

# AGENDA FOR RESEARCH ON WOMEN'S HEALTH FOR THE 21<sup>ST</sup> CENTURY

*A Report of the Task Force on the  
NIH Women's Health Research Agenda  
for the 21st Century*

EXECUTIVE SUMMARY

NATIONAL INSTITUTES  
OF HEALTH  
Office of the Director

1

VOLUME

# AGENDA FOR RESEARCH ON WOMEN'S HEALTH FOR THE 21<sup>ST</sup> CENTURY

*A Report of the Task Force on the  
NIH Women's Health Research Agenda  
for the 21st Century*

EXECUTIVE SUMMARY

NATIONAL INSTITUTES  
OF HEALTH  
Office of the Director  
Office of Research  
on Women's Health

1

VOLUME

U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.  
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 1. Executive Summary. Bethesda, MD.  
NIH Publication No. 99-4385, 1999.

## F O R E W O R D

**O**n the brink of the new century, we face the exciting and unprecedented opportunity to understand the functioning of our bodies and our minds to an extent that could not have been envisioned 100, or even 50, years ago. Along with a rapid pace of scientific discovery, the issue of women's health has risen to prominence during the past decade in the broadest biomedical, political, and social sense. Our Nation has recognized the importance of women's health and, more specifically, the important contributions of culture, ethnicity, race, socioeconomic background, geographic location, and other social and economic factors to women's health status. We now understand women's health as a reflection of multiple elements contributing to the overall quality of women's lives — and men's lives — in the United States today.

After a year of intensive planning, the dream of a coordinated effort on women's health at the National Institutes of Health (NIH) became a much-anticipated reality in September 1991 at a conference and series of workshops in Hunt Valley, Maryland. Experts in the fields of basic and clinical sciences, practitioners interested in women's health, and representatives of women's organizations developed specific and workable recommendations to advance research activities on behalf of all the women, and thus of all the people, of the United States. Participants focused on research needs over the major divisions of a woman's life span and the scientific issues, diseases, and impairments that might affect her health and well being during that life span. The deliberations and findings, published as *Report of the National Institutes of Health: Opportunities for Research on Women's Health*, stated a firm expectation as part of the introduction: "This research agenda, which will guide planning efforts at NIH for the next several decades, is critical to improving the quality of life for all the Nation's women." That report became the firm foundation and touchstone for the work of the Office of Research on Women's Health (ORWH) under its director, Dr. Vivian Pinn, whose appointment was announced at the September 1991 meeting.

During the past 7 years, ORWH at NIH has moved steadily and with confidence toward achieving the far-reaching goals articulated in 1991. The Office has identified and assessed the enormous advances in basic and clinical science knowledge and linked them to a research agenda targeted to improve women's health. There is now widespread, and largely unquestioned, recognition that researchers and clinicians must understand how differences in sex, gender, cultural, and ethnic and socioeconomic backgrounds may influence the causes, diagnoses,

progression, and treatment of diseases. The evolution, or perhaps even more, revolution in activities related to women's health, made the need for a reassessment of the agenda critical. An intensive series of workshops and meetings, culminating in this new report, "Agenda for Research on Women's Health for the 21st Century," extend the vision of a comprehensive women's health research agenda into exciting new directions and areas of research endeavor not anticipated in 1991. The new challenge inherent to continuing progress in research on women's health is to establish sound scientific bases that will permit reliable diagnoses and effective prevention and treatment strategies for all women, from diverse cultural and ethnic origins, geographic locations, and socioeconomic strata. The ultimate goal is to increase medical knowledge through sound research, which, thereby, will inform the development of policies and medical standards from which all women, and men, can benefit equally.

But, the guiding principle regarding women's health research at NIH must remain and has remained unchanged from its original ideal: that biomedical research must be targeted to all of the Nation's women, of all races, all ages, and all socioeconomic and ethnic groups. Researchers must continue to make more intensive efforts to address the health needs of the whole woman — in body and in mind. As citizens of the United States and of the world, we cannot afford to do anything less.

Ruth L. Kirschstein, M.D.

*Deputy Director, National Institutes of Health*

*Former Director, National Institute of General Medical*

*Sciences (1974-1993) and Acting Associate Director,*

*Office of Research on Women's Health (1990-1991)*



## A C K N O W L E D G M E N T S

**D**uring 1996 and 1997, the Office of Research on Women's Health (ORWH) of the National Institutes of Health (NIH), with the assistance of the Task Force on the NIH Women's Health Research Agenda for the 21st Century (Task Force) and the NIH Advisory Committee on Research on Women's Health (ACRWH), convened a series of three meetings at regional sites across the country and a final, national meeting to review NIH's scientific agenda for research on women's health issues. This series of meetings provided a forum during which more than 1,500 scientists, clinicians, public policymakers, advocates, and members of the general public examined the state of women's health research at this point in history and discussed areas of emerging importance for women's health and biomedical research to develop a revised agenda that will address the changing public health and scientific needs and opportunities of the 21st century.

We are grateful to all who participated in these meetings and shared their knowledge, insights, concerns, and commitment to improving the health of women through the formulation of a coherent and comprehensive agenda of basic and clinical biomedical and behavioral research. The recommendations made by participants at the four meetings will enable NIH to continue to foster and sustain multidisciplinary studies that address health and disease in girls and women across the life span.

This series of meetings would not have been possible without the assistance of a great many individuals, including Ms. Joyce Rudick, the Acting Deputy Director of ORWH, who worked tirelessly in the planning, development, and organization of these meetings to review NIH's agenda for research on women's health. In this process, NIH has benefited particularly from the contributions made by members of the NIH scientific community and by the Task Force on the NIH Women's Health Research Agenda for the 21st Century. ORWH has been fortunate to have representatives of the NIH community, as well as women's health advocates, scientists, and health professionals from across the country, serve as members of this important Task Force. We owe a special debt of gratitude to the cochairs of the Task Force, Dr. Donna Dean and Dr. Marianne Legato, who also shared in chairing each of the meetings. Dr. Dean, who was Director of the Division of Physiological Systems within the NIH Center for Scientific Review at the time that these meetings commenced and currently serves as Senior Advisor to the Deputy Director of NIH, is a member of the Coordinating Committee for Research on Women's Health (CCRWH), the advisory body composed of the Directors or designated representatives of NIH's institutes and centers (ICs).

In addition, she is cochair of the CCRWH Research Subcommittee, which on behalf of the ICs assists ORWH in setting priorities for research and developing programs to implement such priorities. Dr. Marianne Legato, Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons, is a charter member of the ACRWH, the body of 18 distinguished physicians, academicians, practitioners, scientists, and other individuals whose clinical practice, research specialization, or professional expertise includes a significant focus on research on women's health, and who provide guidance and direction to ORWH and its policies and programs.

In addition to those who served on the Task Force, ACRWH, and CCRWH, many others have assisted ORWH in these meetings and have played important roles in women's health over the years. ORWH and all who are active in the movement to improve the health of women must also acknowledge the foresight of Dr. Edward N. Brandt, a charter member of ACRWH, who established the first Public Health Service Task Force on Women's Health in 1983, sparking a new level of Federal commitment to addressing women's health issues. This commitment was sustained by Dr. James Mason, Assistant Secretary for Health, by Dr. Audrey Manley, former Deputy Assistant Secretary for Health, and by Dr. William Raub, who, as Acting Director of NIH, established ORWH in September 1990. Dr. Ruth L. Kirschstein, who served as the first and continuous cochair of the PHS Coordinating Committee on Women's Health Issues from 1983 until 1995, has a long history of activism on behalf of women in biomedical science and women's health research; she served as the first Acting Director of ORWH and has continued to provide invaluable guidance and support to ORWH in her present position as Deputy Director of NIH.

ORWH and other efforts of the Federal Government to improve the health of women have greatly benefited from the support and interest of many members of the U.S. Congress, as well as the Executive Branch. Important impetus and support for efforts to improve the health of women and NIH's process of reviewing the research agenda on women's health have been provided by the Secretary of the Department of Health and Human Services, Dr. Donna Shalala. This support was also evidenced by the presence of Senator Barbara A. Mikulski, Congresswoman Connie A. Morella, Congresswoman Louise M. Slaughter, a representative of Congressman Louis Stokes, and the Director of the White House Office for Women's Initiatives and Outreach, Audrey Tayse Haynes, at the final national meeting, "Putting It All Together: The Agenda for Research on Women's Health for the 21st Century," held in November 1997. We gratefully acknowledge their support and contributions in helping NIH to chart a bold plan of action for improving the health of women in the next millennium.

ORWH wishes to acknowledge and thank the working group cochairs of the meetings held in Philadelphia, New Orleans, Santa Fe, and Bethesda, as well as the people who served on committees and working groups and who contributed their collective expertise to the creation of the Agenda for Research on Women's Health for the 21st Century.

***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*





TASK FORCE ON THE NIH WOMEN'S HEALTH RESEARCH  
AGENDA FOR THE 21ST CENTURY

OFFICE OF RESEARCH ON WOMEN'S HEALTH, NATIONAL INSTITUTES OF HEALTH

*COCHAIRS*

**Donna Dean, Ph.D.**

Senior Advisor to the Deputy Director  
(formerly, Director, Division of Physiological Systems  
Center for Scientific Review)  
National Institutes of Health  
Bethesda, Maryland

**Marianne Legato, M.D.**

Professor of Clinical Medicine  
Columbia University College of Physicians  
and Surgeons  
New York, New York

*TASK FORCE MEMBERS*

**Karen Antman, M.D.**

Professor of Medicine and Pharmacology  
Columbia University  
Chief, Division of Medical Oncology  
Columbia Presbyterian Comprehensive Cancer Center  
New York, New York

**Mary J. Berg, Pharm.D.**

Professor  
Division of Clinical and Administrative Pharmacy  
University of Iowa  
Iowa City, Iowa

**Stephanie Bird, Ph.D.**

Special Assistant to the Provost  
Massachusetts Institute of Technology  
Cambridge, Massachusetts

**Edward Brandt, M.D., Ph.D.**

Regents Professor and Director  
University of Oklahoma, Center for Health Policy  
University of Oklahoma Health Science Center  
Oklahoma City, Oklahoma

**George Bryan, M.D.**

Dean Emeritus, School of Medicine  
University of Texas Medical Branch  
Galveston, Texas

**Leah Dickstein, M.D.**

Professor and Associate Chair  
Department of Psychiatry  
University of Louisville School of Medicine  
Louisville, Kentucky

**Mary Dufour, M.D., M.P.H.**

Deputy Director  
National Institute on Alcohol Abuse and Alcoholism  
National Institutes of Health  
Bethesda, Maryland

**Carola Eisenberg, M.D.**

Lecturer in Psychiatry  
Dean, Student Affairs (Retired)  
Harvard Medical School  
Boston, Massachusetts

**John Estrada, M.D.**

Assistant Professor of Pediatrics  
Meharry Medical College  
Nashville, Tennessee

**Bonita Falkner, M.D.**

Professor of Medicine and Pediatrics  
Institute for Women's Health  
Allegheny University of Health Sciences  
Philadelphia, Pennsylvania

**Sheryle Gallant, Ph.D.**

Associate Professor of Psychology  
Department of Psychology  
University of Kansas  
Lawrence, Kansas

**John Greene, D.M.D., M.P.H.**

Professor and Dean Emeritus  
School of Dentistry  
University of California at San Francisco  
San Francisco, California

**Jeane Ann Grisso, M.D., M.Sc.**

Associate Professor of Medicine  
University of Pennsylvania School of Medicine  
Philadelphia, Pennsylvania

**Hazel Harper, D.D.S.**

President, National Dental Association  
Washington, District of Columbia

**Joseph Hurd Jr., M.D.**

Chairman, Department of Gynecology  
Lahey Hitchcock Clinic Medical Center  
Burlington, Massachusetts

**M. Margaret Kemeny, M.D., F.A.C.S.**

Chief of Surgical Oncology  
North Shore University Hospital  
Manhasset, New York

**Judith LaRosa, Ph.D., R.N., F.A.A.N.**

Professor and Chair  
Department of Community Health Sciences  
Tulane University Medical Center  
School of Public Health and Tropical Medicine  
New Orleans, Louisiana

**Angela Barron McBride, Ph.D., R.N., F.A.A.N.**

Distinguished Professor and Dean  
Indiana University School of Nursing  
Indianapolis, Indiana

**Sherry Mills, M.D., M.P.H.**

Prevention and Control Extramural Branch  
National Cancer Institute  
National Institutes of Health  
Bethesda, Maryland

**Donnica Moore, M.D.**

Associate Director  
Sandoz Pharmaceuticals Medical Education Center  
Sapphire Women's Health Group  
Neshanic Station, New Jersey

**Judy Norsigian**

Co-Director  
Boston Women's Health Book Collective  
Boston, Massachusetts

**Jane Pearson, Ph.D.**

Chief, Preventive Interventions Program  
National Institute of Mental Health  
National Institutes of Health  
Bethesda, Maryland

**David Robinson, Ph.D.**

Program Director  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
Bethesda, Maryland

**Helen Rodriguez-Trias, M.D.**

Co-Director, Pacific Institute for Women's Health  
Western Consortium for Public Health  
Los Angeles, California

**Rosalie Sagraves, Pharm.D.**

Dean, College of Pharmacy  
University of Illinois at Chicago  
Chicago, Illinois

**Gloria Sarto, M.D., Ph.D.**

Professor  
University of New Mexico School of Medicine  
Albuquerque, New Mexico

**Anne Sassaman, Ph.D.**

Director, Division of Extramural Research and Training  
National Institute of Environmental Health Sciences  
National Institutes of Health  
Bethesda, Maryland

**Ora Lee Strickland, Ph.D.**

Independence Professor  
Nell Hodgson Woodruff School of Nursing  
Emory University  
Atlanta, Georgia

**Ramona Tascoc, M.D., M.H.S.A.**

Chair, Council on the Concerns of Women Physicians  
Kaiser/National Medical Association  
Oakland, California

**Constance Weinstein, Ph.D.**

National Heart, Lung, and Blood Institute (Retired)  
National Institutes of Health  
Bethesda, Maryland

**Darlene Yee, Ed, C.H.E.S.**

Professor and Director, Gerontology  
College of Health and Human Services  
San Francisco State University  
San Francisco, California

**Members-at-Large**

Coordinating Committee on Research on Women's  
Health Members  
Advisory Committee on Research on Women's  
Health Members

# C O N T E N T S

FOREWORD .....	.iii
ACKNOWLEDGMENTS .....	.v
INTRODUCTION .....	.1
OVERVIEW AND PERSPECTIVES FROM THE TASK FORCE COCHAIRS .....	.9
THE USE OF “SEX” AND “GENDER” TO DEFINE AND CHARACTERIZE MEANINGFUL DIFFERENCES BETWEEN MEN AND WOMEN .....	.15
SUMMARY REPORTS OF THE WORKING GROUPS	
Reports of the Working Groups: Scientific Chapter — Summary of Recommendations	
Alcohol, Tobacco, and Other Drug Use, Disorders, and Consequences .....	.23
Behavioral and Social Sciences .....	.25
Bone and Musculoskeletal Disorders .....	.27
Cancer .....	.31
Cardiovascular Diseases .....	.33
Digestive Diseases .....	.37
Immunity and Autoimmune Diseases .....	.41
Infectious Diseases and Emerging Infections .....	.43
Mental Disorders .....	.47
Neuroscience .....	.51
Oral Health .....	.53
Pharmacologic Issues .....	.57
Reproductive Health .....	.63
Urologic and Kidney Conditions .....	.67
Reports of the Working Groups: Sex and Gender Perspectives Throughout the Life Cycle — Summary of Recommendations	
Prenatal, Infancy, and Childhood Years .....	.71
Adolescent Years .....	.73
Reproductive and Middle Years .....	.75
Perimenopausal and Postmenopausal Years .....	.79
Elderly and Frail Elderly Years .....	.81
Reports of the Working Groups: Differences Among Populations of Women Throughout the Life Cycle — Summary of Recommendations	
Prenatal Years .....	.87
Infancy and Childhood Years .....	.89
Adolescent Years .....	.93
Reproductive and Middle Years .....	.95
Perimenopausal Years .....	.99
Postmenopausal Years .....	.101
Elderly and Frail Elderly Years .....	.105
CAREER ISSUES FOR WOMEN SCIENTISTS .....	.111

SELECTED ISSUES IN RESEARCH DESIGN	
Health of Special Populations of Women	.117
Sex and Gender Differences in Clinical Studies	.119
Racial, Ethnic, and Cultural Diversity	.121
Multidisciplinary Perspectives	.123
SELECTED TOPICS IN HEALTH IMPACT AND HEALTH OUTCOMES	.127
CROSSCUTTING ISSUES AND RECOMMENDATIONS	.135

# INTRODUCTION

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

## REVISITING THE NIH RESEARCH AGENDA ON WOMEN'S HEALTH FOR THE 21ST CENTURY: A COLLABORATION BETWEEN NIH AND THE BROADER WOMEN'S HEALTH COMMUNITY

As the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) engages the scientific, health care, public policy, advocacy, and other communities in a review and revision of the NIH research agenda on women's health for the 21st Century, it is salutary to examine the history of efforts to improve the health of women through research, and the steps that led NIH to the landmark series of four scientific workshops held in 1996 and 1997.

There is no question that research is central to providing the scientific foundation for changes and improvements in health practices and policies. Expanding our understanding of normal and abnormal biologic processes and behavior can result in improved prevention, diagnosis, and treatment of diseases, disabilities, and other conditions that affect the health of women and their families. Yet, despite the importance to the United States of improving the health status of women across the life span, the emergence of women's health issues among our nation's priorities did not occur overnight. We owe much of the increased focus of the scientific community on women's health to many individuals, groups, and organizations that have been working to improve the health of women for some time. These include the Boston Women's Health Book Collective, the National Women's Health Network, the

National Black Women's Health Network, the Society for the Advancement of Women's Health Research, and many others, some of whom provided testimony during our public hearings. For many years, these organizations have been working "in the trenches," calling attention to the need to focus our attention on women's health. Nevertheless, only in recent years has the Federal Government recognized women's health as a real issue requiring a real remedy. Today, thanks to the efforts of advocates and scientists in and outside the Federal Government, we are beginning to make progress.

### *PHS Task Force and Establishment of ORWH*

In 1983, the Assistant Secretary for Health, Dr. Edward N. Brandt, Jr., established the Public Health Service (PHS) Task Force on Women's Health Issues to examine the role of the Department of Health and Human Services in addressing women's health. In a report published in 1985, this Task Force made a number of recommendations on a broad array of women's health issues relevant to the entire life span of girls and women. At that time, Dr. Brandt stated, "I am committed to seeing that this report results in action that is beneficial to the women of America." Among the most pertinent recommendations of the Task Force report was one that said that "Biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women in all age groups."

Following publication of the report of the PHS Task Force on Women's Health in 1985, NIH established a policy for the inclusion of women in clinical research. Two years later, in 1987, the policy was incorporated into and published in the *NIH Guide*

to *Grants and Contracts* in 1987. 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 U.S. General Accounting Office (GAO) study NIH's implementation of the guidelines for inclusion of women. The resulting GAO report stated that the implementation of the policy for the inclusion of women was slow and not well communicated, gender analysis was not implemented, and the impact of policy could not be determined.

In September 1990, just 3 months after the release of the GAO findings, the subsequent media coverage and public reaction catalyzed NIH to establish the Office of Research on Women's Health. The office was set up by Dr. William Raub to serve as the focal point for women's health research at NIH, working in a collaborative partnership with NIH's institutes and centers (ICs). ORWH was announced at an NIH roundtable meeting with representatives of the Congressional Caucus on Women's Issues on September 10, 1990. A press release from the U.S. Department of Health and Human Services at the time of this meeting stated that:

ORWH is charged with assuring that research conducted and supported by NIH appropriately addresses issues regarding women's health and that there is appropriate participation of women in clinical trials . . . The Office will establish NIH-wide goals and policies for research related to women's health. It will also coordinate NIH activities undertaken in performing such research. Finally, the Office will interact with the scientific and medical communities, organizations with an interest in women's health and other components of government to inform them of NIH's programs related to women's health, identify areas of research that need emphasis and involve them in efforts to expand and encourage research on women's health.

At the same time, Dr. Raub stated that "The new Office will have the authority and responsibility to act with and on behalf of the NIH Director to monitor and coordinate the activities of the constituent ICs at NIH in regard to research on women's health . . ."

With these words, ORWH was established and given the broad mission that still directs the activities of the Office today. This mission encompasses:

- Establishing NIH-wide goals and policies for research related to women's health.
- Developing a plan to increase NIH-supported research on women's health, then implementing and monitoring its effects.
- Coordinating NIH activities undertaken in performing women's health research.
- Providing advice and staff support to the NIH Director and senior NIH staff regarding the overall direction of and approaches to NIH programs of research related to women's health.
- Interacting with the scientific and medical communities, organizations with an interest in women's health, and other components of government to inform them of NIH programs related to women's health.
- Developing special initiatives to increase the participation of women as subjects in clinical research and of institutions and investigators in performing research on women's health.

