethnicity, and proven environmental strategies for reducing underage drinking.
- More than 400,000 publication have been ordered and distributed, with 76,605 documents to 47 states and eight foreign countries in the last quarter alone (January through March 2002).

- In October 2001 the leadership's new website was launched and within the first quarter the site had over 11,000 visitors (*www.leadership@alcoholfreechildren.org*).
- The Second National Conference entitled "The Solution is Within Our Reach: Working Together to Keep Children Alcohol Free," was held January 10-11, 2002, in Washington, DC, and attracted more than 300 participants representing 49 states, Puerto Rico, and the District of Columbia. This represented twice as many states and participants than had attended the first national conference in March 2000.

▶ Title: *Curriculum for Colleges of Pharmacy*
Award: $20,000
Contact: Deborah R. Maiese

The Office of Research on Women's Health agrees to transfer $20,000 to Health Resources and Services Administration MCHB to support the work of the American Association of Colleges of Pharmacy, to conduct analytical activities needed to:

- better understand the degree to which women's health issues are addressed within the pharmacy curriculum;
- develop a curricular framework (content and desired student outcomes) on women's health; and
- develop educational resources (instructional materials and assessment tools) to facilitate the incorporation of these outcomes and content into the professional degree program in pharmacy, continuing professional development programs for pharmacists, and interdisciplinary health professions education.

A three-part strategy will be as follows:

PART I: Survey to assess curricular coverage of women's health in colleges and schools of pharmacy

PART II: Analysis of adequacy of existing evidence-based resources and teaching materials; and

PART III: Modular development of new materials for teaching health professions students and practitioners, including interdisciplinary education and practice activities.

▶ Title: *Osteoarthritis Initiative* NIAMS
Award: $800,000
Contact: Steve Katz, M.D.

Osteoarthritis (OA), the most common form of arthritis, is a painful joint disease marked by the gradual wearing away of cartilage that cushions and protects the bones. More than 20 million people in the United States have this disease, which mostly occurs in older people but can affect younger men and women. The knee is among the most commonly affected joints. There are currently no treatments that change the course of the disease, and clinical trials for prospective therapies are long, difficult, and expensive.

The Osteoarthritis Initiative (OAI) is a collaboration between the federal National Institutes of Health and pharmaceutical companies to pool funds and expertise for a public repository of OA patient data, radiological information, and biological specimens. Scientists will be able to use this public resource to test much-needed biochemical and imaging markers of disease progression, to further the development of OA drugs, and to improve public health. Neither the federal nor private sector alone would be able to develop such a resource.

Scientists, health care providers, and drug companies need biochemical and imaging markers of how OA progresses in order to diagnose, monitor, develop, and implement treatments for this condition. Current methods of evaluating disease progression, including x-rays and blood tests, are not accurate enough to be used in clinical trials of potential treatments. The data and specimen repository will establish standards of disease progression against which potential biochemical and imaging markers can be evaluated and clinical trials of promising agents will be facilitated.

NIH solicited and reviewed applications and awarded research contracts for four to six clinical centers and one coordinating center to create the repository. Following participant recruitment, data and specimens will be collected over 5 to 7 years from approximately 5,000 people at high risk for OA. In addition to conducting a longitudinal natural history study, scientists will collect blood and carry out imaging studies of the hips, hands, and knees throughout the study.

The initiative is coordinated by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Aging, with additional support from the National Institute of Dental and Craniofacial Research, the Office of Research on Women's Health, the National Center on Minority Health and Health Disparities, the National Center for Complementary and Alternative Medicine, the National Center for Research Resources, the Office of Technology Transfer, the Office of the General Counsel, and the Office of Science Policy, all parts of NIH. These NIH institutes and offices form the public part of the partnership. The private-sector partners are GlaxoSmithKline, Merck, Novartis, and Pfizer, U.S. Department of Health and Human Services' component involved is the Center for Drug Evaluation and Research of the Food and Drug Administration. Funding for OAI is being managed by the Foundation for the National Institutes of Health, Inc.

*APPENDIX C*

# *Office of Research on Women's Health Conferences and Workshops*

## ORWH-SUPPORTED CONFERENCES AND WORKSHOPS, FISCAL YEAR 2001

▶ Title: *International Conference on Cervical Cancer* NCI
Award: $5,000
Contact: Edward Trimble, M.D., M.P.H.