One of the earliest announcements of activity by this new office was made on that same September day by Dr. Ruth L. Kirschstein, who promised that ". . . As one of its most important activities, the Office, this fall, will convene a planning group to prepare the background for a major conference which will serve to set an agenda for NIH research on women's health . . ."

As a result, 1 year later, in September 1991, ORWH held public hearings and a scientific workshop at Hunt Valley, Maryland, to set NIH's agenda for research on women's health issues. The report from that meeting, *Report of the National Institutes of Health: Opportunities for Research on Women's Health*, commonly referred to as the Hunt Valley Report, served as the basis for NIH's research priorities in women's health for 7 years.

At the Hunt Valley meeting, discussions centered around life span concepts for women's health and crosscutting areas of science. These included:

### **Life Span**

Birth to Young Adulthood

Young Adulthood to Perimenopausal Years

Perimenopausal to Mature Years

Mature Years

### **Crosscutting Science**

Reproductive Biology

Early Developmental Biology

Aging Processes

Cardiovascular Function and Disease

Malignancy

Immune Function and Infectious Diseases

In addition, speakers addressed morbidity and mortality in women, ethical and legal issues, women as research subjects, and women in biomedical careers.

Thus were launched the programs of ORWH to "expand and encourage" research on women's health. In 1993, ORWH was legislatively mandated in the NIH Revitalization Act. Women's health research at NIH is a partnership between ORWH and NIH institutes and centers. During the past 7 years, ORWH's responsibilities and major program efforts have increased and, while there is still a lot to be done, we have made some progress.

## ***NIH Mandate for the Inclusion of Women and Minorities 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 response to the PHS Task Force on Women's Health Issues and in response to the GAO report of 1990. ORWH has assumed leadership in implementing policies requiring the inclusion of women and minorities in human subject research. Wanting to assure that the policies for inclusion were firmly implemented by NIH, the Congress made what had previously been policy into Public Law, through a section in the NIH Revitalization Act of 1993 (Public Law 103-43), entitled "Women and Minorities as Subjects in Clinical Research."

The NIH Revitalization Act of 1993 essentially put forth the existing NIH policies but with four major differences:

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

The guidelines for inclusion developed in response to this law were published in the *Federal Register* in March 1994, and they have been fully implemented. It is now the policy of NIH that women and members of minority groups and their



subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes that inclusion is inappropriate to the health of the subjects or the purpose of the research.

Working in collaboration with the Office of Extramural Research and other components of NIH, we have established a tracking system to monitor inclusion. Indeed, for the first time in NIH's history, we are able to determine the numbers of women and minorities in clinical trials, and we are now beginning to analyze data to establish trends in inclusion and determine better ways to examine these data. Thus far, we have found high compliance with inclusion policies.

The goal of NIH policy is not to satisfy any quotas for proportional representation, but rather to conduct biomedical and behavioral research such that the scientific knowledge acquired will be generalizable to the entire population. In response to the tragedies of the PHS syphilis study in Tuskegee, Alabama, and the effects on those exposed to DES and thalidomide in utero, regulations were put in place to protect women, minorities, and other populations from being exploited in research. As we work to ensure women's appropriate inclusion in clinical studies, we still must grapple with the very sensitive ethical and legal issues of including women of childbearing age in such research. In addressing these issues, we must weigh the risks of such participation to women and their potential offspring against the benefits of participation in clinical studies.

A continued emphasis on the need for innovative and successful strategies to recruit women as volunteers in clinical research, including special populations of women across the life span, must remain a consideration in research design. In fact, the implementation of the NIH policy for the inclusion of women and minorities in human subject research requires the increased participation of women and minority physicians and scientists in the design, implementation, and interpretation of such studies.

## **Women in Biomedical Careers**

With expanding horizons in science and biotechnology, greater participation by women as investigators in studies to explore new frontiers of knowledge about health, disease, and normative development in girls and women is needed. While exact figures are not available for those who are participating in research, there is a need to increase not only the numbers of women who are biomedical and behavioral investigators, but also the numbers of women who are in policy making positions and who can influence or determine the direction of research initiatives.

To help us to determine the best ways to increase opportunities for women in biomedical research careers, in 1992, ORWH convened a public hearing and workshop on the recruitment, retention, advancement, and re-entry of women in biomedical careers. The goal was not only to identify barriers to women's success, but also to devise strategies and programs to enable women to overcome those barriers.

At the 1992 meeting, a number of barriers were identified and published in a report, *Women in Biomedical Careers: Dynamics of Change — Strategies for the 21st Century*. From nearly 70 testimonies, 9 general issues that present barriers emerged. These barriers are common to women in the biomedical professions regardless of racial, ethnic, cultural, socioeconomic, or other backgrounds.

- Recruiting women to biomedical sciences;
- Visibility, role models, and mentors;
- Career paths and rewards;
- Re-entry into a biomedical career;
- Family responsibilities;
- Sexual discrimination and sexual harassment;
- Research initiatives on women's health;

- Sensitizing men about special career concerns of women; and
- Minorities and racial discrimination.

Based on the findings and recommendations of that meeting, ORWH has initiated and sponsored a number of programs, including one that addresses the loss to science of women who have interrupted their research careers to fulfill familial responsibilities, the Re-entry Program for Biomedical Scientists. Started as a pilot project in 1992, the re-entry program was assessed under the leadership of Joyce Rudick and the cochairs of the Subcommittee on Biomedical Careers of the NIH Advisory Committee on Women's Health Issues, Dr. Anne Sassaman and Dr. Julia Freeman. The re-entry program has now been institutionalized across NIH. Since 1992, participants in the program have published 72 papers, with 43 re-entry scientists as the primary author, in such journals as the *Journal of Cell Science*, *Biological Psychiatry*, *Molecular Microbiology*, *American Journal of Epidemiology*, *Journal of Biological Chemistry*, *American Journal of Psychiatry*, *Journal of Clinical Investigation*, and *Journal of the American Medical Association*.

Ensuring that the findings derived from research on women's health are incorporated into the education and training of the next generation of health care providers is an important priority for ORWH. As a part of our effort to address the implementation of the NIH agenda on women's health research and the role of such research in helping to establish improved standards of health care practice that promote multidisciplinary, comprehensive, and effective women's health care, we collaborated with the Health Resources and Services Administration (HRSA) and the Public Health Service Office of Women's Health to prepare a report of surveys of all osteopathic and allopathic schools of medicine to determine women's health in their curricula. The resulting report, *Women's Health in the Medical School Curriculum: Report of a Survey and Recommendations*, also contains examples of curricula that incorporate

women's health issues. We are now working with the dental, nursing, and pharmacy representatives for a similar study of their educational curricula.

We have also put in place a number of other programs and initiatives to enhance participation of women and men scientists in research on women's health. These include workshops on how to speak and write about science, as well as training projects that provide opportunities for high school students, college faculty and students, and minority students to obtain research experience or exposure to current scientific concepts through NIH. ORWH has also developed and supported a number of programs for the advancement of girls and women in science through collaboration with the NIH Office of Science Education. These programs include: outreach on the World Wide Web; a speakers bureau that allows a diverse group of women scientists in the NIH community to provide both role models and information about careers in research; a very popular course designed to teach young scientists to write about science effectively; a series of workshops to teach young scientists how to present scientific data effectively; a program for NIH summer interns that provides a forum for discussion of family and career concerns that can affect their professional and personal lives; and a series of workshops to support the successful career development of young postdoctoral intramural researchers.

### ***NIH National Research Agenda on Women's Health***

Progress has been made in establishing women's health research as an integral part of the fabric of NIH research and programs; but progress gives rise to new questions, a need for an assessment, and a consideration of new priorities and a revitalized research agenda. We believed that it was time to look "beyond Hunt Valley" and to update our agenda. Beginning in September 1996, ORWH convened a series of meetings, "Beyond Hunt Valley: Research on Women's Health for the 21st Century," to foster collaboration among representatives of the NIH

community and the broader women's health community to revise the research agenda on women's health. In planning these meetings, we turned to the model of the first Hunt Valley meeting where broad participation through public hearings and workshops proved so productive and fruitful. This mechanism has provided an opportunity for ongoing collaboration among individuals and groups of women, advocates, scientists, health care practitioners, and public health policy-makers with NIH to establish our research agenda as we move forward into the 21st century.

The original women's health research agenda developed as a result of the Hunt Valley meeting embodied certain underlying principles that will continue to inform our directions for the future. The Hunt Valley report redefined the parameters of women's health to encompass research to better understand sex and gender differences between women and men in development, health, and disease, and to focus on populations of women that have been underrepresented in clinical research in the past. This agenda recognizes the full spectrum of research from basic to clinical research and trials, epidemiological and population studies, clinical applications, and health outcomes. We have embraced an expanded concept of women's health and research that encompasses the health of girls and women across the life span, from the prenatal stage to that of the frail elderly. Most important, the agenda reflects the fact that women's health implies more than the reproductive system. The agenda also emphasizes basic science investigations, not just human subject research.

The research agenda includes biomedical as well as behavioral and psychosocial research, with a focus on multidisciplinary collaboration. It focuses on sex and gender factors in the health and diseases of women, in considering such matters as normal development, disease prevention, health maintenance, response to interventions, disease prognosis, and treatment outcomes. We have also focused on factors that influence

differences in health status and health outcomes among diverse populations of women. Moreover, priorities have been established for populations of women and girls that have been previously excluded from scientific investigation, such as minorities, women of low socioeconomic status and isolated geographic locations, lesbians, and women with disabilities.

In all our efforts to implement our research agenda, ORWH participates in an active and beneficial partnership with all of NIH's institutes and centers. We continually review our research priorities to determine where the major gaps in knowledge exist.

At our first regional meeting, held September 1996 in Philadelphia, where our hosts were the Allegheny University of the Health Sciences and the University of Pennsylvania, we started to examine our research agenda to ensure its relevance as we move toward the next century. At the Philadelphia meeting, we directed attention to some of the major areas of concern for women's health. We later looked at women's health from two perspectives — sex and gender factors, as well as differences in health among diverse populations of women. At the second meeting, held in New Orleans, we examined aspects of the research agenda based upon sex and gender perspectives (i.e., physiological, psychosocial, and pharmacologic differences between women and men). Plenary presentations addressed the role of hormones in sex and gender differences, as well as the role of the environment and genetic heritage. At our third regional meeting, held in Santa Fe, New Mexico, participants focused on factors that contribute to differences in health status and health outcomes among diverse populations of women. These included biological, genetic, racial, cultural and ethnic, psychosocial and behavioral factors, educational influences, traditional and alternative health practices, environmental influences, poverty and socioeconomic status, access to health care, and occupational issues. The plenary sessions also included considerations of health issues for women who have disabilities.

At the final, national meeting in the series, held in Bethesda, Maryland, in November 1997, we addressed issues raised at the three regional meetings and invited participants to consider additional issues to guide our Task Force in developing recommendations for the NIH research agenda on women's health for the 21st century. The specific objectives of this final workshop were to:

- Consider progress in knowledge about women's health through research;
- Determine continuing or emerging gaps in knowledge, and related issues and implications;
- Recommend a new framework for research priorities on women's health, conditions, and diseases;
- Recommend how these research initiatives can best be accomplished;
- Recommend ways to improve dissemination of research outcomes, integration into health education, and implementation in health practices and public policies; and
- Recommend programs and collaborations to increase opportunities for participation and advancement of women in research careers.

We asked participants to consider the following:

- The original Hunt Valley report recommendations;
- Deliberations and recommendations from the three regional meetings;
- Special populations of women;

- Factors that affect different populations of women;
- Sex and gender issues;
- Normal processes, developmental biology, and aging; and
- Life span concepts.

All the recommendations for our research agenda must be based upon science driven initiatives. Thus, the role of the participants was challenging, significant, and meaningful. Our updated agenda must reaffirm the commitment to an integration of scientific disciplines and medical specialties with advocacy and forward-thinking optimism. The goal is to make a positive difference in women's health in the 21st century through an improved research agenda that will yield scientific data to lessen or eliminate continuing or emerging gaps in knowledge about women's health.

During the past decade, with the creation of new laws, policies, and programs, we have made tangible progress toward improving women's health, and we have gained a sure sense of our power to effect real change. With assistance from the scientific and lay communities, as we enter the 21st century, ORWH can build on that progress and markedly improve the health of women and their families. That is the vision for women's health in the United States and worldwide that we have entrusted the members of the Task Force and all participants in this process to help us ensure for the future. No single individual or group can do the job alone. The challenge — and the responsibility — must be shared by all of us.



O V E R V I E W   A N D  
P E R S P E C T I V E S  
F R O M   T H E   T A S K  
F O R C E   C O C H A I R S

*Marianne Legato, M.D., F.A.C.P.  
Professor of Clinical Medicine  
Columbia University College of  
Physicians and Surgeons*

*Donna Dean, Ph.D.  
Senior Advisor to the Deputy Director  
National Institutes of Health*

**T**he 7 years since the Office of Research for Women's Health's (ORWH) original report on the health needs of women have witnessed a remarkable expansion of interest in the female patient. In a very real sense, that interest is the result of the expanding competence and power of women that began with World War II. This global catastrophe facilitated women's entries into positions and professions that had been previously almost exclusively available to men. The emergence of feminism in the 1950s was an inevitable consequence of women's new sense of what was possible for them to achieve on their own rather than through alliances with powerful men: access to the professions and to their own money, and with it, increasing immediate control over the world around them. Feminism was bred of women's new and expanded sense of their identities as individuals beyond their traditional roles of wife and mother, and of what they were due from a society that held them as less valuable than men. Their interest in social justice and appropriate access to the options available within the life of the community extended to a consideration of their health needs.

Women's increasing ability to call attention to their needs gained strength in the decades after World War II and was reflected first in the 1985 report of the U.S. Public Health Service's Task Force on Women's Health Issues, which concluded that women's health care was compromised by the lack of research focus on women's health concerns. By 1986, the National Institutes of Health (NIH) urged that research protocols include appropriate numbers of female subjects wherever relevant, although the 1990 report of the General Accounting Office (GAO) indicated that because of a lack of aggregate or NIH-wide recordkeeping, it was

unable to monitor NIH's performance on ensuring that this was accomplished. This report and other pressures for more attention prompted the NIH Revitalization Act of 1993, which stated the condition that any NIH-supported research must include appropriate numbers of subpopulations (including women) in the cohort of subjects studied. Cost was not a justification for failure to do this. In 1990, the Congressional Caucus on Women's Issues introduced 22 bills to Congress that addressed research, care, and prevention issues in women's health. Six of the research-related provisions were incorporated into the 1991-1992 NIH Revitalization Act, which became law in 1993 and gave statutory authorization to ORWH. The Food and Drug Administration (FDA) was not exempt from the sweeping reforms. In 1992, FDA cosponsored a conference with the Food and Drug Law Institute to debate issues of including women in clinical trials of FDA-regulated products. The GAO released a report examining FDA's policies and the pharmaceutical industry's practices regarding drug testing and women and concluded that for more than 60 percent of the drugs, the representation of women in the test population was less than the representation of women in the population with the corresponding disease. The worst case, ironically, was in the area of cardiovascular disease, where companies were frequently failing to analyze or collect data for gender differences in response to drugs. By 1993, FDA lifted its 1977 edict that reproductive-age women should be isolated from clinical research and recommended that data be analyzed as a function of gender.

Women have demanded to learn more about the normal physiology of females and of the unique ways in which they experience disease. They want to be included in clinical investigations, they want federal

monies devoted to their health needs, and they have been entering medical and other health professional schools in increasing numbers. Clinical researchers have concentrated on exposing, publicizing, and correcting gender prejudice in health care delivery to women. The results have been mixed, but women have achieved some progress. A notable example is the Women's Health Initiative (WHI), an unprecedented prospective \$625 million study on 165,000 women of diverse racial and ethnic backgrounds between the ages of 50 and 79 years of age in large and small communities nationwide. During the past few years, ORWH has flourished, using its resources to focus on and publicize women's health needs, to support research that concentrates on women, and to ensure ways to encourage women's entry into and retention in research careers.

This Task Force had several fundamental questions about women's health, some of which had been addressed by the Institute of Medicine's Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. Because of the lack of a tracking system to monitor inclusion in 1990, that committee had difficulty in demonstrating that women had been understudied or excluded from research. Nevertheless, the report made it clear that investigators frequently did not report the results of data analyzed by sex and gender, did not perform any sex and gender analyses of study results, and did not recruit adequate numbers of women to support conclusions regarding the impact of sex and gender on the observations made.

Several fundamental questions arise, some of which have not yet been answered satisfactorily.

- Has the exclusion of women from clinical research affected their health?

We are just beginning to understand and appreciate the differences between men and women in virtually every system of the body, as well as in the way men and women experience disease. Differences in drug metabolism frequently explain women's vulnerability to medications that have been tested primarily in men.

For example, one study reports that the treatment of mild to moderate hypertension in Caucasian women increased the all-cause death rate by 26 percent, while lowering all-cause mortality in men by 15 percent. Another study (SWORD trial on sotalol in the treatment of postmyocardial infarction arrhythmias) was discontinued because of the increase in mortality of women in the trial.

- Can research on men be extrapolated to women without modification?

Investigators consistently assume that information they glean from clinical and basic studies on male subjects can be extrapolated without modification to women. This traditional assumption was rarely, if ever, directly tested. It is remarkable that we have tolerated this "leap of faith" in an otherwise rigorous research enterprise. In no other area have we permitted unproven assumptions to be accepted as fact. We now have enough information about the differences between males and females to acknowledge the danger of assuming that they are identical. An excellent example is the way in which men and women respond to drugs: The working group on pharmacologic issues has highlighted the differences between men and women in the cytochrome P450 system and the unique role of hormones in drug effects.

- Do government mandated research guidelines to include women restrict the scientific community so severely that they compromise the quality and amount of investigation done? What does it cost to include women in clinical investigation? If it is more, will the result be fewer clinical trials and studies? If so, what will be the impact on the health of the public?

Some diseases occur more frequently in men than in women, or during a quite different age or developmental period. Those factors, as well as the difficulty in recruiting premenopausal women, have been cited as impeding clinical investigations that include both males and females. The scientific community has defended its reluctance to study women

directly on the basis of the relatively more constant physiologic state of males. Complicating the issue is the cyclic variability of women of reproductive age. Including younger females in clinical trial populations would necessitate larger and, therefore, more costly investigations. Regardless of the assertion that cost should not be an obstacle to creating an adequate and accurate protocol, these economic, ethical, moral, and intellectual issues need public debate and clear guidelines. The assumption that studies on men are “good enough” for women, based on the premise that to be human is a homogeneous condition, is flawed. We have not, however, acknowledged the fact that, so far, our attention has been concentrated on postmenopausal women in the major studies devoted to the female patient (e.g., the Postmenopausal Estrogen/ Progesterone Intervention [PEPI] study and the WHI). The unique needs of the premenopausal and pregnant woman must be considered as well. The vulnerability of the premenopausal woman, particularly if she is pregnant, has often been cited as a reason for exclusion from clinical studies and trials of younger females. This general policy of protectionism, codified in PHS regulations promulgated by the Office for Protection from Research Risks (OPRR), characterized FDA and NIH standards for clinical trial populations from the 1970s until the late 1980s. As a direct result, we have been left ignorant of much essential first-hand information about the female patient and her unique responses to therapeutic interventions developed in studies carried out exclusively in men.

The issue of how to describe differences in health status or outcomes between men and women is fraught with conceptual difficulty. Should differences — for example in rates of heart disease, participation in research, or access to specialty services — be attributed to “sex” or to “gender”? Are the two terms equivalent, or do they describe conceptually distinct approaches to understanding difference? Unfortunately, the language of difference in the biomedical literature is often imprecise, conflating the two terms, treating them as virtual synonyms. This imprecise use of language presented difficulty to the Beyond Hunt Valley working groups and Task Force and remains a challenge.

Hence, we wish to acknowledge the significance of the conceptual distinction for women’s health. The Task Force in no way wishes to imply that straightforward biological difference, such as that associated with the action of a particular sex hormone, is an adequate explanatory model for research on health differences between men and women. Since confusion is the order of the day throughout the biomedical literature, it is impossible within the confines of this report to offer a definitive clarification. Readers will note that authors differ in their use of the terms, with some maintaining a clear distinction between biological versus social or cultural elements of difference and others using the terms as virtual synonyms. Ideally, a women’s health research agenda would recognize the need for studies on all aspects of differences between men and women, maintaining the conceptual clarity necessary for high quality research. During the next 5 years, ORWH will take on that challenge as well. An excellent conceptual framework is presented in the section of this report on sex and gender terminology (see page 15).

## B A S I S O F R E P O R T R E C O M M E N D A T I O N S

The chapters of this report present the recommendations of the 1997-1998 Task Force for Beyond Hunt Valley: Research on Women’s Health for the 21st Century, appointed by ORWH to determine the most fruitful and useful directions for medical research conducted by NIH on women during the next 5 years.

### *Current NIH Research of Particular Importance to Women*

Mindful of the rich and varied portfolio of research efforts already supported by NIH, the Task Force first reviewed current NIH-supported activities and research of particular importance for women. Some examples of major ongoing investigations at NIH are as follows:

1. *Neurosciences and brain biology.* Given the sexual dimorphism in the structure and function of the human brain, as well as in the incidence of degenerative and affective diseases of the brain,



the following areas of ongoing research promise to be particularly useful for women: (a) the development and degeneration of neurons; (b) the therapeutic effects of St. John's Wort; (c) the nature of pain; (d) behavioral research on obesity and substance addiction (including smoking); (e) development of new drugs for the treatment of alcoholism and drug addiction; and (f) the brain molecular anatomy project, which studies the patterns of gene expression and the role of single genes in brain function of mice with altered genomes.

2. *Cardiovascular disease.* The phenomenon of why many aspects of the risk factors for, clinical presentation of, testing modalities of, therapeutic choices of, and outcomes of cardiovascular disease are different for men and women has been explored extensively by cardiovascular experts during the past decade. The following gender-specific studies are of particular interest to women: (a) the role of hypertension in accelerating vascular disease; (b) the role of plaque in atherosclerosis and the mechanism of how it is formed; and (c) the role of genes in progression and experience of diseases of the heart and blood vessels, particularly regarding the involvement of other organs.
3. *Asthma.* The prevalence of asthma in women, particularly in Hispanic females, makes it a disease of particular interest to clinicians interested in treating the female patient. Clinical trials to prevent environmentally induced asthma in children are of special interest to women. The prevention of asthma in children is an area of heavy concentration at NIH, particularly the prevention of morbidity and mortality by monitoring trends and risk factors for this disease.
4. *Infectious diseases.* Infectious and parasitic diseases still claim more lives than any other disease category in the world. Research relevant to women includes (a) the search for novel approaches for the treatment of infectious diseases, particularly tropical and viral diseases, tuberculosis, and

hepatitis C; and (b) work on the genome of the AIDS virus, which has offered expanding promise for development of effective therapy and serves as a model of how genetic information may help defeat disease.

5. *Diabetes.* Diabetes poses particular problems for women, not the least of which is the four- to sixfold increase in vulnerability of the diabetic woman, regardless of age and menopausal status, to coronary artery diseases. Hence, the following investigations are of particular importance: (a) the role of nutrition and obesity in the pathogenesis of diabetes; (b) efforts to effect the regeneration of insulin producing cells; (c) the development of enhanced methods for drug delivery; and (d) research into the pathogenesis of the various types of diabetes.
6. *Women's Health Initiative.* The Women's Health Initiative (WHI), one of the largest primary prevention studies in postmenopausal women in the United States has three components: (1) a randomized controlled clinical trial (67,000 participants) that will evaluate the effect of a low-fat diet on prevention of breast and colon cancer and coronary heart disease, examine the effect of hormone replacement therapy on prevention of coronary heart disease and osteoporotic fractures, and evaluate the effect of calcium and vitamin D supplementation on prevention of osteoporotic fractures and colon cancer; (2) an observational study (100,000 participants) that will delineate new risk factors and biological markers in women and identify predictors of disease; and (3) a community prevention study (20,000 participants), conducted with the Centers for Disease Control and Prevention, to evaluate strategies for the adoption of healthful behaviors including improved diet, nutritional supplementation, smoking cessation, increased physical activity, and early detection of diseases for women of diverse races, ethnic groups, and socioeconomic strata. WHI will provide important, scientifically valid information

for women, their health care providers, and their communities. This information will reflect the benefits and risks of preventive approaches and the means of achieving adoption of these behaviors.

7. *Other fundamental investigations.* Studies on the following are of particular relevance to women:

- The genes involved in producing long QT syndrome (a risk factor for cardiac arrest) and the genes essential for bone formation in a mouse animal model have been identified. The latter is particularly useful in studying how to induce new bone development in patients with osteoporosis or injury.
- Visualization of the brain in action with neuroimaging techniques.
- New categories of drugs to treat depression.
- The role of abnormal cell death and abnormal cell reproduction in disease. Telomere length determines whether or not a cell will divide; disruptions in telomere function may explain abnormal cell division or premature aging.
- Drugs blocking angiogenesis in tumors.
- Factors governing metal transmembrane flux. These studies will aid treatment of anemia and elucidate the mechanisms and usefulness of inflammation and processes of cell repair.
- Antimalarial drugs aimed at destroying the three proteins necessary for malarial parasite development.

8. *New and advanced technologies.* Laser capture microdissection, a technique of isolating individual cells from tissue, may lead to the earlier diagnosis of malignancies. Other technologies relevant to women's health include: GenBank, a central repository for genetic information; the Cancer Genome Anatomy project, which identifies molecular fingerprints of genes turned on during

the development of cancers; and new ways to deliver drugs previously available only by injection.

9. *Outreach to special populations.* Many outreach programs to minority populations are actively under way, including special programs promoting cardiovascular health for Latinos, and in treatment of hypertension and dyslipidemia for African Americans. Inducements to increase the interest of women and underrepresented minorities in research careers are under way as part of NIH's increasing outreach efforts to minority groups for careers in science.

The Task Force based the research recommendations provided in these reports on the conclusions reached by the working groups at the four scientific symposia. The report recommendations go well beyond the above NIH research topics to incorporate the concerns of the Task Force and the working groups about other aspects of women's health.

### ***Overarching Issues***

Despite their wide scope, the scientific reports herein reveal several overarching themes.

- "Women's health" is expanding into the larger concept of gender-specific medicine. Women's health is no longer an isolated phenomenon, divorced from mainstream medicine and regarded as a political or feminist issue. Instead, thoughtful scientists now see women as important sources of new information that will correct essentially male models of normal function and the pathophysiology of disease.
- The changing needs of women over the course of the life span are a common theme in most of the reports. Research on women's health must include the full biological life cycle of the woman and the concomitant physical, mental, and emotional changes that occur. This concept was made particularly clear at ORWH regional scientific workshops in Santa Fe, which addressed health issues as they relate to women at all stages of life

— during prenatal years, infancy and childhood, adolescence, reproductive and middle years, peri- and postmenopausal years, and the elder years.

- Multidisciplinary research is essential. Such research might be conducted under models like that of the program project grant, and involve teams of investigators with expertise in fields ranging from molecular biology to sociology and anthropology. It is suggested that the best results will come from a team in which each member is convinced of the intrinsic value of working together rather than working individually to address an issue or question of interest to all. Practically speaking, this will not be easy to achieve in academic medicine.
- The importance of social and behavioral science to research on women's health is unquestionable. Nevertheless, social and behavioral science needs to communicate the principles of its discipline to the longer-established and more "mainstream" medical disciplines. It is not now a familiar resource or partner for conventional research.
- Most clinical studies have been performed in men, and virtually all reports urge the collection of first-hand information from women to correct male models of normal function and of the pathophysiology of disease.

### *Strengths of the Subcommittee Reports*

One of the highlights of these reports is the increased appreciation for the importance of racial, cultural, and gender diversity in research populations. The rich suggestions for future research paths provided in the immunology and bone and musculoskeletal diseases reports are another strength. Other reports, particularly those addressing cardiovascular diseases and cancer, are well on their way to realizing new and particularly innovative programs that will advance not only women's health but gender-specific biology. The pharmacology report provides an excellent review of

the status of our understanding of gender-specific differences in drug metabolism in any given medical field. This report makes a persuasive case for assessing the impact of gender on normal human physiology.

The value of the public testimony (an innovative feature of these symposia) is indisputable. We learned things that otherwise would not have been heard, and the lay public and advocacy groups became involved in important dialogues with the scientific community.

This report is the culmination of a 2-year intensive effort on the part of more than 1,500 individuals nationwide, reflecting a broad spectrum of interests and expertise in women's health. Under the guidance of the Task Force members and working group cochairs, a diverse array of participants evaluated progress made, identified critical gaps in knowledge, and formulated cogent recommendations for future directions in research. We recognize that this massive effort, although not perfect, has laid the key groundwork from which fruitful partnerships will evolve during the next millennium in women's health research.

# THE USE OF “SEX” AND “GENDER” TO DEFINE AND CHARACTERIZE MEANINGFUL DIFFERENCES BETWEEN MEN AND WOMEN

Jennifer R. Fishman, B.S.  
Janis G. Wick, M.A.  
Barbara A. Koenig, Ph.D.  
Stanford University Center for Biomedical Ethics

## INTRODUCTION

The issue of how to describe differences in health status, or in the etiology, progress, and treatment of disease between men and women, is fraught with lexical and conceptual difficulty. Should differences — for example in rates of heart disease, participation in research, adherence to treatment, or access to specialty services — be attributed to “sex” or to “gender?” In the social sciences, the two terms usually describe conceptually distinct approaches to understanding difference, “sex” denoting biologically based differences and “gender” indicating culturally shaped variations between men and women (or between notions of masculinity and femininity).

Unfortunately, the language of difference in the biomedical literature is often imprecise, conflating the two terms and treating them as virtual synonyms. This imprecise use is not only linguistically problematic but has serious implications for future research, clinical practice, and treatment, as well as our very understanding of the nature of the health outcomes and status differences that we are studying. Without a strong conceptual and theoretical understanding of the distinction originally intended by those who clarified the difference between sex and gender, confusions are replicated. Choosing one term over another may seem like an innocent matter of semantics; however, the effects of such language choices and the meanings that they carry with them have had a significant impact on the equitable treatment of women in biomedical research and clinical practice. We must be able to

define difference to take into account states of wellness and disease that women share with men and those that they do not. As the research agenda presented in this volume is implemented, a sophisticated lexicon of difference will be essential to ensure the just treatment of women.

## THE SEX AND GENDER DISTINCTION

To understand the tenets of the sex and gender debate and its effects on current concerns in women’s health, one must first review the origins of the lexicon itself. The original distinction between “sex” and “gender” emerged in the mid-20th century. Feminist (and other) scholars distinguished between those qualities conventionally attributed to biologically based differences about a person’s “sex,” male or female, and those qualities that were understood as the result of cultural and social processes that constitute a person as man or woman: one’s “gender.”

This distinction was one part of the challenge to the dominant beliefs of the late 19th and early 20th centuries, which held that difference was biologically determined and that women’s constitutions were more biologically driven than those of men. A similar challenge was made to the notions of biologically determined racial characteristics attributed to African Americans and others, which allegedly accounted for differences in affect, intelligence, and economic status. During the past 25 years, use of the sex and gender distinction and lexicon has been fairly widespread throughout

both the social sciences and the humanities. In fact, more often than not, “gender” is used in these fields to describe differences between men and women to emphasize the idea that differences cannot merely be attributed to biological or physiological processes, but rather are almost always influenced by cultural, social, and historical contexts.

## SEX AND GENDER IN BIOMEDICAL LITERATURE

By contrast, in the biomedical sciences the distinction between “sex” and “gender” has been almost uniformly ignored. In fact, a quick glance at any database of medical literature reveals that not only are the terms “sex” and “gender” used synonymously, but that “gender” is often used instead of “sex” for describing biological factors, presumably because it is considered more “politically correct” to do so. This conflation is common in popular culture as well. However, in light of the history of the emergence of “gender” as a conceptual framework, the imprecise and oftentimes careless usage of “gender” in the biomedical literature leads to misinterpretation and imbues the reported research results with unintended meanings. At the very least, the use of the term “gender” implies an acknowledgment and recognition of the sex and gender distinction, and, at most, it implies the understanding that “sex difference” is the result of complex arrangements between “biology” (e.g., genetics, hormones, physiology) and “culture” (e.g., hierarchical relationships, historical and geographical location, social interactions). Yet this implicit meaning often belies the results themselves, for they reveal that no such understanding is intended. For example, a recent conference entitled “Gender Differences in Pain” actually focused exclusively on biological differences between men and women, and therefore might have more correctly been titled “Sex Differences in Pain.” Inclusion of “gender” in the title implies an understanding of the social and cultural components of sex differences in pain perceptions, and, in particular, would include discussions of the well established and recognized

observations of the culturally and socially embedded assumptions that physicians make that women, as opposed to men, overestimate and inflate their painful symptoms. However, these topics were not discussed at the meeting, which instead focused solely on the biological determinants of pain perception. The conference title, striving for political correctness, yielded only mystification.

This confusion is exemplified by recurrent debates in the “letters to the editor” sections of many medical journals. In the *Journal of the American Medical Association*, a letter under the heading “The Eternal Battle of Sex vs Gender” expressed the author’s distress that, in the “Instructions for Preparing Structured Abstracts,” “gender” was used instead of “sex.” However, the complaint was issued not because the author felt that “gender” implied something in particular about sex differences that should be considered, but rather that “gender” should be reserved as a grammatical term referring to the masculinity or femininity of nouns (as in most Romance languages). In other words, nouns can have a gender; people only have a sex. The editor’s response is equally revealing: while citing various sources for definitions of gender she concludes that the “evolving nature of the word gender causes some fuzzy usage . . . perhaps the time is ripe for a book on One Hundred and One Things You Wanted to Know About Gender and Were Not Afraid to Ask.” Although this letter was published in 1991, the confusion and uncertainty in medical journal publishing persists. One correspondent argues that the use of gender in scientific writing as anything other than the grammatical classification of a noun is improper use and “unpardonable.” Echoing this sentiment, the *New England Journal of Medicine* asked an author to “correct” the title of his paper on gender differences in health insurance, as the editors felt that the word “gender” referred only to the grammatical case of foreign nouns. The unwillingness of biomedical journals to consider other uses and meanings of “gender” exacerbates the confusion over the matter, as the term continues to be used both within and outside of biomedical literature.

## NEW DIRECTIONS IN THE DEBATE

To further complicate matters, social scientific research on the sex and gender distinction continues to reveal the ways in which this distinction itself does not reflect the complex relationship between or meanings of both sex and gender. Thus, while biomedical discourse has not even grappled with the original lexicon of sex and gender, the sex and gender debate in the social sciences continues to move in new directions, leaving biomedicine further behind. One such direction is the way in which the designation of “biological sex” itself as a binary concept of male versus female ignores the realities of both biology and sex. Social scientists argue that the category biological sex is a complex arena in which a variety of genetic, metabolic, and hormonal factors create individuals for whom a sex is socially assigned. Although one’s sex is most often determined by one’s genotype (i.e., XX or XY chromosomes), some scholars argue that the binary assignment is itself a cultural construct, and perhaps it is more appropriate to classify sex on a continuum, or at least a categorical system that includes more than two categories. Still other scholars study the fairly arbitrary assignment of sex that is made for individuals for whom no specific “sex” (read: male or female) assignment is possible due to physical ambiguities. In developed countries, such arbitrary assignment is often accompanied by genital surgery to “fix” any uncertainty in the child’s visible sex. These cases beg the question of what is “sex.”

Our understanding of the sexed body, particularly the female body, and the aspects of it that are deemed biologically “determined” has actually shifted substantially in the last century. In the late 19th century, biologically determined “femaleness” was thought to be localized in a particular organ, first the uterus and then the ovaries. In the early 20th century, the locus of the biologically determined “essence” of “femaleness” was viewed as hormonal. In fact, a hormonal conception of the body is now one of the dominant ways of thinking about the biological roots of sex differences.

Certainly the interest of biomedicine in the hormonal bases for health and disease in women is critically important, particularly in light of recent research on the potential protective benefits of estrogen against heart disease, the popularity of both birth control pills and hormone replacement therapies, and the increase in use of hormones in infertility treatments. However, attention to the hormonal bases of health and disease to the exclusion of other contributing factors in women continues to relegate women’s health to narrow biological definitions.

In addition, we are facing the possibility of yet another return to biological determinism with the emerging dominance of genetic models of disease causation within biomedicine. Already in many ways, the female body is a “genetic” body: her sex is determined most definitively by her genetic sex or genotype. It is certainly the case that many are attempting to define disease states based on genotype. Studies are underway to locate genetic components of breast cancer, alcoholism, Alzheimer’s disease, and many others. This trend may have distinctive consequences for women’s health as the new genomics may serve as a paradigm for biologically determined “femaleness” as well.

The nature of the relationship between sex and gender has also been examined by social scientists who argue that our notions of the ways that gender “maps onto” sex may be simplistic and may neglect the diversity of experiences of both men and women. Although there is the desire to separate that which is biologically determined about sex differences and that which is social, cultural, and environmental, scholars have since argued that neither sex nor gender — nor the relationship between sex and gender — can be understood so simplistically. However to lump everything into either the sex or gender category, depending on political or disciplinary persuasion, is equally problematic, for one’s linguistic decision implies assumptions about the nature of difference. As a result, feminist scholars have been attempting to move past the sex and gender distinction without neglecting or dismissing the pull of biological determinism whenever discussing sex or the complex real life experiences of men and women.

## EQUITABLE AND JUST TREATMENT FOR WOMEN

The lack of an appropriate lexicon of sex difference in biomedicine has had a serious impact on the just and equitable treatment of women in biomedical research and clinical medicine. The ambiguity and confusion about appropriate language speaks of a larger ethical problem of how it is that sex difference has been conceived, studied, and addressed in biomedicine. Our understanding of the nature, importance, and implications of sex difference is growing, as should our understanding of the complexities and dilemmas of researching and reporting such differences. It was not long ago that women were routinely excluded from large-scale clinical trials. For instance, most trials for the prevention of heart disease studied middle-aged males and excluded women because of a complex set of assumptions, including the perception that women's hearts were the same as men's. In this case an assumption of sameness led to unethical and neglectful treatment of women. Yet, one of the reasons women were not included in these trials is because of the perception that women's bodies (hormonally and reproductively) behaved very differently than men's and that these factors would complicate the collection of safe and reliable data. Therefore, women were enough like men to warrant exclusion from clinical studies, yet they were too different to be included as part of the same study. This confusing and paradoxical attitude toward sex difference in clinical trials demonstrates the complexities and problems attending to sex difference. The human subject guidelines have changed to require the inclusion of women in clinical trials, yet the question remains as to how similarities and differences between men and women will be explored, studied, and compared.

In some cases of biomedical research and clinical treatment, sex difference is not explicitly attended to, yet its implications lie just below the surface. An example of this phenomenon is the treatment for women

with depression. Although we have sufficiently documented the higher proportion of women than men who are medically treated for depression, we have not turned our attention to the implications of this difference. It is here that the sex and gender debate may well be able to provide a backdrop for studying this observed difference. In other words, does noting this difference between men and women unknowingly imply that the difference can be attributed to biological factors? Are women at higher risk for depression simply by virtue of being female? We can hypothesize many explanatory models for this observation, ranging from biological and hormonal factors that predispose women to depression to a "cultural" model that would explore the mental health consequences of sociocultural stratification, including women's greater tendencies to seek medical care in concert with physicians' tendencies to pathologize women's mental health problems. The model we hypothesize depends on our perceptions and conceptualization of the nature of sex difference itself; leaving that conceptual base unexamined is dangerous for women's health and women's health research. It is also of potential harm to men. Pfeffer (1985) argues that men's reproductive health problems have conventionally been treated similarly to women's health problems, that is, pathologized.

Accompanying the conceptual difficulties associated with the lack of an appropriate lexicon of difference is an inability to explore underlying causes of "women's" diseases. The effects of this inability on treatment are enormous. One example is the way in which tranquilizers have been prescribed to large numbers of women, based on the assumption that such drugs are "safe" and "non-addictive," and that women must be "naturally" more nervous and anxious than men. The treatments offered women in these cases, most often prescription drugs, have been unnecessarily limited due to a lack of conceptual understanding of the underlying causes for the differences in women's experiences.

A further ethical concern stems from the recurrent debates about “nature” versus “nurture” that have become an inherent part of the emergence of the biotechnologies of genetic testing. With the Human Genome Project more than halfway complete, biomedical researchers and clinicians face questions daily about what exactly is biologically determined and what can be attributed to “environment,” or perhaps the even harder question of how do genes (or one’s biological make-up) interact with one’s environment? Sex differences become part of this complex set of questions: in the same way that we must look at the complex interplay between “biology” and “culture” to understand disease causation, prognosis, and treatment options, we must also look at the differences between men and women. Ethically, this is a difficult task. In the case of the new biotechnologies that allow for genetic testing for susceptibility to disease, the ethical implications of developing, offering, or performing such tests are enormous. If we offer someone a genetic test for a disease that cannot be prevented or cured, are we offering patients meaningful choices? This is equally true for questions about the nature of sex difference. To assume that the differences in health status or outcomes between men and women is biological leaves us a restricted set of choices for research and treatment. If we do not explore the complex relationship between “nature” and “nurture,” how can we conduct appropriate research into health and disease in women and treat them fairly?