Funding of this project supported the International Conference on Cervical Cancer hosted by the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute. The purpose of the conference was to provide conference participants with a summary of the perceived deficiencies in our knowledge regarding cervical cancer, outline a series of investigations, and list the important discoveries.

▶ Title: *Older Adults Health Information and the World Wide Web* NIA
Award: $5,000
Contact: Daniel Berch, Ph.D.

Funding of this project was used to support the cost of Older Adults Health Information and the World Wide Web Conference at the National Institutes of Health on February 26-28, 2001. The 3-day conference brought together leaders in the fields of technology, aging, policy, and health.

The goals of the conference were:

- Identify the basic applied cognitive and behavioral research being conducted to increase the use of computers and the World Wide Web (WWW) by older adults, their care givers, and health service providers;
- Identify key impediments that older adults face as they use the WWW to access health information; and present possible solutions to these impediments through a cross-fertilization of ideas between researchers in cognition, aging, computer use and design, and health information providers;
- Address current issues on presenting quality health information on the WWW to older adults and their care givers;
- Increase knowledge of how to develop local and regional applications of new research findings'. This goal is to be addressed in the Day One workshops on topics such as accessing health websites for older adults, designing health websites for older adults, and educating older adults about how to use websites to gather health information.

▶ Title: *Federation of American Society for Experimental Biology Research Conference on Autoimmunity* NIAID
Award: $5,000
Contact: Larry Prograis, M.D.

Funding of this project was used to support the cost of the Federation of American Society for Experimental Biology Research Conference on Autoimmunity. The conference will focus on relevant autoimmune diseases including diabetes, multiple sclerosis, lupus, arthritis, myasthenia gravis, myocarditis, and other autoimmune disorders. Strengths of this meeting include the need to bring investigators together because the autoimmunity field is rapidly changing, and the outstanding caliber of the organizers. The meeting focused on the latest developments in the field of autoimmunity; especially how recent advances in basic immunology and cell biology have influenced the field of autoimmunity.

The major topics for the conference are:

- Autoantigen Responses in Autoimmunity
- Central and Peripheral Tolerance
- The Role of Infection in Autoimmunity
- B Cell Activation and Autoimmunity
- Mechanism of Peripheral Counter-regulation
- Antigen-presenting Cells in Shaping Pathogenic T-Cell Repertoire
- The Role of the Innate Immune System in Autoimmunity
- Cytokines and Autoimmunity, and
- Immunotheraphy

The conference presented a comprehensive view of basic immunological mechanism related to autoimmunity, as well as mechanism involved in the autoimmune process, and immune intervention.

▶ Title: *Chronic Fatigue Syndrome Conference* NIAID
Award: $37,500
Contact: Keith Lamirande

Funding of this project was used to support the cost of the Chronic Fatigue Syndrome Conference. The conference will be devoted to seven topical areas, including: 1) neuroendocrinology, 2) cognition, 3) chronic pain, 4) sleep, 5) immunology, 6) orthostatic intolerance and neurally mediated hypotension, and 7) fatigue, functional status, and disability.

The goals for this meeting were to:

- Focus on chronic fatigue syndrome (CFS) research areas in which information is both most mature and exciting;
- Summarize what we know and identify important gaps in our knowledge;
- Garner the perspective of expert investigators not currently working on the problem of CFS; and
- Identify expert investigators who might be attracted to study CFS as a clinical problem.

▶ Title: *Health Disparities in Arthritis and Musculoskeletal and Skins Diseases – A Scientific Conference* NIAMS
Award: $5,000
Contact: Reva Lawrence

Funding of this project will be used to support NIAMS Health Disparities Conference. The purpose of this conference was to:

- Highlight current knowledge on genetic and environmental factors that play a role in the marked differences in the prevalence, morbidity, and disability associated with specific rheumatic, musculoskeletal, and skin conditions in various populations;
- Identify challenges and emerging opportunities for research in these areas; and
- Highlight intervention strategies that could provide models for reducing these disparities.

▶ Title: *2001 ADD Health Users Conference and Skins Diseases – A Scientific Conference* NICHD
Award: $5,000
Contact: Christine Bachrach, Ph.D.

Funding of this project will be used to support the 2001 ADD Health Users Conference. The purpose of this conference is to draw together users of the ADD Health data to discuss research goals, findings, and issues on topics, including:

- Mental Health
- Substance Use
- Violence
- Sexual Behavior
- Measurement and Modeling
- The Use of ADD Health Special Design Feature
- Researchers Information Sharing, Their Findings, and Their Methodological Approaches

▶ Title: *6th International Conference on the Extracellular Matrix of the Female Reproductive Tract* NICHD
Award: $5,000
Contact: Phyllis Leppert, M.D.

Funding of this project was used to support the 6th International Conference on the Extracellular Matrix of the Female Reproductive Tract. The conference focused on the uniqueness of the adult female reproductive tract, from ovulation to gestation, parturition, involution and through menopause, and how the extracellular matrix plays a critical role in physiology.

- Title: *Endometriosis: Emerging and Intervention Strategies* NICHD
  Award: $5,000
  Contact: Estella Parrott, M.D., M.P.H.

  Funding of this project was used to support the "Endometriosis: Emerging and Intervention Strategies" workshop. The purpose of the workshop is to formulate a framework for a basic science, translational, and clinical research agenda on endometriosis. This workshop brought together a multidisciplinary group of clinicians, endocrinologists, immunologists, reproductive and developmental biology investigators, and other experts in the field to examine issues critical to endometriosis.

  The meeting featured scientific presentations that addressed the current state of knowledge, recent findings, emerging issues, and continuing gaps in knowledge, which served as a catalyst for discussion during the final session on future research directions.

- Title: *Clinical Pharmacology during Pregnancy: Addressing Clinical Needs through Science* FDA
  Award: $5,000
  Contact: Margaret Ann Miller, Ph.D., DBAT

  Funding of this project supported the Clinical Pharmacology during Pregnancy: Addressing Clinical Needs through Science Conference. The purpose of the conference was to raise awareness of the need for more information on the proper use and effectiveness of prescription medications in pregnant women. The goals of the conference were:
  - To summarize the state of knowledge regarding clinical pharmacology in pregnancy;
  - To raise awareness among clinician researchers and leaders about the need for clinical research and collaboration in this area; and
  - To garner support for such research from health advocacy groups and other.

- Title: *The American Society for Cell Biology Meeting* NIEHS
  Award: $5,000
  Contact: Elizabeth Marincola

  Funds for this project was used to support the American Society for Cell Biology career programs for the 40th anniversary meeting. Topics of the meeting focused on:
  - Negotiation Strategies
  - Women in Cell Biology Committees
  - The Unwritten Rules for Advancing Your Career
  - Transitions to Independence: A Discussion of Training in Cell Biology for Today's Job Market

- Title: *The Science of Mind-Body Interactions Conference* NIMH
  Award: $5,000
  Contact: Dr. Robert Roser

  Funding for this project was used to support the Science of Mind-Body Interactions Conference. This was an interactive conference to discuss scientific topics that include addressing various cutting-edge questions and answers in mind-body science. Discussions included the exploration of the latest advances and emerging concerns about mind-body connections.

▶ Title: *Using Research to Inform Patients of Breast Cancer Surgery Options* AHRQ
Award: $5,000
Contact: Cindy Lunley

Funding of this project supported the Using Research to Inform Patients of Breast Cancer Conference. The conference is part of a new project of the National Center for Policy Research for Women and Families, which is designed to ensure that breast cancer patients and their health care providers are aware that research indicates that breast-conserving surgery, combined with radiation, is safe and effective for the treatment of most women with early-stage breast cancer.

The purpose of the conference is to bring clinicians, advocates, and consumes together to develop several strategies to improve patient's access to accurate information, so that women with early-stage breast cancer and ductal carcinoma *in situ* receive research-based information that fully informs them of their surgical options.

▶ Title: *The National Lesbian Health Conference 2001: Challenges of the New Millennium* OWH/DHHS
Award: $5,000
Contact: Susanne Haynes, Ph.D.