The use of an imprecise lexicon for describing differences between men and women in biomedical research has consequences for the conduct of science as well as for the clinical treatment of women. In each of the above examples, and in numerous others, the use of categories of “men” and “women” for describing difference assumes that the differences between the two categories are greater than differences within the two groups. By relying on sex category differences as the primary marker of difference other potentially important factors may be ignored, for example the

complex interaction of race, sex, and social class within our health care system. This case has been effectively made for the social category of race, where both the ethics and the science of research based on differences between racial categories has been questioned. Within biomedical research that studies racial difference, there is often the implicit assumption that the differences between racial groups are biologically based or genetically determined. Yet many have problematized this assumption, pointing out the ways in which there are often larger differences within categories than between them. Moreover, documenting differences based on supposedly categorical differences between races within biomedicine not only assumes that such differences are somehow inherent to those within that racial category, but also has the potential to stigmatize and blame those considered within that category for falling ill. This affects clinical visits and treatment options for such individuals. Assumptions about categorical differences between the sexes is no different, and should be held equally suspect. Indeed, both “race” and “sex” characterizations have often been used not for delineating important differences in terms of treatment but for underlying political and cultural reasons that have proved highly detrimental to both women and racially stigmatized groups. Developing a precise lexicon of sex difference would be a primary step away from such deleterious distinctions, for it demands that we focus on the ways in which we measure and report differences between men and women, and most importantly allows us to specify what these differences mean for biomedical research and ultimately for patients in clinical settings.

*The authors wish to thank Adele E. Clarke and Nancy Fugate Woods for helpful comments on earlier drafts of this manuscript.*







REPORTS OF THE WORKING GROUPS:  
SCIENTIFIC CHAPTER —  
SUMMARY OF RECOMMENDATIONS



# ALCOHOL, TOBACCO, AND OTHER DRUG USE, DISORDERS, AND CONSEQUENCES

Women's use of alcohol has resulted in a major public health problem; women represent one-third of the estimated 14 million alcohol-abusing or alcohol-dependent people in the United States. In 1995, the National Household Survey on Drug Abuse reported that, of an estimated 12.8 million Americans ages 12 and older who used an illicit drug during the past 30 days, 4.3 million were women of childbearing years. Although fewer women than men use drugs, the potential consequences of drug abuse are often different for women. Tobacco use is responsible for more than 500,000 deaths in the United States each year; nearly a third of these are women. Although tobacco smoking has declined among men by 84 percent during the past three decades, smoking rates among women declined only 21 percent during this same period.

## A C H I E V E M E N T S

Recent research has contributed the following knowledge to the alcohol and other drug field:

- *Gender as a Research Variable.* Researchers now pay significant attention to gender differences in the analysis and reporting of epidemiologic data, for example in surveys such as the national probability

sample survey focusing on alcohol and other drug use among women. Studies are beginning to examine the role of the menstrual cycle in patterns of alcohol and other drug use.

- *Study Design Issues.* Improved study designs recognize the importance of effective dosage when prescribing medications for female patients as well as issues of access, entry, and retention of women in treatment.
- *Domestic Settings.* The family as the unit of analysis is a major new focus, in particular the interaction of prenatal alcohol and drug exposure and postnatal environment and status of the mother and family. Violence and sexual abuse are now recognized as factors in alcohol and drug use among female victims, leading to recognition that abused women need comprehensive services beyond drug and alcohol treatment.
- *Studies To Examine the Genetic Basis of Alcoholism in Women.* Although not conclusive, these studies do permit tentative conclusions about the role of inheritance in alcoholism among women, which can be applied to future research.

## RESEARCH RECOMMENDATIONS

- *Drug Use Patterns and Treatment Models.* Studies should be undertaken that describe the role of gender in sensitivity to pain medication, the biochemical effects of drug use, self-medication, and use of psychotropic prescription drugs, including health benefits, in the development of treatment strategies for alcohol and drug use.
- *Developmental Effects.* An examination of the effects of maternal alcohol and drug use on children's use of alcohol and drugs should be undertaken.
- *Predisposition to Mood, Eating, and Anxiety Disorders.* Further research should be conducted with a view to better understanding the role of mood, eating, and anxiety disorders in alcohol and drug use, as well as those psychological, social, and biological factors that predispose young women to these disorders.
- *Effects of Victimization and Violence.* Conduct research on sexual abuse during childhood, and the interaction between other sexual or violent victimization of women and their use of alcohol and drugs.
- *Biological and Physiological Gender Differences.* Studies should be conducted that detail gender differences in health consequences that occur across a spectrum of consumption and use levels.
- *Media and Advertising.* The influence of the media and advertising on a woman's use of alcohol and drugs including tobacco should be further examined.
- *Gender-based Treatment.* Studies that examine the role of ethnic and gender variation in how alcohol and drug users perceive the need for treatment should be encouraged, from childhood through adulthood.
- *Prevention Strategies.* Develop counseling techniques for adolescent and adult females who may have a genetic risk of alcohol and drug use and/or abuse. Develop prevention strategies to account for the role of childhood violence and sexual abuse in adolescent and adult females' use of alcohol and drugs; related studies to appropriate interventions.
- *Intervention Strategies.* Emphasize early intervention with girls and adolescents in prevention studies designed to reduce individual and social environmental risk factors. Base interventions on etiology and pathway findings for females versus males.

*“In view of the trends toward an aging American population, and the relative longevity of women in comparison to men, special attention should be paid to the impact of alcoholism and drug abuse on the health of perimenopausal and postmenopausal women.”*

Nancy K. Mello, Ph.D.  
Harvard Medical School

# BEHAVIORAL AND SOCIAL SCIENCES

The World Health Organization defines health as “a state of complete physical, mental, and social well being and not merely the absence of disease or infirmity.” This definition not only expresses the interrelatedness of mind, body, and social context but also stresses the positive meanings of health. The NIH Office of Behavioral and Social Sciences Research (OBSSR) has identified five crosscutting themes in behavioral and social sciences research: an emphasis on theory-driven research; the search for general principles of behavioral and social functioning; a developmental, life span perspective; an emphasis on individual variation across sociodemographic categories such as gender, age, and sociocultural status; and a focus on both the social and biological contexts of behavior.

## A C H I E V E M E N T S

Recent research has contributed the following knowledge to the behavior and social science fields:

- *Research Design.* As a result of increased awareness and knowledge of gender and behavioral and social factors and of explicit law and regulations, survey samples and study populations more routinely include women and are more likely to reflect at least some of the geographic, racial, and ethnic diversity of the general population. A large body of methodological research has illuminated the

influence of context on the study or interview situation and the need to match interviewers and respondents on certain characteristics (e.g., language) to elicit the most valid and reliable data.

- *Behavioral Methodologies.* Health researchers on health topics are increasingly using the methods developed by behavioral and social scientists, especially focus groups, to gather information on attitudes and behaviors. There is a growing recognition among policymakers and researchers of the need to involve community members in defining key research questions and collecting data on those communities, and of the merits of other community-based and participatory forms of research.
- *Violence and Women’s Health.* Violence has recently been recognized as an important issue in the study of women’s health. Great progress has been made in a relatively short time in understanding the extent to which women experience violence in their lives, the consequences for women, and the development of effective treatments.
- *Heart Disease.* Heart disease has long been the major cause of death among women in the United States, but it was not recognized as a major health problem in women until recently. Since 1991, a number of studies have been and are being

conducted to fill in gaps in knowledge about heart disease in women (e.g., the Nurses Study, Postmenopausal Estrogen/Progesterone Intervention, the Women's Health Initiative, Study of Women's Health Across the Nation). These studies examine behavioral factors (e.g., exercise, diet, stress, social support) and their relationships to cardiovascular health outcomes.

- *Genetic Screening and Breast Cancer.* The rapidly advancing world of genetic research is leading to the availability of genetic screening for an increasing number of diseases. Important research has been conducted examining women's perceived risk of breast cancer, evaluating counseling programs and identifying women who may benefit most from counseling.

## R E S E A R C H R E C O M M E N D A T I O N S

- Basic behavioral and social science should study decisionmaking processes regarding adoption and maintenance of health behaviors, investigate gender roles, and study culture and social context.
- Collaborative, multidisciplinary research that incorporates behavioral and social science into biomedical and clinical studies should explore preventive factors, study treatment, and investigate the care and caregiving experience.
- Methodological research should be used to determine innovative measures that reflect women's lives, devise innovative data gathering strategies including qualitative and community-based approaches, and explore effective methods of recruiting and retaining women in studies.
- Funding and training policies and practices should be altered to:
  - Sponsor a workshop on multiple factors affecting women's health decisionmaking.

- Develop mechanisms to ensure funding of research on relevant behavioral and social components.
  - Ensure that study sections have adequate expertise to review behavioral and social science components of women's health proposals.
  - Fund training grants for behavioral and social scientists working in medical areas.
  - Provide boilerplate language for appropriate Request for Applications in every NIH institute or center.
- The institutions that educate and train health professionals should integrate behavioral and social science relevant to women into health professional curricula, develop a process for integrating new advances, and devise ways to test students on their knowledge in this area.
  - Special initiatives should be undertaken to conduct clinical trials related to behavioral interventions, explore physical activity, and study violence.

# BONE AND MUSCULOSKELETAL DISORDERS

**B**one and musculoskeletal disorders are responsible for high disability and high cost to society and thus are of significant public health importance. Arthritis and orthopaedic conditions, including fractures due to osteoporosis, are among the leading causes of disability and activity limitation in the United States. Many of these conditions are more prevalent in women than men and have gender-specific manifestations, etiology, impact, and possibly outcomes of treatment. The initial focus and efforts in women's health have been appropriately on the diseases with acute mortality or female specificity; now it is timely to focus on the diseases and conditions that reduce the quality of women's lives and limit their activities as well as contribute to large health care expenditures.

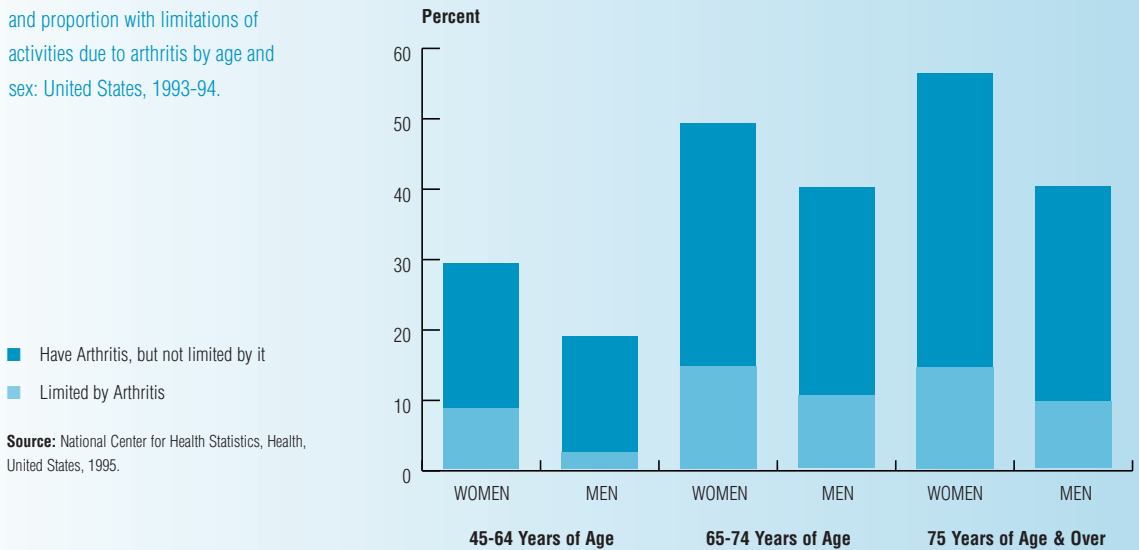
## A C H I E V E M E N T S

Recent research has contributed the following knowledge to the bone and musculoskeletal fields:

- *Arthritis and Musculoskeletal Disability.* Basic science related to the pathophysiology of arthritis has been advanced in the last several years, and there has been enormous progress in understanding the role of self-management in living with arthritis. Specific advances in our knowledge of arthritis and its treatment and management include:
  - Better understanding of cartilage cell physiology, matrix factors, and enzymes cofactors.
  - Improvements in joint replacement surgery.
  - Progress toward the goal to achieve a better quality of life and acceptance of impairment or disability in a wider range of the arthritic population.
  - Exercise studies indicating beneficial outcomes for arthritis patients, including pain relief.
  - Reliable and validated tools for assessing functional capacity, activity limitations, psychological status, and quality of life.
- *Osteoporosis and Fractures.* Significant advances have been made in understanding the biology of bone remodeling and functions of various cells in the skeleton, and new treatment options and sophisticated assessment technologies are now available. Recent progress assists in understanding how calcium and physical activity affect bone health.
- *Orthopaedics and Physical Activity.* Total joint replacements have provided enormous relief from pain and disability for individuals with end-stage joint disease. Improved fracture fixation techniques and surgical techniques for soft tissue injuries have returned people to work and sport activity quickly. Carpal tunnel syndrome has been recognized, and some of the factors that may predispose to this condition have been uncovered.



Proportion of persons with arthritis and proportion with limitations of activities due to arthritis by age and sex: United States, 1993-94.



Source: National Center for Health Statistics, Health, United States, 1995.

## RESEARCH RECOMMENDATIONS

### Arthritis

- Investigate the greater prevalence and triggers of arthritis in women.
- Explore the biological and mechanical factors that influence the progression of arthritis.
- Examine biological repair processes and bio-engineering approaches to tissue regeneration.

### Osteoporosis

- Understand the factors that contribute to the development of peak bone mass (e.g., diet, exercise, puberty, pregnancy, smoking, environment).
- Focus on clinical trials to develop treatment and prevention studies that will not be conducted by the private sector — combined drug therapies, exercise, and nutrition studies.
- Further refine biological markers and other assessment technology.

- Focus on maintenance of bone mass throughout life — identify genetic and lifestyle factors associated with bone loss.
- Explore quality-of-life issues in women with osteoporotic fractures.
- Explore the role of physical activity in preserving muscular strength, balance, and coordination as a means of preventing falls in the elderly.
- Develop specific exercise regimens that affect the bone at the major sites of fracture (i.e., hip, spine, and wrist).

### Orthopaedics

- Investigate the role of women's footwear in pain, disability, and falls.
- Determine the prevalence and etiology of stress fractures and other overuse syndromes — repetitive stress injury.
- Investigate the molecular signals that control repair and growth in cells of the musculoskeletal system.

- Develop synthetic replacements for muscle, soft tissue, and bone damaged beyond repair.
- Explore knowledge of the interaction of the immune system and its role in transplantation of bone and ligaments.
- Study the relative influences of osseous anatomy, ligamentous laxity, and sex hormones on musculoskeletal disorders.
- Explore gender variation in treatment outcomes.

### ***Physical Activity and Sports Medicine***

- Improve measures of energy expenditure and its benefits to the musculoskeletal system — whether leisure time exercise plays a different role from household or occupational activities.
- Determine the type, intensity, duration, and frequency of physical activity that is important for musculoskeletal health.
- Investigate gender differences in sports injuries — endocrine, structural, and training factors that lead to injury.
- Explore the “female athlete triad,” including contributing factors such as nutrition, energy expenditure, and stress.
- Understand the role of physical activity in the development of bone, tendon, ligament, and muscle.

### ***Data Needs and Information Dissemination***

- Provide information from national data surveys and large cohorts on prevalence and treatment outcomes.

“ . . . women’s health issues are long on numbers, large on disability and suffering, and enormous in cost. To reduce suffering and disability, we need to prevent these disorders when we can, diagnose them early to minimize their impact, and provide interventions to maximize functioning in patients who have them. We want our daughters and their daughters to travel a different road than we have.”

Laura Tosi, M.D.  
American Academy of  
Orthopaedic Surgeons

- Improve surveillance of injury patterns in physically active women of all ages.
- Improve, develop, and validate instruments that measure physical activity and relate it to health outcomes — improved performance measures.
- Develop effective information dissemination processes.
- Develop methods for tracking and improving compliance with effective therapies.



# CANCER

Cancer remains a major public health problem, causing untold anxiety and suffering for patients and their families and generating a substantial part of the nation's health care expenditures. In 1997, an estimated 596,000 women were diagnosed with cancer, and 265,900 women died of the disease. Cancer is the leading cause of death for 35- to 74-year-old women. Lung cancer continues to be the leading cause of cancer deaths for women, followed by breast and colorectal cancers.

## ACHIEVEMENTS

Recent research has contributed the following knowledge to the cancer field:

- U.S. mortality rates for breast and colorectal cancers have decreased among Caucasian women.
- Scientists have identified genes associated with cancer and signaling pathways responsible for loss of cellular control mechanisms, greatly improving the understanding of carcinogenesis.
- New associations between infections and cancers have been found, and a mechanism for viral carcinogenesis has been identified.

- The idea that cancer may be a preventable disease is closer to reality. Clinical trials have evaluated retinoids to prevent various cancers and tamoxifen to prevent breast cancer.
- Many researchers now examine gender, socioeconomic, and racial and ethnic differences when studying cancer incidence, mortality, and prevention.

## RESEARCH

### RECOMMENDATIONS

- Identify and develop effective diagnostic screens for all cancers.
- Develop chemoprevention strategies and vaccines against cancer.
- Develop improved treatments, reliable biomarkers, and imaging technologies for the early detection of lung cancer.
- Give high priority to smoking prevention and intervention programs.
- Evaluate the cumulative effects of environmental, exogenous, and endogenous estrogens (including DES, HRT, and oral contraceptives) on cancer risk, and develop safer medications, if needed.

- Study the social, ethical, legal, and economic effects of new commercially available genetic tests, and develop appropriate counseling models linked to genetic testing.
- Design, evaluate, and implement culturally competent interventions to overcome barriers to women’s participation in cancer prevention, detection, treatment, and outcomes research. Include older women, minorities, and rural women, traditionally underrepresented, as a high priority.
- Continue basic research to define cancer mechanisms, identify high risk individuals, and develop new strategies for treatment.
- Develop prevention and screening strategies that will increase the survival of persons at risk.
- Teach health care providers communication skills that encourage health-promoting behavior in their patients and the public.
- Address quality of life issues in cancer survivors.

*“The tragic and commanding fact about ovarian cancer is that more than 50 percent of the women who have it die within 5 years of diagnosis.”*

Ann Kolker  
Ovarian Cancer  
National Alliance:  
Ovar’coming Together

**Percentage of High-School Students Who Were Smokers in the Previous Month, 1990-1994\***

	AMERICAN INDIANS & ALASKA NATIVES	ASIAN AMERICANS & PACIFIC ISLANDERS	BLACKS	HISPANICS	WHITES
GIRLS	39.4	13.8	8.6	19.2	33.1
BOYS	41.4	20.6	11.6	28.5	33.4

# CARDIOVASCULAR DISEASES

**H**ear disease has been the number one killer of women for nearly a century. Cardiovascular disease (CVD) accounts for about 57 percent of all deaths among American women. Of the more than 960,500 deaths from heart attack each year, more than 52 percent occur in women. Cardiovascular disease kills almost twice as many American women as all cancers combined and more than 11 times as many women as does breast cancer. Older women who have suffered heart attacks are twice as likely as men to die from them within a few weeks. About 44 percent of women who have heart attacks die within 1 year, whereas only about 27 percent of men die within 1 year. Among women who die suddenly of coronary heart disease, 64 percent have no previous symptoms, compared with 48 percent of men. The heart attack death rate for African-American women between the ages of 35 and 74 is about twice that of Caucasian women and three times that of women of other races. Stroke, America's number three killer, killed about 158,000 people in 1995, and of these, 61 percent were women. Stroke kills twice as many women as does breast cancer.

## A C H I E V E M E N T S

Recent research has contributed the following knowledge to the cardiovascular field:

- Basic and applied CVD research funding for women's health has increased.

- Types of research (health services, cost effectiveness, population-based, community) pertaining to women's health have increased.
- Participation of women in clinical studies, especially diverse groups of women, has continued to increase.
- New cardiovascular treatment regimens in women's health have been developed.
- The CVD death rate in women is 37 percent lower than it was in 1900.

## R E S E A R C H R E C O M M E N D A T I O N S

### *Developmental Biology of the Vascular System and Role of Fetal Environment in Programming Lifelong Cardiovascular Function*

- Study the developmental biology of the vascular system and role of fetal environment in programming lifelong cardiovascular function.
- Evaluate the interaction of nutrition and cardiovascular development, using animal models.
- Study the maturation of central nervous system functions and how they regulate the functioning of the cardiovascular system.
- Explore the interrelationship of renal development and cardiac function.

### ***Molecular and Physiologic Mechanisms of Hormone Action in the Cardiovascular System***

- Characterize estrogen receptors in vascular tissue and vascular cells, including vascular endothelial cells and smooth muscle cells.
- Identify the relative amounts of mRNA and protein for estrogen receptor alpha and estrogen receptor beta in different vascular cells and beds, in women versus men, in premenopausal versus postmenopausal women, and in the presence or absence of hormone replacement therapy.
- Study molecular mechanisms of estrogen action in vascular cells, with an emphasis on novel pathways in vascular cells, including ligand-independent activation of vascular estrogen receptors and vascular cell co-activator and co-repressor molecules.
- Examine molecular mechanisms of estrogen's nongenomic vasodilatory effect on the vasculature and estrogen's longer-term effects to inhibit atherosclerosis and the response to vascular injury.
- Identify and study vascular genes regulated by estrogen, including identification of novel vascular gene targets of estrogen and study of vascular estrogen response elements in these genes.
- Characterize and study other steroid (progesterone and androgen) hormone receptors in the vasculature of women and men and their gene targets.