Funding for this conference will be used to support the National Lesbian Health Conference 2001: Challenges of the New Millennium. Conference topics included:

- Cancer and Tobacco Use
- Substance Abuse: Prevention and Treatment
- Mental Health: Trauma Recovery, Domestic Violence, and Hate Crimes
- Wellness and Nutrition Including Weight, Exercise, and Alternative Medicines
- STDs and HIV/AIDS
- Life Space Issues: Youth, Mid-Life, Seniors
- Disability/Impairments/Immune Disorders
- Family Issues: Maybe Baby, Insemination, Parenting
- Access to Care
- Underserved Populations: Racial and Ethnic Minorities, Bisexual and Transgendered, and Rural

▶ Title: *A Generational Journey: Women Carrying the Vision; Common Issues, United Voices Conference* SAMHSA
Award: $7,500
Contact: Duiona Baker

Funding for this project was used to support A Generational Journey: Women Carrying the Vision; Common Issues, United Voices at the Substance Abuse and Mental Health Administration's 3rd National Conference on Women, on June 18-21, 2001.

- Title: *Treatment of Salivary Gland Disorders: Alternative Approaches, An International Conference* NIDCR
  Award: $5,000
  Contact: Guo Zhang, Ph.D.

  Funding for this project will be used to support the Treatment of Salivary Gland Disorders: Alternative Approaches, An International Conference.

- Title: *Native American Cancer Survivors/Thrivers Conference* OMH/DHHS
  Award: $5,000
  Contact: Linda Burhabnsstipanov, M.S.P.H., Ph.D., CHES

  Funding for this project will be used to support the Native American Cancer Survivors/Thrivers Conference. The 2-day conference included:
  - The National Native American Cancer Survivors' Support Network
  - Dealing with Cancer Pain – Traditional and Contemporary Adaptations
  - Traditional Indian Medicine and Healing from Cancer
  - Physical Activity and Therapy and Recovery from Cancer and Cancer Treatments
  - Update on Cancer Treatments
  - Palliative Care and End-of-life Issues.

- Title: *Concepts and Strategies to Actively Monitor the Risk of Medication in Pregnancy: Enhancing Post-marketing Surveillance* CDC
  Award: $5,000
  Contact: Janet D. Cragan, M.D.

  Funding was used to support the Centers for Disease Control and Prevention workshop on post-marketing surveillance.

- Title: *Dietary Supplement Use in Women of Reproductive Age: What Do We Know?* NICHD
  Award: $5,000
  Contact: Daniel Raiten

  Funding for this project was used to support a 2-day conference/workshop involving 15 to 20 scientists to present current data and research in both U.S. and international populations. The goal of the conference is to develop a focused research program.

- Title: *Intercultural Cancer Council 8th Biennial Symposium* NCI
  Award: $5,000
  Contact: Dr. Diana Jeffrey

  Funding for this project was used to support the Intercultural Cancer Council's 8th Biennial Symposium.

▶ Title: *Stigma and Global Health: Developing a Research Agenda* FIC
Award: $5,000
Contact: Karen Hoffman

Funding for this project was used to support the Stigma and Global Health: Developing a Research Agenda international conference.

▶ Title: *Native American Cancer Survivors/Thrivers Conference* OMH/DHHS
Award: $5,000
Contact: Linda Burhansstipanov, M.S.P.H., Ph.D., CHES

Funding for this project was used to support the Native American Cancer Survivors/Thrivers Conference. The purpose of the conference was to provide a forum for Native American cancer survivors to address issues related to cancer treatments, quality of life, and recovery. Likewise, family members and loved ones of cancer survivors will have the opportunity to discuss support issues, perceived personal cancer risks (e.g., first-degree relatives), and long-term support-coping strategies.

▶ Title: *American Diabetes Association Session "Do Herbal Products Affect Quality of Life Issues for Women?"* ODS
Award: $5,000
Contact: Dr. Rebecca Costello

Funding for this conference was used to support the Office of Dietary Supplements/American Diabetes Association conference. The conference brought together experts in the field of botanicals to present current safety and efficacy information on herbs for women's quality-of-life issues, including menopause, premenstrual syndrome, depression, and dementia.

▶ Title: *The Role of Innate Immunity in the Etiopathology of Autoimmune Diseases* NIAID
Award: $5,000
Contact: Belinda Ash-Shaheed

This program brought together researchers working in innate immunity and autoimmune diseases to identify new research opportunities regarding the role of innate immunity in the etiopathology of autoimmune diseases.

▶ Title: *Animal Models of Autoimmune Diseases – Are Current Models Adequate?* NIAID
Award: $5,000
Contact: Belinda Ash-Shaheed

This meeting brought together experts in animal models and clinical researchers to explore the strengths and weaknesses of each animal model, and determine if other models can and need to be developed to efficiently translate animal studies to humans.

- Title: *Third International Conference on Women's Health* NCI
  Award: $5,000
  Contact: Dr. Sheila Zahm

  This scientific program will include occupational asthma, women's work and health, musculoskeletal disorders, use and ethics of biomarkers in occupational health studies, and job insecurity and precarious employment.

- Title: *Differential Drug Use, HIV/AIDS, and Related Health Outcomes among Racial and Ethnic Populations* NIDA
  Award: $5,000
  Contact: Dr. Dionne J. Jones

  The goal is to critically examine the current knowledge about drug abuse, HIV/AIDS and associated social, medical, and health consequences within and across racial and ethnic minority populations. The workshop will focus on gender issues, women's health, and research.

## ORWH-SUPPORTED CONFERENCES AND WORKSHOPS, FISCAL YEAR 2002

- Title: *Endometrial Cancer Biology Workshop* NCI
  Award: $2,500
  Contact: Edward Trimble, M.D., M.P.H.

  Funding of this project supported the Endometrial Cancer Biology Workshop hosted by the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, held April 5, 2002 in San Francisco, CA. The purpose of the conference was to provide conference participants with a summary of the perceived deficiencies in our knowledge regarding endometrial cancer biology, outline a series of investigations, and list the important discoveries. Topics to be covered included hormonal biology, molecular markers, models of carcinogenesis, and access to specimens.

- Title: *Joint and Muscle Dysfunction of the Temporomandibular Joint* NIDCR
  Award: $5,000 (1R 13 DE014542)
  Contact: Norm Braveman, Ph.D.

  This conference, held May 6-8, 2002 in Bethesda, MD, was the second Scientific Meeting of the TMJ Association. Major topic areas addressed included: osteoarthritis and inflammatory-immune processes in joints; cartilage degradation (mechanics/biochemistry/metabolism); microvascular structure and function of synovial joints, and mechanisms and implications of angiogenesis for arthritis; clinical symptoms and current and emerging therapeutic approaches; and skeletal muscles and the jaw.

- Title: *2nd International Cervical Cancer Meeting* NCI
  Award: $5,000
  Contact: Ted Trimble, M.D.

  The Second International Cervical Cancer Meeting was held in Houston, TX, April 11-14, 2002. The conference is an interdisciplinary conference focused on innovative research in cervical cancer. The 1st International Conference on Cervical Cancer, held in 2001, was organized by the same committee and was immensely successful. The 2nd International Conference touched upon subjects not addressed in the first conference including: decision science, behavioral science, optical imaging, diagnostic imaging, chemoprevention trials, innovative treatments for invasive cancer, innovative advances in the biology of cervical cancer, the role of nursing in cervical cancer prevention and treatment, and grant writing. Progress in this area will rely on the synthesis of knowledge from many fields including clinical medicine, epidemiology, fundamental optical science, biomedical engineering, medical imaging, and device technology. This conference was a vehicle facilitating the interdisciplinary interaction necessary to see ideas brought to fruition as research proposals.

- Title: *Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century* NIDDK
  Award: $5,000
  Contact: Ron Margolis, Ph.D.

  The conference took place April 8-9, 2002, in Bethesda, MD. Asymptomatic primary hyperparathyroidism has a particularly high prevalence among women. In 1990 NIDDK held a Consensus Development Conference after which a consensus statement was issued (*http://odp.od.nih.gov/consensus/cons/082/082_intro.htm*). After 11 years, there is a need to reassess the results of that statement as it has been translated into clinical practice. In addition, several basic science advances have occurred in the years since 1990, with important implications for treatment of the disease. The workshop has been designed to consider progress in the disease since 1990. Major topics to be addressed include: differential diagnosis of hypercalcemia, the clinical spectrum of primary hyperparathyroidism, surgery in primary hyperparathyroidism, and medical management of primary hyperparathyroidism.