### ***Cardiovascular Implications of Diabetes and Obesity***

- Develop and evaluate strategies to improve the outcome of women with diabetes.

*“As obesity is becoming more prevalent, particularly among women, and affects a number of risk factors as well as risk for coronary heart disease itself, further research into its causes and treatment are needed.”*

Marian C. Limacher, M.D.  
American College  
of Cardiology

- Study the interactions between estrogen and diabetes on blood vessels and the heart, and the potential role of ERT in protecting postmenopausal diabetic women from developing cardiovascular disease.
- Examine the impact of aggressive modification of other risk factors on cardiovascular outcomes in diabetics.
- Study prenatal precursors to obesity.
- Study genetic, molecular, and hormonal factors in obesity and why they cause obesity to be a greater problem in women than in men.
- Examine environmental factors in the expression of a predisposition to obesity, and the development of approaches to alter the environment to avoid or address obesity.
- Study the roles that various stages of life play in placing women at increased risk for obesity and how to address these risks.

- Investigate modifiable societal and community factors that result in increased obesity and ways in which to change these factors to reduce the prevalence of obesity.
- Study effective therapeutic modalities to prevent or treat obesity, especially physical activity.

***Prevention, Detection, and Management of Cardiovascular Disease in High-risk Populations***

- Examine the dimensions of cardiovascular disease in high-risk populations, including women who are octogenarians and older, racial and ethnic minorities, and disabled women.
- Study the impact of patient and health care professional behaviors on cardiovascular disease development and prevention in women.
- Evaluate why the general public, patients, and health care professionals do not act on well-known prevention information despite its widespread availability.
- Determine exercise, nutrition, smoking, and other lifestyle behaviors related to the development of cardiovascular disease among women patients.

**Women's Perceived and Real Health Risks**

PERCEPTION	PERCENT	CAUSE OF DEATH	PERCENT
Breast cancer	46	Heart disease	34
Unspecified cancer	16	Other cancer	12
Heart disease	4	Stroke	8
AIDS	4	Lung cancer	5
Uterine/Ovarian cancer	3	Breast cancer	4

Source: Vital Statistics of the U.S., National Center for Health Statistics

- Develop methods to increase the effectiveness of cardiovascular disease prevention interventions and education efforts.
- Evaluate the education, prevention, diagnostic, treatment, and management procedures followed by health care professionals with respect to cardiovascular disease and how these differ by gender, age, and race and ethnicity of patients.





# DIGESTIVE DISEASES

Recent research has yielded important information on gender differences in digestive diseases. Gender-based differences have been identified in several areas, including irritable bowel syndrome and functional bowel disorders, colorectal cancer detection, gallstone disease, liver disease, and metabolic bone disease. The discovery of genetic bases in certain colon cancers, gallstone disease, and liver diseases is another advance of vital importance.

## ACHIEVEMENTS

Recent research has contributed the following knowledge to the digestive diseases field:

- The functions of specific brain peptides, nitric oxide, carbon monoxide, and other factors in gastrointestinal motility that affect irritable bowel syndrome (IBS) and functional bowel disorders (FBD), and in relating sensory dysfunction, pelvic floor dysfunction, motor dysfunction, and psychosocial factors, including physical and sexual abuse, to these disorders.
- Identification of four distinct genes that, when inherited in altered form, cause increased susceptibility to colorectal cancer at unusually early ages, plus identification of a gene associated with familial adenopolyposis.

- Screening for colorectal cancers in that studies have shown that screening with fecal occult blood testing or sigmoidoscopy is associated with decreased mortality from these cancers.
- Identification in an animal model of genes associated with gallstone disease, the evolution of laparoscopic cholecystectomy as the most common technique for gallbladder removal, and the determination that certain drug therapies may prevent the formation of gallstones in patients experiencing rapid weight loss.
- A greater understanding of the mechanisms of nonsteroidal anti-inflammatory (NSAID)-induced damage to the gastrointestinal tract, along with a greater understanding of the mechanism for cytoprotection of the gastric mucosa.

## RESEARCH

## RECOMMENDATIONS

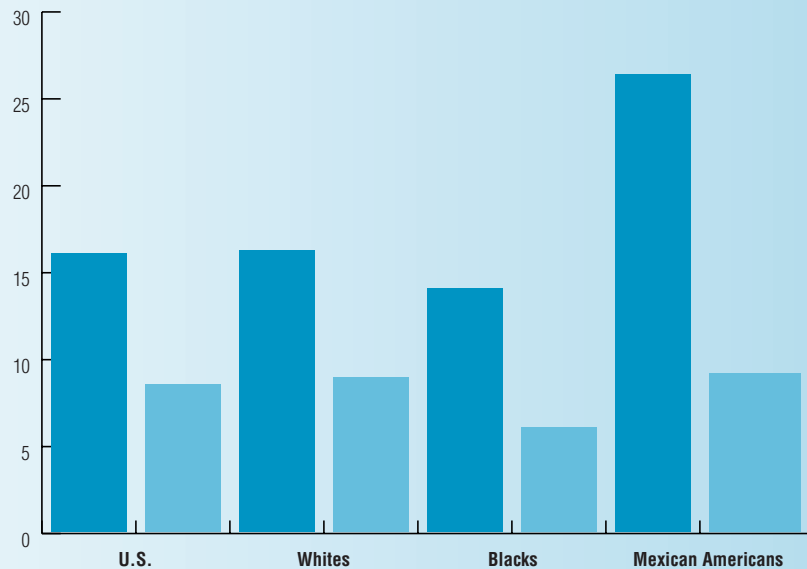
### *Irritable Bowel Syndrome and Functional Bowel Disorders*

- Determine why these conditions affect so many more women than men.
- Further elucidate the mechanisms of gut motility.

Age-adjusted Prevalence of Gall Bladder Disease Among Adults According to Ethnicity and Sex

■ FEMALES  
■ MALES

Source: Third National Health and Nutrition Examination Survey



- Clarify smooth muscle physiology.
- Identify and characterize the influences on gut motility and smooth muscle physiology of various brain peptides and neurotransmitters such as carbon monoxide and nitric oxide.
- Develop a clearer understanding of the functioning of the enteric nervous system.
- Explain how heightened sensitivity to pain and other sensory dysfunctions are involved in IBS and FBD.
- Examine the relationship between pelvic floor dysfunction and IBS and FBD.
- Study the effects of the menstrual cycle on IBS and FBD.
- Elucidate the role of environmental and other stressors, developmental influences, and biopsychosocial factors in these conditions.

- Validate diagnostic criteria.

- Further identify and target specific pharmacologic and other therapeutic interventions (such as stress reduction techniques), and alternative health interventions (such as acupuncture and family therapies) for IBS and FBD.

#### *Colorectal Cancer*

- Determine how interventions such as postmenopausal estrogen therapy and low-fat diets affect the risk of colorectal cancer in women.
- Develop more cost-effective methods for early detection of colorectal cancer.
- Devise methods to educate women and health care providers about the importance of screening for colorectal cancer.
- Explore genetic identification of high-risk groups.

- Explore the relationship between hereditary colon cancer and ovarian and endometrial cancers.

### **Gallstone Disease**

- Investigate gender differences in cholesterol metabolism and excretion in bile.
- Explore the effects of gender on interactions between gallbladder physiology and gut motility.
- Identify how sex hormones influence the expression of recently identified genetic factors.
- Elucidate the physiological functions of the gallbladder and factors that influence the gallbladder functions of motility, secretion, and absorption.
- Improve diagnosis and methods to predict patients who will develop complications of gallstone disease.
- Investigate the etiology and natural history of gallstones formed during high-risk periods such as pregnancy and weight loss.
- Explore the reasons for ethnic variations in gallstone disease (such as the high incidence among American Indians and Mexican Americans).
- Investigate potential preventive measures.

### **Liver Disease**

- Better understand non-alcoholic steatohepatitis, including (a) why women are more susceptible; (b) what the natural history is, including who develops cirrhosis; (c) what the molecular mechanisms and genetic and environmental susceptibility factors are; and (d) treatment and prevention strategies.
- Explore pathogenesis, immunology, and therapeutic approaches to primary biliary cirrhosis (PBC).

*“Irritable bowel syndrome predominantly affects women. Approximately 75 percent of individuals with IBS in the community are female, with the incidence being reported as high as 90 percent in some medical centers. This is a major women’s health issue.”*

Nancy Norton  
International Foundation  
for Functional  
Gastrointestinal Disorders

- Explore influences of sex hormones on elements of the immune system related to autoimmune liver diseases.
- Better understand hepatic cell growth and investigate the influence of sex hormones on the proliferation of liver cells and the growth of tumors.
- Identify safe and effective therapies for PBC and autoimmune hepatitis.

### **NSAIDs and Peptic Ulcer Disease**

- Develop tolerated medications for preventing gastrointestinal ulceration and bleeding experienced as side effects by those who rely heavily on NSAIDs to control pain from arthritis and other disorders. Involve women in sufficient numbers so as to yield meaningful information on prevention strategies for women.

### *Metabolic Bone Disease*

- Better understand the mechanisms of calcium absorption through the intestines in health and disease and how they change with age.
- Clarify the relationship between inflammatory bowel disease and osteoporosis and osteopenia in order to develop improved treatment modalities.
- Clarify the relationship between primary biliary cirrhosis and osteoporosis and osteopenia in order to develop improved treatment modalities.
- Develop better methods for evaluating and treating bone loss that accompanies chronic liver disease.
- Determine the extent to which bone loss in chronic liver diseases may be restored after liver transplantation.
- Investigate whether the absorption and metabolism of drugs used to treat chronic gastrointestinal conditions changes during pregnancy.
- Further clarify the causes of acute fatty liver of pregnancy and develop improved treatment and prevention strategies.

### *Digestive Diseases During Pregnancy*

- Investigate the influence of hormones on various digestive disorders that may be present during pregnancy.
- Investigate the etiology and natural history of gallstones formed during pregnancy.
- Determine the safety profiles in pregnancy of procedures used to diagnose and treat gastrointestinal conditions.
- Determine the safety profiles in pregnancy of drugs used to treat chronic gastrointestinal conditions.

# IMMUNITY AND AUTOIMMUNE DISEASES

**W**omen's health depends significantly on the appropriate function of the immune system. Asthma and allergic diseases are important sources of morbidity in women. Autoimmune diseases, in which the immune response is directed at the body's own tissues, disproportionately afflict women. In addition, the immune response is important in protection against many infections, such as sexually transmitted diseases, and their sequelae. Evidence exists that there may be differences in the function of men's and women's immune systems, including the fact that women are able to tolerate without rejection a fetus during pregnancy.

## A C H I E V E M E N T S

Recent research has contributed the following knowledge to the immunity and autoimmune field:

- Degradation of antigens intracellularly and their presentation to the immune system.
- Identification of subtypes of T cells and their role in immune activation and regulation.
- Development of B cells and their role in cellular immune responses.
- Identification of many soluble molecules including cytokines and chemokines, and their role in the immune response.
- Trafficking of immune cells to various areas of the body.
- Inter- and intracellular signaling cascades.
- The pathways leading to cell death.
- Interactions of the various components of the immune system.
- The critical role played by the immune system in many diseases that were not previously thought to be immunologically mediated, increasing the need to understand immune function throughout the life span.
- Development of new research tools, for example, polymerase chain reaction (PCR).
- Analysis of large numbers of samples facilitated by synthetic and recombinant peptide libraries.
- Screening of defined populations for genetic differences, made possible with the development of large patient and family repositories as well as newer genetic screening and sequencing methods.

## RESEARCH RECOMMENDATIONS

- Address the gaps in knowledge and exploit the opportunities defined above.
- Design information systems that allow easier access to archival material on clinical and genetic studies.
- Increase multidisciplinary research.
- Increase sharing of resources among researchers (this includes sharing of clinical samples, DNA banks, serum banks, animals, and reagents).
- Communicate more effectively between the lay public and the scientific community, making information readily accessible to researchers, health care providers, and consumers.
- Stratify future and existing data from basic and clinical studies for sex and age of subjects.
- Identify resistance and susceptibility genes for multigenic diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, scleroderma, Sjögren's syndrome, Type I Diabetes, and asthma.
- Identify the effects on immune function of environmental influences such as diet, stress, allergen exposure, and exogenous estrogens.
- Study the comparative effects of sex and age on normal and abnormal immune function in animals and humans; determine the role of stages of the menstrual cycle on immune function.
- Determine the effects of sex steroid hormones (estrogens and androgens), other hormones, and hormone fluctuations on different aspects of the immune response.
- Identify the immunologic environment in the target organ in various autoimmune diseases — the brain in multiple sclerosis, the joint in rheumatoid arthritis, the beta cells in diabetes, the kidney and vasculature in systemic lupus erythematosus, the lung in asthma, and the skin in scleroderma.
- Determine successful methods to inactivate autoreactive immune cells in autoimmune disease. T-cell antagonists, mucosal tolerance, and methods to promote lymphocyte deletion are likely possibilities.
- Determine the role of innate immune mechanisms in immune and allergic diseases and devise therapeutic interventions.
- Establish improved surrogate markers to measure disease activity and response to therapy in diseases such as rheumatoid arthritis, multiple sclerosis, scleroderma, systemic lupus erythematosus, and Sjögren's syndrome.

*“Basic research will yield information that benefits the treatment and diagnosis of all autoimmune diseases and represents the most promising approach to finding a cure.”*

Virginia T. Ladd, R.T.  
American Autoimmune  
Related Diseases  
Association

# INFECTIOUS DISEASES AND EMERGING INFECTIONS

Sexually transmitted diseases (STDs), including HIV/AIDS, require a continued concentrated research effort. Many of the STDs are more difficult to detect in women than in men and, in many ways, these diseases affect women more severely. As a consequence of STDs, women may experience infertility, tubal pregnancy, genital cancer, early fetal loss, and congenital or perinatal infection. Efforts should be continued to reveal more about the microbial and behavioral etiology of these infections, their differential effects on women across the life span, measures women can take to prevent contracting them or prevent their progression to later stages, and the effects of these diseases on the communities and subcommunities in which women live.

## ACHIEVEMENTS

Recent research has contributed the following knowledge to the infectious diseases field:

### *Basic Science*

- Funding by the National Institute of Allergy and Infectious Diseases of STD centers that are focusing on an examination of the vaginal ecosystem.
- Characterization of the endogenous defense systems of the vagina and cervix.

- Vaginal immunology and physiology, including an examination of normal and abnormal vaginal ecosystem responses to preventive and therapeutic agents.
- Development of single-dose azithromycin for treatment of chlamydia.
- Research on mucosal factors in relation to STDs.

### *Epidemiology*

- Epidemiologic research has highlighted both the extent of the STD epidemic in the United States and its consequences.
- Understanding the epidemiology of STDs and HIV is the finding that the diagnosis and treatment of STDs decreases the risk of HIV transmission
- Natural history studies of HIV in women have helped determine how HIV is acquired and the appropriate clinical utility and prognostic significance of viral load and CD4 counts. The gynecologic manifestations of HIV are also being defined. The risk factors for heterosexual transmission of HIV are now better defined.

*Clinical practice* triumphs of the past 5 years are evident in the availability of new diagnostic tests and new drugs, including antiretrovirals (especially protease inhibitors).



*Epidemiologic data* have helped to describe the occurrences and transmission of STDs and have helped bring about an increased sensitivity to the importance of behavior as an area that should be studied and addressed.

*Scientific perspective* — No longer is the vagina viewed, in research terms, merely as a repository for semen and a vessel for fetal and/or microbial growth, but rather as a complex ecosystem that should be studied in this context in order to advance biomedical knowledge about the infectious diseases that afflict women.

## RESEARCH RECOMMENDATIONS

### *Basic Science*

- Focus STD research on the human vagina to increase knowledge about the vaginal ecosystem: the “normal” state; alterations caused or enhanced by exogenous factors; effects of the menstrual cycle on disease; effects of the frequency of intercourse, with single and multiple partners, on disease; and changes in the vaginal ecosystem across the life span.
- Focus research on primary prevention tools on the effectiveness of exogenous hormones, topical microbicides, barrier methods, and vaccines as primary prevention of STDs, including HIV.
- Address microbial, host-genetic, and host-immunologic factors in the pathogenesis of STDs.
- Elucidate the pathogenesis of HIV/AIDS in women and include the study of the influences of hormonal and other natural defenses.

“ . . . the need for woman-controlled methods of STD and HIV prevention has only recently been recognized as a priority, and much remains to be done to move this issue to the forefront of the women’s health agenda.”

Amy Allina  
Reproductive Health  
Technologies Project

- Continue and increase research to prevent the myriad of adverse outcomes of pregnancy caused by STDs and HIV. Conduct research on infertility, its causes, and methods to reverse it.
- Study the potential effects of hormonal birth control methods on a woman’s susceptibility to infection.

### *Epidemiology*

- Conduct followup studies to determine the long-term sequelae of vaccines, treatments, and disease progression.
- Conduct research to determine whether a relationship exists between race-based factors and specific infectious diseases.

### *Clinical Practice*

- Use clinical trials on microbicides and other barrier methods to define the efficacy, safety, and long-term sequelae of STD and HIV therapy, not only on the “typical” patient but also on pregnancy and neonatal outcome.

- Conduct studies on patients with multiple infections.
- Continue research to find cures for viral STDs and HIV, to develop methods to combat microbial resistance, and to develop treatments and vaccines to prevent or eradicate these infections entirely.
- Study the consequences of inadequate comprehensive prevention and therapy for STDs and HIV in prisons.
- Study the impact of needle exchange programs on the spread of HIV.

### ***Behavior and Education***

- Develop a catalog of sexual behaviors as a base for any intervention strategy.

### ***Other Diseases***

- Study other women's health issues related to infectious diseases including urinary tract infections, tuberculosis, the relationship of chlamydia to heart disease, chronic fatigue syndrome, malaria, Group B strep, bacterial vaginosis and other nonsexually transmitted vaginal diseases, hepatitis C, H. pylori, infectious etiologies of rheumatoid diseases, toxic shock syndrome, and the long-term immunologic sequelae of rubella vaccinations.
- Participate in cooperative research and information sharing with other countries regarding emerging infections.



## MENTAL DISORDERS

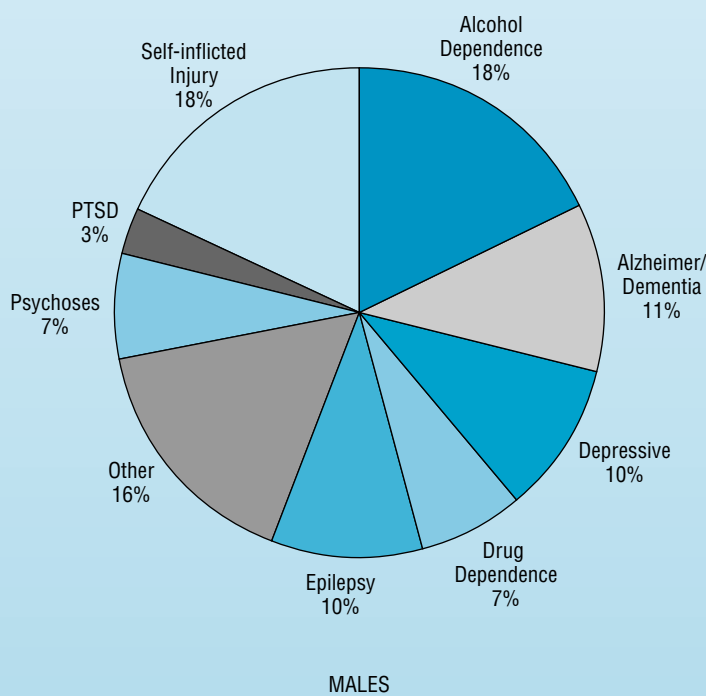
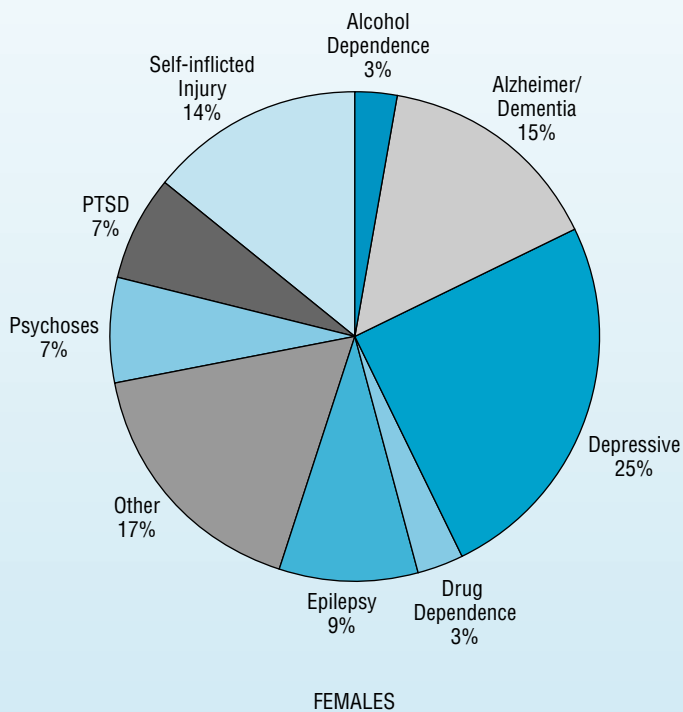
**A**lthough major mental disorders affect women and men to almost the same extent, depression, anxiety disorders, and eating disorders affect women more often than men. Across societies and social contexts, symptoms of depression and anxiety as well as unspecified psychiatric disorders and psychological distress are more prevalent among women, and women are more likely to have more than two disorders. Anorexia nervosa and bulimia nervosa occur 8 to 10 times more frequently in women than men; together they affect 0.5 to 2 percent of adolescent girls and young women, and the prevalence of both is increasing. Panic disorder occurs about twice as often in women as in men and 2 to 3 times as many women as men are affected by phobias. Anxiety disorders affect 2 to 3 times as many women as men and are significantly more prevalent in girls than in boys, which leads to higher incidence of depression in women than in men. Anxiety disorders rank as the most prevalent forms of mental illness in the United States, affecting more than 20 million Americans. Women are prescribed and use psychotropic medication at twice the rate of men.