- Title: *Workshop in Pelvic Pain* NICHD
  Award: $5,000
  Contact: Estella Parrott, M.D., M.P.H.

  This conference, held April 8-9, 2002, in Bethesda, MD, brought together a broad spectrum of experts, including clinicians and basic and translational scientists, to define a multidisciplinary framework for developing a research agenda in chronic pelvic pain in women by addressing the current state of knowledge, identifying emerging issues or continuing gaps in knowledge, and exploring future opportunities for research. To address the full spectrum of research from basic science to clinical applications, the meeting examined the diverse components of pain syndromes to discern their broad systemic effects and specific impact on the reproductive system.

- Title: *Systemic Lupus Erythematosus: Targets for New Therapeutics* NIAMS
  Award: $5,000
  Contact: Elizabeth Gretz, Ph.D.

  Funding for a conference entitled "Targets for New Therapeutics for Systemic Lupus Erythematosus," is a subject of high interest to researchers who study systemic lupus. Advances in basic research have made it possible to envision the possibility of new approaches in immune-modulating therapy for lupus, but actual drug development is fraught with problems, some of which might be addressed by bringing together, in one forum, those with high interest in this field.

▶ Title: *Minority Trainee Research Forum* NIDDK
Award: $5,000
Contact: Rose Pruitt, M.B.A.

The Minority Trainee Research Forum was held in San Diego, CA, March 16-18, 2002. This NIH-funded scientific meeting showcased underrepresented minority trainees in the biomedical pipeline who are committed to a research career, and who have engaged in serious research. The forum selected 72 winners from a national abstract competition: 12 postdoctoral trainees, 12 Ph.D. trainees, 12 M.D./Ph.D. trainees, 12 M.D. trainees, 12 college trainees, and 12 high school trainees. The Minority Trainee Research Forum's (R13 DK 59645) goals are to enact a comprehensive scientific meeting for trainees to showcase their biomedical research and focuses on career opportunities; to establish a national registry of trainees in the pipeline from which academia, industry, and NIH can draw to increase initiatives designed to eliminate health disparities; and to offer long-term resources to attendees and track the participants through the biomedical pipeline.

▶ Title: *Coming Face to Face with the Impact of Gender on Medical Care*
Award: N/A
Contact: Marianne Legato, M.D.

ORWH and the Partnership for Women's Health at Columbia University sponsored the Third Annual Conference on Gender-Specific Medicine: Coming Face to Face with the Impact of Gender on Medical Care, at the U.S. Chamber of Commerce in Washington, DC on April 22-23, 2002. The goal of this conference was to provide an appreciation of gender differences across a variety of disease states and to review current options for treatment to an audience of primary care physicians, researchers, and academic faculty.

▶ Title: *ADD Health Users Conference* NICHD
Award: $5,000
Contact: Christine Bachrach, Ph.D.

Funds were used to support travel to the workshop for students and postdocs who presented papers. There were 34 papers for the 2002 Workshop (July 24-25), and seven to eight methodological sessions planned. There were 21 requests for travel stipends. The papers focused on teen health and risk behaviors. Most included both males and females, but some specifically focused on girls. Last year the conference drew 200 people and, based on evaluation forms and comments from participants, was highly successful. The conference draws not only people who are working with the ADD Health data but also a large contingent from NIH institutes and DHHS offices such as OPA and ASPE.

▶ Title: *Perinatal Mood Disorders* NIMH
Award: $5,000
Contact: Mary Blehar, Ph.D.

This meeting focused on what is known about the etiology, biology of treatment, and services delivery for antenatal and postnatal mood disorders. In all presentations, emphasis was placed on the research and clinical evidence in relation to severe mood disorders, including postpartum psychosis and less severe outpatient mood disorders.