### A C H I E V E M E N T S

Recent research has contributed the following knowledge to the mental disorders field:

- The possibility that estrogen's interactions with the circadian pacemaker may be involved in seasonal affective disorder and rapid-cycling bipolar disorder.
- Clinical depression can have a compounding deleterious effect on a person's general health. One study prospectively examined whether a major depressive episode increases the risk of myocardial infarction, finding that people who had been diagnosed with a major depressive episode 10 years earlier were found to have a fourfold increased chance of having a heart attack during the ensuing 10 years.
- NIMH-supported research focusing on four of the most serious anxiety disorders: panic disorder, posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and phobias; new, effective therapies offer significant relief for most of these disorders.
- Studies of women victims of violent crimes showing that cognitive-behavioral interventions can reduce post-trauma problems and relieve anxiety and depression that can limit daily activities. (Unfortunately, few women receive such therapy.)
- Selective serotonin reuptake inhibitors (SSRIs), such as Prozac, to alleviate symptoms of OCD and to treat depression.

Mental health problems of females and males: Worldwide percentage of DALYs\* lost. (\*DALY - Disability Adjusted Life Year)



Source: Adapted from the World Bank, 1993, in Desjarlais et al. World Mental Health 1995.

- Successful behavioral interventions developed to address the risk factors of specific groups with increasing rates of HIV transmission, including women and people with severe mental illness.
- Refined methods for the early detection of cognitive impairment in people infected with HIV who have no other medical symptoms.
- Scientific understanding of the biochemical events that take place in the brain and central nervous system during various stages of HIV infection.
- Animal models that permit closer investigation of different aspects of HIV infection of the central nervous system.
- Treatment of mental disorders that are comorbid with physical disorders has been found to reduce hospitalization and rehabilitation services and to improve functioning.

## RESEARCH RECOMMENDATIONS

- Study mental disorders across the life span. Encourage research on the interactions among biological, psychological, and social factors related to mental disorders across the life span of women.
- Identify the social, developmental, and biological factors that predispose adolescent girls and young women to mood, eating, and anxiety disorders.
- Explore the findings that levels of neuroactive peptides, such as cholecystokinin (CCK), may be altered in women with bulimia and that lower levels of this peptide also correlate with higher scores on measures of anxiety and anger.
- Study the long-term effects of violence and victimization. Research 1) psychological and biological effects of sexual assault in childhood and 2) interventions designed to prevent and/or treat the long-term mental health effects of

experiencing abuse and violence, especially so that women can engage in self-protective health behavior.

- Conduct research on the co-existence of drug dependence with psychiatric disorders, especially depression, PTSD, anxiety disorders, and eating disorders.
- Study the effects over time of psychotropic drugs and hormones.
- Examine why female children in some families are resistant to mental disorders such as eating disorders.
- Examine not only the relationship between drugs and alcohol and mental disorders and mental disorders with physical disorders, but examine the relationships among mental disorders.
- Study reproductive hormones and their role in women's mental health, especially during the critical life transitions — menarche, pregnancy, postpartum, and menopause.
- Study mood and mental illness associated with menopause and how major mental illnesses are affected by changing gonadal hormones.
- Investigate the effect of hormone replacement on mood.
- Identify, prevent, and treat the serious mental illnesses in women who are overburdened by the added responsibilities of caregiving resulting from changes in the health care and social services systems.
- Investigate how women and men vary in addictive behaviors ranging from drugs to food.
- Study the causes, prevention, and treatment of all forms of depression with emphasis on bipolar disorder.

- Investigate the role of steroidal hormones in mental disorders.
- Integrate cross-disciplinary research from molecular level through societal level. Prime topic areas for cross-disciplinary collaborations in women's mental disorders include AIDS/HIV, abuse, PTSD, and depression.
- Conduct mental disorders research outside the traditional clinical settings in which women seek treatment more frequently than men — for example, differing brain development in boys and girls, studies of mental disorders of poor women living in the community, and mental disorders studies in jails, domestic violence centers, and primary health care settings.

# NEUROSCIENCE

**N**euroscience research is expanding rapidly because of the refinement of theories and principles, advances in genetics and molecular biology, and new imaging techniques. New understandings about genes and their expression, as well as the activities of neurotransmitters, nerve growth factors, and other signals, are opening new avenues for study. With the increased attention given to research on women's health and to gender differences, studies using combinations of neuroanatomical and behavioral techniques have identified sex differences in the manifestation of brain disorders and the influence of reproductive endocrine disorders in women and men suffering from a variety of diseases. Research has expanded on the influence of hormonal states on important behavioral function such as cognition and on conscious emotion in health and disease.

## ACHIEVEMENTS

Recent research has contributed the following knowledge to the neuroscience field:

### *Development of the Brain and Nervous System*

- Explorations of genetic and environmental influences have begun.
- The defective gene responsible for about two dozen neurological disorders has been identified, as has the chromosomal location of the defect in 50 to 100 — in the muscular dystrophies, some forms of mental retardation, manic-depression, and other neurological disorders.

- New evidence has been found for genetic imprinting in cognition and behavior.
- Personality effects in Turner's syndrome has been discovered, depending on whether the X chromosome is inherited from the mother or father.
- Mutations in mitochondrial genes cause rare neurological disorders.
- Communication between the endocrine system and the nervous system seems to cause anatomical differences in the developing brain.
- Along the hypothalamic-pituitary-adrenal (HPA) axis, responses to stress and to changes in circadian and reproductive cycles stimulate hormone production.
- New developments in imaging techniques enable the examination of functional neuroanatomy and the effects of therapies on the brain.

### *Sex Differences in Cognition and Effects of Hormones*

- Scientific evidence has demonstrated the effects of sex hormones on adult cognition.
- Estradiol and progesterone have shown important effects on adult brain structure and function.

### *Sex Differences in Manifestations of Brain Disorders*

- Reproductive hormones (gonadal steroids) may play an important role in pathophysiology and possibly treatment.



- Levels of ovarian hormones are linked to timing and incidence of migraine headache and epileptic seizures, as well as to sleep disorders (especially sleep apnea) and torticollis.
- Meningiomas and neurofibromas have estrogen and progesterone receptors, and these neoplasms are sensitive to hormone levels.
- Sex differences exist in the manifestations of Alzheimer's disease.
- Estrogen and HRT affect the frequency and severity of symptoms of depression, anxiety, and eating disorders; interactions of HRT with antidepressants and tranquilizers.

#### ***Sex Differences in Sensory Perception and Pain***

- Sex differences exist in response to noxious stimuli, trauma, and the experience of pain, with females often reporting higher pain levels than males for the same stimulus intensity.
- Estrogen appears to induce analgesia through a different pathway in female mice than in male mice.
- Sex-linked genes are associated with nonopioid analgesia in female mice.
- Sex differences are evidenced in coping strategies, internal responses to pain, endogenous pain modulation, and reactions to pain medication.

#### ***Sex Differences in Balance and the Vestibular System***

- Women and men often differ in their organization of body movement, which is possibly related to hormone levels and which may then place women at greater risk for falls in old age.
- Some younger women experience falls that appear to be linked to hormone cycles.
- In the forebrain, ovarian hormones affect the nigrostriatal system and the cerebellum, as well as motor coordination.

“ . . . hormones affect epilepsy and epilepsy affects hormones, and there is a relationship between hormones and seizures at puberty, over the menstrual cycle, and at menopause. . . ”

Linda Lindahl  
Epilepsy Foundation  
of America

#### ***Methodological Developments***

- The combination of basic and clinical neuroscience methodology has enabled examination of sexual dimorphism developmentally.
- Neuroimaging techniques, when combined with clinical and neurocognitive assessment, are powerful tools for identifying the mechanisms for sex differences in healthy brain function and in specific disease states; investigators using these technologies are now able to extend and test hypotheses that have implications for intervention.

#### **R E S E A R C H**

#### **R E C O M M E N D A T I O N S**

- Raise awareness in the neuroscience research community about the importance of sex differences and hormonal influences on all aspects of brain function.
- Research basic mechanisms to develop better prevention and treatment strategies.
- Focus on attention to life span issues, developmental stages, and hormonal states.
- Study the neurobiology of interactions of gender and gonadal hormones with endocrine, immune, and other systems and disorders.
- Explore the impact of social and physical environment on neural development and function.

# ORAL HEALTH

Most oral problems are “complex” diseases in that the manifestation of the condition is the result of multiple genes and gene susceptibility factors interacting with behavioral and environmental variables. A variety of demographic, general health, economic, social, and behavioral factors may be operative in placing subgroups of women at high risk for development of oral diseases. These factors include extended longevity, experience with multiple chronic conditions, medications, cognitive impairments, compromised functional status, and physical confinement, each of which can induce biological or behavioral changes that adversely affect oral health. Because oral problems are typically repetitive and cumulative across the life span, disabling and handicapping outcomes are maximized among people in the later stages of life.

## ACHIEVEMENTS

Recent research has contributed the following knowledge to the oral health field:

- Saliva is used as an investigational aid to monitor levels of hormones and therapeutic medications.
- Poor maternal periodontal health increases an infant’s potential for low birthweight and for preterm or premature birth.
- Epidemiological findings indicate a nearly two-fold risk for fatal myocardial infarction and stroke for persons with established periodontal disease.

- Female dental patients respond more favorably than males to kappa opioid analgesics for control of postoperative pain.
- Studies of oral HIV in the areas of mucosal immunity, synthetic drugs and vaccines, and innovative drug delivery systems will be of benefit to women as the fastest growing AIDS population.

## RESEARCH

### RECOMMENDATIONS

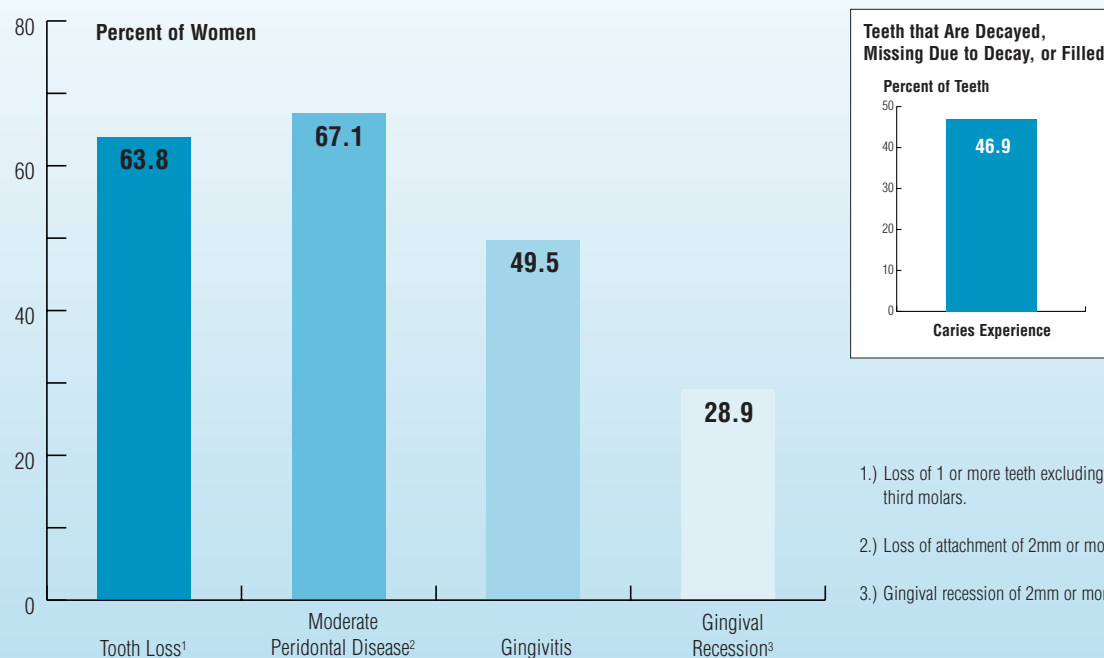
#### *Biomimetics*

- Study the effect of hormonal status on the efficacy of guided bone and tissue engineering procedures.

#### *Diagnostic Markers*

- Investigate the utility of saliva as a matrix for studying biological markers important to women’s health and diseases.
- Determine how best to utilize oral examination findings and the dental clinic encounter in domestic violence, child abuse, and eating disorders intervention programs.
- Explore whether dental radiographs can be useful in identifying aberrant skeletal bone changes.

Prevalence of Select Oral Conditions Among Women 18 Years of Age and Older: United States 1988-94.



Sources: National Health and Nutrition Examination Survey III

### *Sjögren's Syndrome and Autoimmune Diseases*

- Investigate the role of gender in autoimmune conditions, including the role of sex hormones in induction and perpetuation of these conditions.
- Study gender-controlled transcription differences that influence autoimmune disease penetrance.
- Conduct research on the impact of hormonal therapy on women with Sjögren's syndrome and other autoimmune conditions.
- Identify appropriate and sensitive clinical outcome measures for the exocrine dysfunctions associated with Sjögren's syndrome.
- Conduct controlled clinical trials testing new biological therapies for Sjögren's syndrome.

### *Pain*

- Study the relations among fluctuations in reproductive hormones and pain experiences including cognitive, emotional, and behavioral components.
- Investigate the hormonal influences on nociception and pain modulation pathways, and investigate the effects of replacement therapies on pain and analgesia.
- Examine women's stress response to pain and coping behaviors.
- Study sociocultural effects on women's responses to pain across the life span and in different cultural milieus.

- Examine predictors of chronic pain development in women, including diminished activation of endogenous pain control systems.
- Conduct basic research to examine the effects of estrogens and other hormones on nociception and pain modulation pathways.
- Study the interactions between oral taste and pain sensations, particularly as they relate to painful oral lesions and oral pain in the absence of visible oral pathology, as in burning mouth syndrome.
- Explore the mechanisms and models (both animal and human) underlying gender differences in responses to noxious stimuli and analgesic medications.
- Study the role of genomic and nongenomic mechanisms mediating actions of gonadal hormones on pain perception and pain control.
- Investigate the role of steroid hormone response elements in regulation of gene expression in pain pathways.

#### ***Temporomandibular Disorders***

- Conduct studies to elucidate the etiology and pathogenesis of TMDs, including the contributions of segmental versus heterosegmental hyperalgesia to TMD myogenous pain.
- Design evidence-based research studies to determine optimal treatments and outcomes for specific TMD clinical presentations.

#### ***HIV***

- Investigate the prevalence of oral lesions among infected women and determine their prognostic significance for HIV disease progression.
- Determine if there are gender differences in response to, and compliance with, oral lesion therapies.

*“An alarming shortage of research-trained, full-time female dental faculty exists at our dental schools.”*

Debra Studen-Pavlovich, D.M.D.  
American Association  
of Dental Schools

- Explore the relation between oral and vaginal candidiasis and study the effects of oral versus systemic antifungal therapies on oral candidal lesions.
- Determine the relationship of oral diseases in HIV-infected women and their children, including perinatal transmission.
- Investigate the barriers to accessing oral care for HIV-infected women and evaluate the resultant effects on health and oral health.

#### ***Interrelationships of Oral and Systemic Disorders***

##### *Osteoporosis*

- Study the relationship of periodontal disease, alveolar bone loss, residual ridge resorption, osteopenia, and osteoporosis.
- Explore how stress, coping behaviors, and depression modify the relationship among oral bone loss, osteopenia, and osteoporosis.
- Determine whether bone density in the oral cavity correlates with systemic bone mineral density.
- Determine if common therapeutic strategies can be exploited for treating alveolar bone loss and systemic bone loss.

- Determine the influence of hormonal status and hormone replacement therapy on oral bone loss and tooth retention.

#### *Diabetes*

- Determine the role of periodontal infection as an aggravating factor for diabetes mellitus in women.

#### *Cardiovascular Disease*

- Study periodontal infection as a risk for CVD in women.

#### *Spontaneous Preterm Births*

- Study fundamental mechanisms that combine oral disease measures and microbial, immunological, and inflammatory parameters to understand how oral infection may modify the maternal-fetal interaction.
- Conduct population-based, prospective studies to assess the independent contribution of periodontal infection to the risk of spontaneous preterm birth (SPB).
- Carry out intervention studies to determine whether periodontal therapy reduces the incidence or morbidity associated with SPB.
- Expand animal studies on the underlying mechanisms of SPB and the influence of distant infection on pregnancy.

# PHARMACOLOGIC ISSUES

Clinically significant pharmacodynamic differences in drug-induced responses exist between men and women. The changing hormonal milieu in postmenopausal women in relation to their overall health and the occurrence of certain diseases requires extensive study. Despite the impressive advances in policies regarding the participation of women as subjects in research and analysis of data for gender effects, gaps in knowledge remain regarding the behavior of drugs in women. Areas where much additional research is needed include mechanisms of drug action, which include pharmacokinetics (PK), pharmacodynamics (PD), and pharmacogenetics; biological and molecular bases of pharmacological effects such as ion channels and membrane transporters; chronopharmacology; and modulators such as sex steroid hormones that can influence PK and receptor sensitivity in target end organs. Over-reliance on traditional male-oriented medical practices may ill serve women and, in some instances, may actually harm them.

## A C H I E V E M E N T S

Recent research has contributed the following knowledge to the pharmacology field:

- Detailed scientific information relating to drug pharmacokinetics and pharmacodynamics in women, as a result of women of all ages being included in all phases of clinical trials.

- Progress in identifying and understanding the role of various metabolic enzymes in causing gender differences in PK or PD.
- Surrogate endpoint information related to overall health and the occurrence of certain diseases, provided by studies in postmenopausal women such as the Postmenopausal Estrogen/Progesterone Intervention (PEPI) trial.
- Major research efforts to identify and assess impacts on various estrogen receptors, the influence of such receptors on PD variation, and newer forms of hormone-analog molecules such as the selective estrogen receptor modulators (SERMs).

## R E S E A R C H

### R E C O M M E N D A T I O N S

- Use whole animal studies to evaluate therapeutic efficacy and potential side effects of drugs.
- Develop decision-analysis tools to help determine when, and under what circumstances, PK and PD studies should be performed: Assess gender-related PK and PD differences in multiple populations including women with childbearing potential, pregnant women, lactating women, perimenopausal women, menopausal women, and senior women. Perform research into the mechanism of these differences to enable identification and

prediction of gender differences that may result in increased drug toxicity or lack of responsiveness in either sex.

- Investigate the role of sex hormones as possible causes of receptor sensitivity. Differences in receptor sensitivity need to be studied, particularly with regard to effects on the QT interval, which may differentially predispose women to cardiac arrhythmias.
- Develop improved methods for collecting and analyzing data on the use of pharmacologic agents in pregnancy with respect to safety and efficacy for the mother and safety for the fetus.
- Examine the broad spectrum of possible drug-drug and drug-nutrient interactions both for available pharmacologic agents and for those currently in clinical trials.
- Examine underlying mechanisms that contribute to gender differences in drug action and disposition. Define the pharmacokinetics, pharmacogenetics, chronobiology, modulators, biologic and molecular factors, and pharmacodynamics of pharmacologic agents across the life span and across racial and ethnic groups.
- Conduct preclinical research in the development and validation of in vitro and whole animal models to test and predict gender specific pharmacologic differences.
- Evaluate PK and PD of new drugs by incorporating research on potential adverse effects on the pregnant woman, the fetus, and the newborn. Develop methods of assessing subtle effects, such as possible neurodevelopmental and immunologic impairment in children.
- Ensure that attention to studying mechanisms of pharmacologic effects become an integral component of the review process across institutes and offices whenever a pharmacologic

*“To provide optimal pharmaceutical care, pharmacists should be aware of the ethnic and racial composition of their patient populations and the distinctive characteristics that may elicit ethnic and racial differences in pharmacologic responses to medicines, as well as the psychosocial and economic parameters that influence drug use or misuse.”*

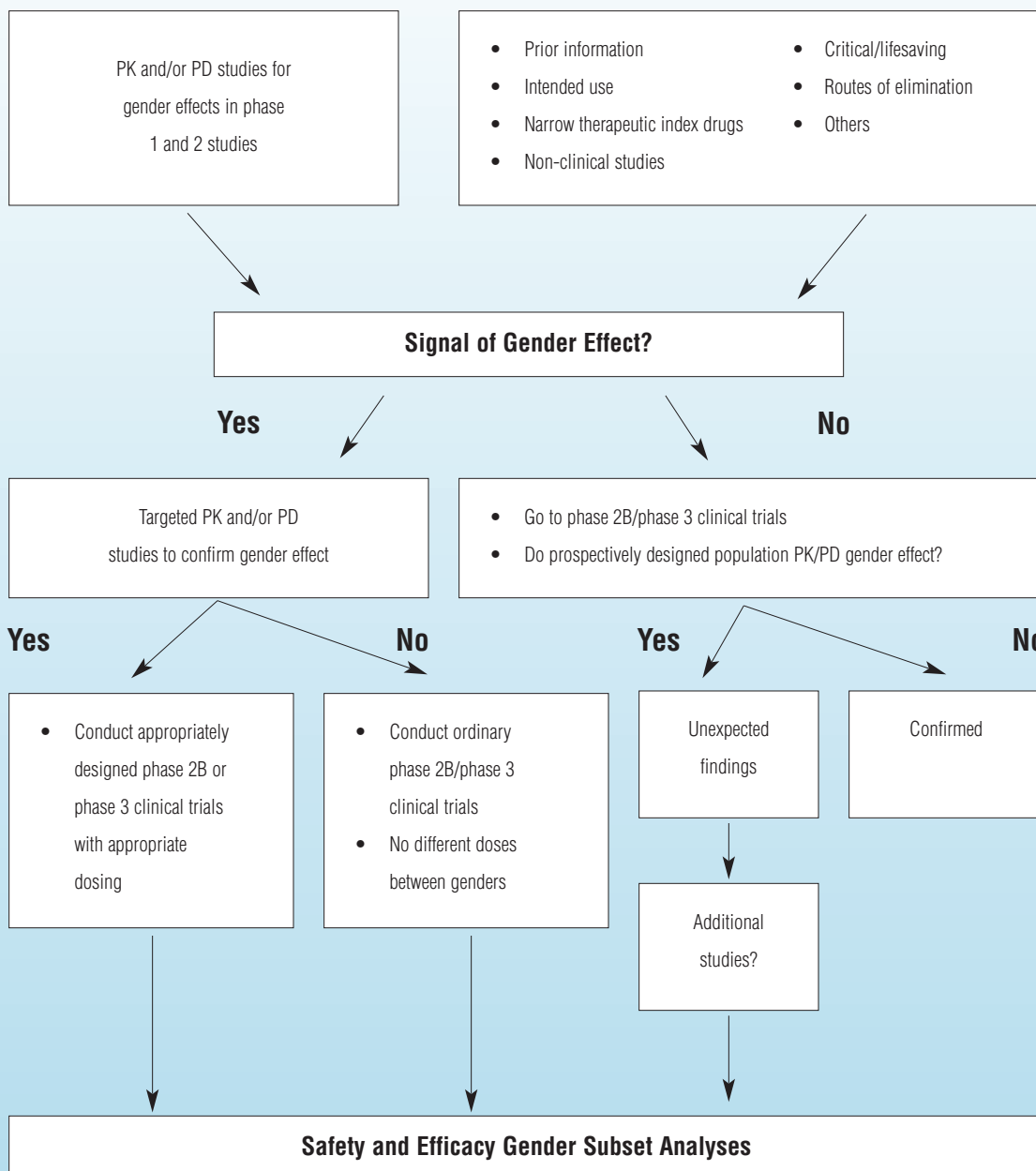
Gloria J. Nichols, Ph.D.  
Catherine A. White, Ph.D.  
University of Georgia  
College of Pharmacy

agent is part of a study protocol for prevention or treatment of a disease or condition.

### **Components of Pharmacologic Effects**

- Examine the underlying mechanisms that contribute to gender differences in drug effects and disposition including membrane transport pumps, ion channels, chronobiology, metabolic enzyme differences, sex hormone receptors, drug interactions between hormonal contraceptives and hormone replacement therapy, and drugs affecting chemical compounds such as the neurotransmitters.
- Carry out basic and applied research on pharmacokinetics, pharmacodynamics, and the importance of combining PK and PD data:
  - Develop decision-analysis tools to help determine when, and under what circumstances, PK and PD studies should be performed. Assess gender-related PK and PD differences in multiple populations including women with child-bearing potential, pregnant women, lactating

## Gender Studies



women, perimenopausal women, menopausal women, and senior women.

- Study the effects of drugs in women across the life span in relation to drug absorption,

distribution, metabolism, and elimination, with special focus on postmenopausal women (with and without hormone replacement therapy) and senior women who experience changes in organ function.



- Conduct research on other specific topics including:
  - Conventional hormone therapy vs. SERM.
  - Long-term effects of lifetime estrogen exposure.
  - Gender differences in response to chemotherapy.
  - PK and PD of specific drugs or drug classes such as chemotherapeutic agents, and potassium channel blocking anti-arrhythmic drugs.
- Examine drug-drug and drug-nutrient interactions.
- Carry out basic and applied research on pharmacogenetics:
  - Research studies are needed that have sufficient statistical power to determine the nature of the interaction between gender and genetic polymorphism.
  - The role of CYP 1A2 and 3A4 in gender differences of drug metabolism, as well as the interface between these isoenzymes and estrogen metabolism, induction, or inhibition merits further investigation with respect to oral contraceptive failure and cancer induction.
  - There is evidence that CYP 3A4 activity is greater in younger women compared with men and postmenopausal women. Demonstrated decreased metabolism in postmenopausal women may make them more liable to adverse effects of certain medications. Careful study of this possibility is needed.
  - Study the posited gender-related differences in CYP 1A2 expression. The potential inhibition of CYP 1A2 by estrogen is demonstrated by decreased caffeine metabolism in women receiving estrogen replacement therapy.
- Carry out basic and applied research on membrane transporters. Study potential gender-specific expression of p-glycoprotein and MRP related drug efflux pumps and other membrane transporters. Such differences have important value for decisions regarding selection of drug type and dosage (e.g., in cancer chemotherapy).
- Carry out basic and applied research on ion channels. Further pre-clinical and clinical research is needed to better define differences in sodium and potassium channel sensitivities between men and women that may explain differential adverse effects observed following intake of certain medications.
- Carry out basic and applied research on modulators. Examine differences in receptor sensitivity possibly caused by sex hormones.
- Carry out basic and applied research on chronopharmacology:
  - Study gender differences related to biologic rhythms and their application to efficacy of drugs.
  - Study the chronopharmacology of disease because biologic rhythms may change during the disease process and affect drug dosing requirements.

### ***Preclinical Studies***

- Focus special attention on the continued development of animal and other models to predict with some accuracy the reproductive and developmental effects of drugs in humans.
- Evaluate therapeutic efficacy and potential side effects through whole animal studies.
- Place receptor and cell-signaling research in the context of the whole organism, including physiological and therapeutic considerations in animal research.

## *Drug Use in Pregnancy*

- Develop improved methods for collecting and analyzing data on the use of pharmacologic agents in pregnancy with respect to safety and efficacy for the mother as well as the fetus.
- Develop scientifically valid and rigorous methods of evaluating potential risks in humans including frequency of structural and functional birth defects and reproductive effects such as rates of spontaneous abortion.
- Perform critical research to determine the best systems to link data from a mother to her newborn. This should be followed by implementation of such systems for Medicaid data, at HMOs, and at academic centers.
- Perform clinical trials in pregnant women for those drugs commonly used by pregnant women, particularly in the second and third trimester. These trials should address pharmacokinetics and dosing recommendations. All trials of drugs in pregnant women should collect maternal safety data for the purpose of comparison with the safety profile of the drug in nonpregnant women.
- Research birth anomalies that are more difficult to detect, such as those that are neurodevelopmental or immunologic.
- Study the effects of maternal medications on the breast-feeding infant. Drug concentration measurements in breast milk should be considered for inclusion in studies of the PK and PD of new drugs, and methods should be developed to predict infant exposure levels.



# REPRODUCTIVE HEALTH

**H**istorically, “women’s health research” was generally limited to the study of obstetrics and gynecology. In the late 1970s, societal shifts, notably feminist concerns about women’s interactions with the medical system, resulted in a broader national research agenda that encompassed a more comprehensive definition of women’s health. This drew attention to the lack of research on major issues such as cardiovascular disease and cancer in women, and the problem of ineffective or inappropriate treatment of diseases and conditions in women.

## A C H I E V E M E N T S

Recent research has contributed the following knowledge to the reproductive health field:

### *Pregnancy*

- The biology and management of pregnancy.
- Research on infectious diseases of pregnancy and preterm labor and on other pathophysiologic aspects of abnormal pregnancy.
- Effects of somatic disease on pregnancy.
- Genetic testing and other diagnostic tests providing information on prevention of malformations.
- The relationship of implantation (normal vs. abnormal) and fetal development.

- External factors with potential effects on pregnancy, including environmental factors, diet and nutrition, exercise, smoking, violence, and the effects of hormones and medications.
- Diagnostic systems that are better focused on and address the needs of specific populations.

### *Contraception*

- Knowledge of contraceptive use behavior and generating new contraceptive technologies.
- Availability of Norplant (levonorgestrel subdermal implants), Depo-Provera (medroxy-progesterone acetate injection), and the female condom for pregnancy prevention.
- Advances in microbicides and spermicides and in their use among women.

### *Infertility*

- Greater awareness that infertility is a “couple problem” rather than a female problem, and recognition that male infertility is also a women’s health problem.
- Genetic causes of male infertility with the potential for heritable infertility.
- Ovulation induction based on developing knowledge of ovarian physiology.

- Better selection of treatments for infertility.
- Knowledge about ectopic gestation; new treatments, such as methotrexate, are improving the medical management of ectopic pregnancy and reducing the need for surgical intervention.

### *Reproductive Tract Diseases and Disorders*

- Promoting greater awareness of reproductive tract diseases and disorders and their prevalence and morbidity, including myoma, abnormal uterine bleeding, premenstrual syndrome, endometriosis, pelvic pain, and pelvic floor relaxation.
- New information on abnormal biology of reproductive tract diseases and disorders and in medical and conservative surgical therapies; recently identified steroid receptor subtypes may hold clues to development of diseases and approaches for treatment.

## **R E S E A R C H**

## **R E C O M M E N D A T I O N S**

### *Pregnancy*

- Conduct more research to better understand the context of maternal health and pregnancy with special attention to preterm labor, ectopic pregnancy, intrauterine growth retardation (IUGR), preeclampsia, spontaneous abortion, labor and delivery, and lactation.
- Study basic physiology, management, and sequelae of pregnancy.
- Develop technology for improved monitoring of pregnancy — genetic testing, medical and surgical interventions, and other alternative therapeutic modalities.

- Examine external factors extensively affecting women's physical and psychological health — lifestyle, environment, diet, exercise, alcohol, smoking, violence, and pharmacology of prescription and over-the-counter drugs.

### *Sex and Contraception*

- Focus on research, based on current knowledge of contraceptive use, to increase responsible contraceptive and sexual behavior (decisionmaking and compliance), especially among adolescents and women with gynecological infectious diseases. More research is needed regarding the role of contraceptives in the prevention of STDs.
- Target the biology of the human oocyte to develop new contraceptives.
- Optimize and develop contraceptive options for specific circumstances and populations (e.g., women with STDs, AIDS/HIV-positive status) and study the long-term effects and interactions of existing and emerging contraceptives.

### *Fertility and Infertility*

- Learn from biology of the reproductive system to focus on developing and improving diagnostic and therapeutic measures.
- Understand the etiology and pathophysiology to improve fertility and reduce infertility.
- Select the appropriate treatment and management for specific populations.
- Research the behavioral effects of infertility, e.g., reducing the negative sequelae of assisted-reproductive technology and other infertility treatments and their effects on gamete donors and surrogate mothers, social concerns of reproductive ethics, and socioeconomic effects of multiple births.

### *Benign Diseases and Disorders*

- Study the etiology and pathophysiology of each of the above diseases or disorders leading to the evolution of safer and more acceptable treatments.
- Examine the long-term effects of these gynecological diseases and disorders and their treatments.
- Discover genetic and molecular factors in disease development and identify noninvasive markers of disease activity.
- Research nonsurgical management of the above diseases and disorders.

### *Maturation and Aging*

- Study consequences of maturational changes of the hormonal axes and their effect on fertility, menopause, and hormone dependent diseases and behavior.
- Study hormone replacement therapy (HRT), both existing (estrogen and/or progesterone) and potential (androgens, DHEA, etc.) — their roles in development of novel treatments based on hormone actions and interaction, including receptor subtypes; safety and efficacy of therapy; detection and reduction of adverse effects; effects on initiation, growth, or reactivation of hormone dependent pathologies; and the impact on the quality of life over time.



## UROLOGIC AND KIDNEY CONDITIONS

**D**iseases of the kidney and urinary system have a major impact on women's health. Permanent kidney failure, called end-stage renal disease, affects more than 120,000 women in the United States alone. Treatment with dialysis or transplantation, although necessary to sustain life, does not restore normal, or even near-normal, life expectancy. The average death rate for end-stage renal disease patients is approximately 25 deaths per 100 patient years. Thus, at all ages and for both genders, kidney failure results in a markedly shortened life expectancy. Kidney disease is increasing in incidence in the United States, where the number of new patients requiring either dialysis or transplantation approximately doubled between 1985 and 1995. Particularly important for women is an increase in the incidence of Type II Diabetes Mellitus. Also important for women's renal health is the impact of pregnancy-related kidney disorders. Other forms of renal disease that are more frequent in women than men are analgesic nephropathy and the nephritis associated with systemic lupus erythematosus. Women's urological disorders are very common, afflicting virtually all women at some point in their lives. While less frequently life threatening than renal failure, these conditions often have a major impact on the quality of life.

### ACCOMPLISHMENTS

Recent research has contributed the following knowledge to the field of urology:

- Recognition that dialysis dose, nutrition, vascular access, and proper treatment of anemia are all

important considerations that affect end-stage renal disease patient morbidity and mortality.

- Development of new drugs for the prevention of organ rejection in transplant patients.
- Development of new forms of insulin and advances that facilitate intensive therapy. These include human insulin produced through genetic engineering, better techniques for blood glucose monitoring, and external and implantable insulin pumps that deliver appropriate amounts of insulin.
- Improved characterization of the clinical presentation of analgesic nephropathy and of the specificity of noncontrast computerized tomographic imaging of the kidney for its diagnosis.
- New insights into immune cell activation and death, pathways of tissue destruction, and modulators of lymphocyte or target cell function in experimental models of lupus, specifically the role of Fas and the Fas ligand, with the surprising demonstration that deficiency in this pathway accelerates lupus nephritis.
- Subcategorization of pregnancy-induced hypertension as a heterogeneous entity comprised of several different subgroups including chronic renal disease, borderline chronic hypertension, genetic susceptibility to hypertension, and genuine pregnancy-induced hypertension.
- Development of treatment guidelines on urinary incontinence by the Agency for Health Care



Policy and Research and the American Urological Association.

- Diagnostic standards for genital prolapse, established by the International Continence Society and accepted by the American Urogynecologic Society and the Society of Gynecologic Surgeons.
- Acceptance and understanding that childbirth is a major etiological cause of pelvic floor disorders.
- Development of molecular genetic techniques to characterize uropathogens that colonize the urinary tract and track the course of individual infections.
- Increased understanding of behavioral risk factors.
- Availability of new pharmaceutical treatments for interstitial cystitis.

## RESEARCH

## RECOMMENDATIONS

- Attract more basic science researchers, from a variety of scientific disciplines, into these fields by workshops that target a variety of disciplines and by increasing funding for research and training programs.
- Establish the effects of chronic analgesic use on renal function, and the incidence of analgesic nephropathy in the end-stage renal disease population in the United States.
- Initiate prospective observational studies on the impact of pregnancy on renal function in women with underlying kidney disorders and renal transplants. Studies should define the effect on both short- and long-term renal prognosis, as well as pregnancy outcomes.
- Determine the causes of altered renal hemodynamics during pregnancy.
- Establish the optimum approach to hormone replacement therapy in women with chronic renal insufficiency and end-stage renal disease.

*“Interstitial cystitis (IC) was considered, and still is considered by some urologists, as an ‘hysterical female condition.’ Unfortunately, this blatantly incorrect label still haunts IC victims with the sufferer taking on average 4.5 years to get a correct diagnosis and often having to see an average of five physicians before IC is diagnosed.”*

Vicki Ratner, M.D.  
Interstitial Cystitis  
Association

- Expand research on the pathogenesis of lupus nephritis to exploit current insights in inflammatory mechanisms and cytokine pathways.
- Improve strategies for preventing diabetic nephropathy due to Type II Diabetes.
- Conduct basic science research on bladder and pelvic floor disorders including physiology and pathophysiology.
- Develop and validate standard measures for assessment (baseline conditions and outcomes) for urinary incontinence, interstitial cystitis, and pelvic floor disorders.
- Initiate new (and utilize existing) longitudinal epidemiological and interventional studies using diverse populations on urinary incontinence, pelvic floor disorders, and urinary tract infections including the impact of childbearing and aging.
- Initiate valid and controlled clinical trials for the treatment and prevention of incontinence, pelvic floor disorders, urinary tract infections, and interstitial cystitis. These clinical studies should not be relegated to the industrial sector.



REPORTS OF THE WORKING GROUPS:  
SEX AND GENDER PERSPECTIVES THROUGHOUT  
THE LIFE CYCLE — SUMMARY OF RECOMMENDATIONS



# PRENATAL, INFANCY, AND CHILDHOOD YEARS

## N O R M A T I V E   D E V E L O P M E N T

**B**ecause understanding normative development allows for a clearer understanding of pathological processes, research that looks at normative development needs to be stratified according to developmental stage, gender, and ethnicity. A multidisciplinary approach that includes the social, environmental, behavioral, and physical aspects of development is recommended as the best approach for research.

### *Research Recommendations*

- Gene expression and the interaction of the environment with genes.
- Implantation and the first trimester development, including gender differences in development.
- Normative placental function and the function of the placenta as a protective barrier.
- Development of organ systems using a multidisciplinary approach.
- The impact of and the gender differences in response to stress and nutrition in this stage of the life cycle.
- Determination of the critical developmental periods and the critical periods of sensitivity to environmental factors during this stage of the life cycle.
- Regulation of normal labor and the mechanisms of preterm labor.

- Importance and effect of preconception health, plus how to disseminate this information effectively.

## P H A R M A C O K I N E T I C A N D   P H A R M A C O D Y N A M I C E F F E C T S   O F   D R U G S   I N N O N - A D U L T ,   N O N - M A L E P O P U L A T I O N S

Gaps in knowledge exist about the effects of prescription and over-the-counter medications, xenobiotics, and herbal remedies on women and children. In researching these areas of pharmacokinetics and pharmacodynamics, a stratification must be adopted that addresses the differences of age, gender, and ethnicity.

### *Research Recommendations*

- Absorption, distribution, metabolism, and elimination of drugs, beginning early in the prenatal stage and following a system of stratification that takes into account age, weight, and development through the breast-feeding stage and early childhood to the beginnings of puberty.
- Biological responses to drugs of the fetus, the breast-feeding infant, and the prepubescent child.
- Effects of exposure to drugs during critical prenatal and perinatal stages of development.
- Long- and short-term effects of drugs on the fetus and the child.

## P R E V E N T I O N A N D E D U C A T I O N

Prevention and education are key to promoting overall wellness that extends into adulthood. The data for prevention and education needs to be acquired in a gender- and culture-sensitive manner, and then disseminated appropriately to the intended audience, based on culture, gender, and age.

### *Research Recommendations*

- Longitudinal evaluations of preventive strategies, taking into account short- and long-term behavior changes.
- Rapid dissemination of research results in a gender-, culture-, and age-appropriate manner.
- Inclusion of alternative medicine approaches, such as massage therapy and homeopathic remedies, in education and prevention programs.

## E N V I R O N M E N T A L A G E N T S

Environmental factors influence wellness in the prenatal through prepubescent stages of the life cycle. Toxins associated with industry, water supplies, and commercial and residential expansion affect health through nutrition and exposure, threatening the well being of women and children. Especially for ethnic minorities, the effects of toxins on women and children are often overlooked in environmental studies.

### *Research Recommendations*

- Effects of environmental agents on gene expression.
- Impact of environmental agents on implantation and first trimester development.
- Effects of environmental agents on placental function.
- Effect of the environment on organ systems and the impact of prenatal events on development.
- Narrow windows of critical periods of exposure to environmental agents, plus the long- and

short-term consequences of exposure during these windows.

- Critical pathways of exposure, such as nutrition, lactation, and formula.
- Community-based prevention and research pertaining to environmental exposure and effects.

## N O R M A T I V E G E N D E R - S P E C I F I C B E H A V I O R A L A N D P S Y C H O L O G I C A L D E V E L O P M E N T

Major gaps exist in our knowledge of normative behavioral and psychological development. Even at early ages, the differences in behavior between the genders are noticeable.