- Title: *National Lesbian Health Conference 2002: Healing Works* OWS/DHHS
  Award: $5,000
  Contact: Suzanne Haynes

  The National Lesbian Health Conference (NLHC) brought together more than 350 healthcare providers, medial and social researchers, care givers, clients, grassroots activists, organizers, public advocates, and federal and local government officials from across the country to exchange information about all aspects of lesbian health. The goals of NLHC 2002: Healing Works! was to:
  - Connect advocates, providers, researchers, policy makers, health educators, clients, and care givers for the purpose of networking, information sharing, and support
  - Increase inclusion of, and service to, underserved populations within our own community, including people of color, disabled, economically disadvantaged, seniors, youth, rural, and incarcerated.
  - Disseminate information on all aspects of lesbian health, including access to care, cancer, cardiovascular health, life span issues, mental health, STDs/HIV and AIDS, family and reproductive issues, substance abuse, provider education, current research, complimentary and alternative health care, and healthy living strategies
  - Increase lesbian health services, research, programming, and organizations
  - Increase awareness of lesbian health issues among policymakers, the media, the healthcare community, the LGBT community, and the general public

- Title: *International Workshop on Autoantibodies as Predictors of Diseases*
  Award: $5,000
  Contact: John P. Ridge, Ph.D.

  This meeting gathered clinicians and basic scientists that deal with a focused group of autoimmune diseases to discuss the use of autoantibodies as predictive markers of disease. While the practical value of autoantibodies has been realized in some clinical conditions, little is known in the majority of diseases. This meeting addressed methodologies for the standardization and validation of assays that would allow their use as a predictive diagnostic tool. Development of high throughput methodologies for those assays was also discussed. Many rare autoimmune diseases (<200,00 affected persons in the United States) are characterized by the development of autoantibodies. These diseases provide a unique challenge for performing preventive clinical trials.

- Title: *The Eighth Annual John Diggs Lecture*
  Award: $1,500
  Contact: Sharon H. Jackson, M.D.

  The Eighth Annual John Diggs Lecture, sponsored by the National Institutes of Health (NIH) Black Scientists Association (BSA), was delivered by Olufunmilayo F. Olopade, M.B., B.S., FACP, Associate Professor, Department of Medicine and Committee on Genetics, Director, Center for Clinical Cancer Genetics, The University of Chicago Medical Center. The Office of Research on Women's Health has been an cosponsor of several past NIH/BSA-sponsored events and offered financial assistance for roundtrip airfare, 2 nights lodging, and an honorarium for Dr. Olopade.

# APPENDIX D

# *Office of Research on Women's Health Women's Health Seminar Series*

***Incontinence in Women***
***March 1, 2001***

*Overview: Etiology and Epidemiology*
Jeanette S. Brown, M.D.
University of California–San Francisco

*Diagnosis of Incontinence: Techniques and Procedures*
O. Lenaine Westney, M.D.
The University of Texas Health Science Center at Houston

*What We Know about Surgery for Stress Incontinence*
Veronica Mallett, M.D.
Oakwood Hospital, Dearborn, MI

*Behavioral and Medical Treatment of Incontinence*
Kathryn Burgio, R.N., Ph.D.
University of Alabama at Birmingham

***Women and Addictive Behaviors***
***June 7, 2001***

*Women and Drug Abuse: Prevalence, Problems, and Treatments*
Mary E. (Betsy) McCaul, Ph.D.
The Johns Hopkins University

*Women and Nicotine*
Dorothy K. Hatsukami, Ph.D.
University of Minnesota Medical School

*Illicit Drug Abuse in Pregnancy*
Loretta P. Finnegan, M.D.
NIH Office of Research on Women's Health

*Panel Moderator*
Cheryl A. Kitt, Ph.D.
National Institute of Neurological Disorders and Stroke

***Violence against Women***
***September 6, 2001***

*Violence against Women: An Overview*
Ileana Arias, Ph.D.
The University of Georgia

*The Impact of Domestic Violence on Children and Families*
Jacquelyn C. Campbell, Ph.D., R.N., F.A.A.N.
The Johns Hopkins School of Nursing

*Advocacy and Community-based Initiatives*
Michaele Cohen
Maryland Network Against Domestic Violence

*Judicial Perspectives on Domestic Violence*
Judge Ronald B. Adrine
Cleveland Municipal Court

***Successful Aging***
***December 6, 2001***

*New Thoughts on Old Minds*
Laura L. Carstensen, Ph.D.
Stanford University

*Differential Changes in Endocrine Systems with Aging*
Nanette Santoro, M.D.
Albert Einstein College of Medicine

*Power Aging: Eating and Moving for Optimal Aging*
Pamela Peeke, M.D., M.P.H.
University of Maryland–Baltimore

*Thoughts on Successful Aging*
Thomas E. Malone, Ph.D.
Retired from the National Institutes of Health

*Aging with Attitude*
Gloria E. Sarto, M.D., Ph.D.
University of Wisconsin Center for Women's Health

### *Anxiety and Post-traumatic Stress*
### *February 19, 2002*

*The Underlying Mechanisms of Anxiety and Post-traumatic Stress*
Dennis Charney, M.D.
National Institute of Mental Health

*Risk and Resilience in the Face of Disaster*
Carol S. North, M.D., M.P.E.
Washington University School of Medicine

*Coping with Anxiety and Fear*
Sally Winston, Ph.D.
The Anxiety and Stress Disorders Institute of Maryland, LLP

### *Promoting Healthy Living: Diet, Fat, and Cholesterol*
### *June 6, 2002*

*Cholesterol: The Good, the Bad....*
Frank M. Sacks, M.D.
Harvard University

*Diet: To Diet or Not To Diet*
Gary D. Foster, Ph.D.
University of Pennsylvania School of Medicine

*Facts About Fats*
Pamela M. Peeke, M.D., M.P.H.
University of Maryland

### *Promoting Healthy Living: Nutrition, Physical Activity, and Dietary Supplements*
### *September 10, 2002*

*Good Nutritional Practice*
Sachiko T. St. Jeor, Ph.D., R.D.
University of Nevada School of Medicine

*Diet and Activities to a Healthy Life*
Samuel Klein, M.D.
Washington University School of Medicine

*Dietary Supplements: What to Look For*
Brian Sanderoff, Ph.D.
University of Maryland College of Pharmacy

# *Acronyms*

## Acronyms Used in This Report

| | |
|---|---|
| ACRWH | Advisory Committee on Research on Women's Health |
| CC | Clinical Center |
| CCRWH | Coordinating Committee on Research on Women's Health |
| DCRT | Division of Computer Research and Technology |
| DHHS | Department of Health and Human Services |
| DRG | Division of Research Grants |
| FDA | Food and Drug Administration |
| FIC | Fogarty International Center |
| GAO | U.S. General Accounting Office |
| HRSA | Health Resources and Services Administration |
| IC | Institutes and Centers of the National Institutes of Health |
| IOM | Institute of Medicine |
| NCHGR | National Center for Human Genome Research |
| NCCAM | National Center for Complementary and Alternative Medicine |
| NCI | National Cancer Institute |
| NCRR | National Center for Research Resources |
| NEI | National Eye Institute |
| NHLBI | National Heart, Lung, and Blood Institute |
| NHGRI | National Human Genome Research Institute |
| NIA | National Institute on Aging |
| NIAAA | National Institute on Alcohol Abuse and Alcoholism |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIAMS | National Institute of Arthritis and Musculoskeletal and Skin Diseases |
| NICHD | National Institute of Child Health and Human Development |
| NIDA | National Institute on Drug Abuse |
| NIDCD | National Institute on Deafness and Other Communication Disorders |
| NIDCR | National Institute of Dental and Craniofacial Research |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| NIEHS | National Institute of Environmental Health Sciences |
| NIGMS | National Institute of General Medical Sciences |
| NIJ | National Institute of Justice |
| NIMH | National Institute of Mental Health |
| NINDS | National Institute of Neurological Disorders and Stroke |
| NINR | National Institute of Nursing Research |
| NLM | National Library of Medicine |
| OAM | Office of Alternative Medicine |
| OAR | Office of AIDS Research, Office of the Director, NIH |
| OASH | Office of the Assistant Secretary for Health |
| OBSSR | Office of Behavioral and Social Sciences Research |
| OD | Office of the Director, NIH |
| OE | Office of Education, NIH |
| OEO | Office of Equal Opportunity, NIH |
| OER | Office of Extramural Research, Office of the Director, NIH |
| OIT | Office of Information Technology |
| ORDR | Office of Rare Disease Research |
| ORMH | Office of Research on Minority Health, Office of the Director, NIH |
| WHI | Women's Health Initiative |
| WSA | Women Science Advisors |

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