### *Research Recommendations*

- Behavioral and psychological attributes of children, taking into account gender and ethnic differences and developmental diversity.
- Attributes of the development of health-related behaviors in children.
- Critical stress points in these stages of the life cycle and the development of coping strategies.

## G E N D E R - S P E C I F I C T R A N S G E N E R A T I O N A L P A S S A G E O F D I S E A S E

Children become predisposed to diseases in the early stages of their development.

### *Research Recommendations*

- Role of the “programming hypothesis” and the effects on women and children.
- Relationship of programming to varied physiological systems.
- Functional genomic research.
- Reversal of unwanted prenatal programming.

# ADOLESCENT YEARS

**D**uring adolescence, every part of young women's lives are in flux. Cognitive, social, and mental health issues change in response to and in concert with biological changes. Although great diversity in race, culture, and age exists among adolescent women, few norms have been established, little tracking of growth and development has been completed, and only a small amount of information has been collected.

## *General Research Recommendations*

- A longitudinal study of a national cohort including common measures and youngsters from a wide variety of ethnic, racial, economic, specific-risk, and regional groups and subgroups.
- Comprehensive guidelines for adolescent participation in clinical trials.
- A workshop to study the barriers and facilitators to adolescent research, including current guidelines, Institutional Review Board (IRB) approvals, and ethical and legal issues for gathering data from this age group.
- Assess the legal, moral, and ethical issues involved in conducting clinical research in the adolescent population, possibly through the Institute of Medicine.

## DEVELOPMENT ISSUES ACROSS THE ADOLESCENT YEARS

Research should focus on:

- Biological development — how biology affects behavior and how the immune system changes body composition and affects behavior.
- Social development — how body development affects social behavior.
- Psychosocial development.
- Environmental effects — how the environment affects body composition and development.
- Cognitive development.
- Mental health.

## RISK - TAKING BEHAVIORS

Research should concentrate on:

- Sexual behavior — primary and secondary prevention of pregnancy, implications for STDs and pregnancy, girls' masturbation habits, the role of coercion in an adolescent girl's sexual debut, and age of the sex partner and how that affects development.

- Substance use and abuse.
- Other areas including violence, injury, suicide, runaways, homelessness, and a cross-sectional study of girls in gangs.

#### P R O M O T I N G   H E A L T H Y B E H A V I O R S

Research should concentrate on:

- Nutrition — communicating healthy eating habits.
- Physical activity — how adolescent girls can be encouraged to get regular exercise and how to promote healthy behaviors like delaying smoking, alcohol use, and sex.
- Sexual health and hygiene.
- Oral health.
- Effective, accessible, user-friendly screening tools.

#### A D O L E S C E N T P A R T I C I P A T I O N I N   R E S E A R C H

Research should focus on:

- Normed assessment tools.
- Institutional Review Board issues around adolescent consent.
- Diversity.
- Inclusion in clinical trials.
- Support of secondary analyses.
- Supplements for ongoing studies.

#### C O P I N G   S K I L L S

Research should focus on:

- Chronic disease.
- Family issues, including teaching parenting skills to teens.
- Life events.
- Violence.
- Resilience, including the skills needed to deal with emotions like anger.

# REPRODUCTIVE AND MIDDLE YEARS

## SEXUAL AND REPRODUCTIVE HEALTH

**R**esearch needs to approach the prevention, diagnosis, and treatment of STDs with an emphasis on utility, effectiveness, availability, and education in the diverse populations of women.

### *Research Recommendations*

- Research the causes of STDs emphasizing the holistic approach, investigating the hormonal and immunologic influences on susceptibility to these diseases and the relation of risk-taking behavior, substance abuse, and other behaviors and disorders commonly associated with the diseases.
- Research decisionmaking and compliance factors of contraceptive use to develop contraceptive options tailored to different circumstances and different populations.
- Continue research of gender-sensitive prevention, diagnostics, treatment, and outreach efforts for STDs, with special emphasis on pregnant women.
- Develop less expensive, faster diagnostics and treatments for STDs.
- Develop topical microbicides that are nonirritating and effective against resistance.
- Develop research on a male contraceptive.

- Develop more female-controlled barrier contraceptive methods.

## ACCESS TO HEALTH CARE

Recommendations in this category focus on efforts that will bring science closer to the people it serves, lifting barriers among scientists and clinicians and the public and encouraging these groups to collaborate.

### *Research Recommendations*

- Develop models of comprehensive services across the life span of women, with research regarding basic biologic systems to educate providers.
- Develop a gender-specific model of information and communication that responds to the manner in which diverse groups of women receive and process information — utilize grassroots efforts, print and television media, telemedicine, the Internet, and distance learning.
- Develop successful models of outreach to special populations, such as minorities and inhabitants of transitional housing (e.g., prisons, homeless shelters).
- Conduct epidemiologic studies to define the diverse populations and their distinct health care needs.



- Incorporate and, through followup, evaluate constituent participation in all facets of research targeting women. Emphasize partnerships among consumers, clinicians, and scientists, and coordination among federal agencies.

## ENVIRONMENTAL EXPOSURES

Research on environmental exposures should be all-inclusive of physical, chemical, atmospheric, and social exposures that affect women in their various roles in the home, workplace, and community, and should also consider transgenerational effects. Special emphasis should be placed on recognizing the nonhomogeneous nature of women and the holistic approach to clinical study.

### *Research Recommendations*

- Identify hormonal disrupters, especially in the home and workplace.
- Examine gender differences in the effects of hormonal disrupters, especially in the workplace.
- Examine eco-estrogens and the subsequent influence on development of benign and malignant tumors and the disruption of hormonal regulation.
- Continue to examine transgenerational effects associated with physical and social environmental exposures.
- Assess structural design and ergonomic issues, considering the unique features of the female body.

## INCLUSION OF PREGNANT WOMEN IN CLINICAL STUDIES

Recommendations involve finding the group of women from which data can presently be obtained, establishing from whom and in which situations pregnant women can and cannot be involved in research, and considering women of reproductive potential when planning clinical studies and followup. Pregnant women and women of childbearing age should be included in all studies, not just those directly addressing pregnancy issues.

### *Research Recommendations*

- Recognize and use opportunities to collect passive data to study the effects of drug use on pregnancy.
- Include the investigation of effects of medical interventions in women of reproductive potential in existing clinical trials and followups.
- Study interactions of prior drug use and medical intervention on conception and pregnancy.
- Sponsor a conference to establish a consensus to approach the inclusion of pregnant women in clinical studies, recognizing that careful, long-term thought and planning are necessary.
- Define and find cohorts of pregnant women that can be enrolled in clinical studies, including studies not directly related to pregnancy issues.
- Establish when Phase I and Phase II trials are appropriate for inclusion of pregnant women, even trials not directly related to pregnancy issues.

**A L T E R N A T I V E  
( C O M P L E M E N T A R Y )  
M E D I C I N E**

Because so many women are using alternative medicine, the medical community must acknowledge and accept these therapies as valid forms of medical intervention and must approach the study of their use accordingly.

**Research Recommendations**

- Conduct epidemiologic studies to establish the prevalence and existence of the use of alternative therapies.
- Use social and behavioral studies to ascertain consumption patterns and understand the appeal of alternative therapies.
- Conduct Phase I, II, III, and IV clinical trials to determine the effectiveness, safety, and complications and adverse effects of alternative therapies.
- Increase provider awareness and education regarding alternative therapies so patients can make informed decisions regarding their use.

**E N D P O I N T   D I S E A S E  
S T A T E S   O F   H I G H  
P R I O R I T Y**

*Autoimmune disorders* — Increase research to clarify how the female immune system functions and how those functions change over the course of the menstrual cycle and during pregnancy, and the influence of environmental factors on those functions.

*Cardiovascular diseases* — Increase research on the basic mechanisms of reproductive hormones in cardiovascular disease states and increase gender-specific clinical trials to identify female-specific risk factors and pharmacokinetics.

*Depressive and mental health disorders* — Increase research on hormonal, behavioral, and genetic factors predisposing women to these disorders and identify gender-specific pharmacokinetics.

*DES exposure* — Continue research to determine the effects of second-generation exposure to diethylstilbestrol (DES), with special attention to its effects on fertility drugs, use of hormone replacement therapy during menopause, risk and incidence of female cancers, and risk of transmission to a third generation.

*Endometriosis, infertility, and uterine fibrosis* — Increase basic molecular and cellular regulation research with specific attention to defining the basic biology of these diseases and to identify components of their causes.

*Female cancers* — Particularly for breast, lung, and ovarian cancers, increase research initiatives for finding early markers for detection, gene and molecular therapy, environmental impact, risk factors, and modification.

*Infertility and fertility control* — Develop more cost-effective treatments for ovulation induction and increase understanding of fertilization and implantation, ovulatory disrupters, and male infertility.

*Obesity* — Increase research initiatives in the basic understanding of genetic, behavioral, and environmental factors in obesity.

*Polycystic ovarian syndrome* — Increase research on androgen impact on CVD and the insulin resistance mechanism.

*Stress-related gastrointestinal disorders* — Educate and sensitize the medical community about early and/or preventive diagnosis of gastrointestinal disease in women, with special consideration of the brain-gut connection linking abuse, stress, anxiety, and panic

disorder to gastrointestinal diseases. Implement existing technology and procedures to establish early diagnosis of symptomatic patients in order to define groups that will benefit most from early intervention and treatment modalities.

*Substance abuse* — Conduct basic, epidemiologic, and longitudinal research to identify gender differences in the causes, consequences, risks factors, and preventive factors of drug use, abuse, and dependence. Develop effective drug abuse treatment and prevention models that are specific to the unique needs of women, with consideration to the impact of coexisting factors such as violence, victimization, and psychiatric disorders.

# PERIMENOPAUSAL AND POSTMENOPAUSAL YEARS

**T**he basic premise of research on women's health is that it must be studied and understood in the context of culture, ethnicity, and socioeconomic status for research in all areas of peri- and postmenopause; all research hypotheses should start with ethnic-specific criteria. More specific research priorities fall into three broad categories: the process of the menopausal transition, pharmacological aspects of peri- and postmenopause, and behavioral and psychosocial aspects of peri- and postmenopause.

## RESEARCH RECOMMENDATIONS

### *The Menopausal Process*

- Clarify and define the various stages comprising the transition from premenopause to perimenopause to postmenopause.
- Characterize the normal antecedents and sequelae of the menopause transition and, in so doing, distinguish this stage of the female life cycle from disease processes and the processes of aging; specifically bleeding abnormalities, development of obesity in the menopausal years, and the role of the postmenopausal ovary on the manifestation of menopausal symptoms subsequent to morbidity.
- Evaluate the effects of surgical versus spontaneous menopause on morbidity and mortality and on factors related to women's sexuality. Hysterectomy

and the factors affecting it should be emphasized in the research agenda. Areas of investigation should include fibroids and their treatment, hormonal aberrations, physician and patient preferences, analysis of the outcomes of hysterectomy (with and without oophorectomy), and alternatives to hysterectomy.

- Explore environmental, cultural, and lifestyle influences on menopause, including what constitutes optimal primary care for women in this stage of life, the effects of physician training on the health care of menopausal women, whether women would be better served if gynecology were separated from obstetrics, women's needs and appropriate strategies for contraception during the perimenopause, and the influence of environmental agents on estrogen receptors.

### *Pharmacological Aspects of Peri- and Postmenopause*

- Evaluate the effects of endogenous and exogenous hormones on tissues and physiological processes of multiple target organs.
- Continue and expand studies of hormone replacement therapy (HRT). Specific areas to be explored include the effects of administering conjugated versus pure forms of estrogen and natural versus synthetic progestins; oral versus transdermal administration; the schedule in estrogen-progestin regimens; methods of reducing side effects and

optimizing and individualizing regimens for patients; factors affecting pharmacokinetics such as lifestyle, smoking, obesity, and diet and other ingested substances; and the effects of HRT on cardiovascular disease from the viewpoint of primary and secondary prevention.

- Research alternatives to HRT, including pharmacological agents such as Raloxifene and other selective estrogen receptor modulators (SERMs), diet and dietary supplements (for example, phytoestrogens), behavioral interventions, and the role of testosterone.

### ***Behavioral and Psychosocial Aspects of Peri- and Postmenopause***

- Explore the psychological aspects of menopause and the transition to menopause, including women's attitudes toward bleeding and the symptoms of menopause.
- Research the effects of caregiving in the menopausal years, including how the stress of this increased burden affects the menopausal process and how caregiving responsibilities affect women's participation in preventive health practices and clinical trials and other studies.
- Determine the attitudes, knowledge, and perceptions of women, health care providers, and society in general toward menopause and toward the aging processes, including examination of the barriers to health care in this period of life and how they can be overcome.
- Explore the psychosocial and the biomedical aspects of genetic susceptibility testing, including such issues as appropriate interpretation of data, confidentiality, psychological impact

of knowledge of the potential for genetic defects, implications for health care, and insurability.

- Research the health effects on menopausal women of such stressors as bereavement, abandonment, the "empty-nest" syndrome, and other forms of loss.
- Devise and implement strategies and channels for disseminating new medical and health promotion information to a variety of audiences including women, health care providers, and society at large.
- Undertake meta-analyses on data from prior studies on weight management and hysterectomy to maximize the value of the extensive research that has already been conducted in this area.

# ELDERLY AND FRAIL ELDERLY YEARS

The following research recommendations use as their base the holistic definition of health as put forth by the World Health Organization: physical, social, and mental well being.

## RESEARCH RECOMMENDATIONS

### *Social and Behavioral Issues*

- Focus on changes in family and social structures, caregiving roles, and new workforce services for women.
- Focus on the feasibility and intergenerational impact of formal and informal caregiving: stress, coping, training lay providers, and respite care.
- Promote personal choice and autonomy in living situations.
- Identify the antecedents and consequences of mandatory elder-abuse reporting by physicians and nurses.
- Develop ways to empower older women in their use of health care, including second opinions, mammograms, and clinical breast exams.
- Increase efforts in health promotion and disease prevention, including encouraging older women to participate in clinical studies and sharing research results with these groups of women.

- Encourage research on the impact of managed care on the health and well being of older women.
- Continue research on mobility and safety issues.
- Develop research on the use of assistive technologies.

### *Mental Health Issues*

- Study gender differences in depression.
- Continue studies of alcoholism and other drug abuse and dependence, including dependence on prescription drugs.
- Study effective coping strategies.
- Investigate dementias.
- Study the impact of living arrangements on mental health.
- Study the impact of chronic pain on mental and physical health.
- Study the impact of fears of death and dying and terminal pain.

### *Cardiovascular Illness*

- Continue research on treatments and outcomes for men and women.

### ***Osteoporosis and Osteoarthritis***

- Continue research on the long-term effects of HRT.
- Research interventions to help women 65+ who have not taken HRT.
- Study alternatives for women 65+ who have taken HRT.
- Identify biomarkers to predict osteoarthritis.
- Study strategies for delaying the progress of osteoarthritis.
- Concentrate on preventive strategies, i.e., increased calcium intake in adolescence and young adulthood.

### ***Musculoskeletal Fitness***

- Research methods for delaying frailty.
- Study the impact of musculoskeletal fitness on comorbid disease progression.
- Research musculoskeletal and cardiovascular response to exercise.
- Investigate why disability rates are decreasing among the elderly, and the impact of this decrease.

### ***Health Promotion Activities***

- Target health promotion activities to increasing appropriate exercise, boosting nutrition awareness and habits, and decreasing disability.

### ***Pain and Its Impact on the Elderly***

- Study the impact of chronic pain on physical health and find ways to relieve the chronic pain of comorbid conditions in older women.

### ***Urinary Incontinence***

- Study normal and abnormal bladder physiology, to suggest treatment for incontinence.
- Research adjunctive treatments such as pharmacologic therapy.
- Investigate behavioral interventions for persons at risk.
- Conduct clinical trials to examine effective therapies for specific types of urinary incontinence.
- Increase educational efforts for health providers and patients regarding the effectiveness of bladder training.
- Review staff management techniques to ensure compliance with treatment protocols.

### ***Impact of Improved Health in the Elderly***

- Undertake studies to investigate the social and physiological impacts of women living longer — implications in the job market, for example, as well as in the development of chronic conditions and comorbidities.

### ***Surgery***

- Develop strategies to enhance recovery from surgery in older women, especially from transplants and prosthetic devices.
- Examine criteria for transplant surgery and the use of prosthetic devices to discover whether older women are considered appropriate candidates for these devices.

### *Delaying and Correcting Sensory Impairments*

- Investigate vision impairments in older women, particularly the increasing problem of macular degeneration.
- Research hearing loss and its impact on quality of life.

### *Impact of Human Genome Research on Genetic Basis of Conditions Affecting Longevity*

- Investigate whether there is a genetic basis for chronic diseases or retention or loss of physical functioning in old age.

### *Issues of Pharmacology and Aging*

- Identify toxic drug reactions in elderly women associated with the use of concomitant medications, including HRT.
- Study drug interactions of commonly prescribed medications, over-the-counter drugs, and nutritional supplements.
- Develop data-mining techniques to extract drug-interaction information from existing databases.
- Investigate safe and effective alternatives to HRT.

### *Research Design and Methods*

- Develop data-mining techniques to extract from existing databases critical health information pertinent to the health of elderly women.
- Identify the toxic drug interactions associated with the use of concomitant medications, including the concomitant use of HRT.

- Develop more effective guidelines that focus on the regulatory and financial issues of conducting research on diseases, disorders, and conditions especially prevalent in elderly women.
- Improve techniques to access existing databases needed by investigators for exploring critical health issues in elderly women, including the use of appropriate key words for searching databases like those of the National Library of Medicine.
- Conduct more research on the process and outcomes of obtaining more appropriate informed consent from older women for research and medical procedures.
- Identify the barriers encountered by older women that prevent them from joining research studies.
- Encourage the development, use, and evaluation of more creative and innovative research methods and designs to study the health of older women.







REPORTS OF THE WORKING GROUPS:  
DIFFERENCES AMONG POPULATIONS OF WOMEN  
THROUGHOUT THE LIFE CYCLE —  
SUMMARY OF RECOMMENDATIONS



## PRENATAL YEARS

The role of population differences in successful pregnancy outcomes has not been emphasized in the research to date. Thus, while the studies of the physiology, biochemistry, pharmacology, and genetics of pregnancy must continue to identify the overall strategies for improving women's health, the challenge of improving the health of women must also emphasize the environmental, psychological, and population effects.

### RESEARCH RECOMMENDATIONS

#### *Observational Studies*

- Study drug use and traditional practices among pregnant women in diverse groups.
- Determine the behavioral basis of motivation for seeking prenatal care.
- Explore and define cultural sensitivity in acquisition of genetic information.
- Encourage greater concern with qualitative studies.
- Examine probable overutilization of technology for pre- and perinatal medicine.

#### *Clinical Studies*

- Build and incorporate community values in diverse groups into outcome measures.

- Compare susceptibility (needs) with strengths (assets) in individuals and groups with regard to adverse fetal outcomes.
- Conduct long-term studies of environmental exposure in human groups and animal models, both preconceptionally and in utero.
- Investigate the pharmacodynamics and pharmacokinetics of drugs in diverse groups.
- Conduct longitudinal studies of multiple approaches to prenatal health — a Preconceptional and Perinatal Health Initiative.

#### *Genetic and Physiological Studies*

- Explore the genetic differences among diverse groups, with an emphasis on fetal outcomes.
- Coordinate genetic information with environmental differences.
- Investigate placental biology in diverse groups.

#### *Educational Initiatives*

- Educate the practitioner and the public to subpopulation needs by consensus, conference, and national programs.
- Use networking to engage appropriate self-identifying groups.
- Use interdisciplinary education.

### *Administrative Concerns*

- Encourage investigations by recurrent regional training programs.
- Sensitize DRG to applications involving diverse human groups.

# INFANCY AND CHILDHOOD YEARS

The infancy and childhood cohort is large and diverse. Problems encountered by this group range from prematurity with multiple congenital anomalies to postpubescent pregnancy. The understanding of many diseases and conditions of infancy and childhood has advanced greatly, but a comprehensive research agenda for this group is imperative.

## RESEARCH RECOMMENDATIONS

### *Research Methodology*

- Include the use of racial and socioeconomic demographic indicators in all research.
- Ensure that the social sciences reinforce and enhance the findings of biomedical science, requiring the development of effective scientific quantitative and social qualitative models, often-times targeting entire families and communities.
- Incorporate cultural sensitivity and flexibility into research models and questions.
- Ensure that morbidity and mortality statistical data be as timely, accessible, and specific as possible.
- Create one single depository for all statistics that is easy to find and is user friendly. Important variables to be included are race, ethnicity, age, socioeconomic status, morbidity, and mortality.

- Use a longitudinal model to investigate the problems of children that manifest later in life.

### *Calcium Intake*

- Uncover additional relationships between childhood calcium intake and the development of adult osteoporosis.
- Establish the relationship of phosphorus (diet and regular soda), smoking, pregnancy, and exercise to the development of peak bone mass in girls.
- Investigate the best source(s) of calcium.
- Research ethnic differences in lactose intolerance and calcium absorption.
- Investigate the relationship between genetics and environment in the development of peak bone mass.
- Study the benefit of childhood mineral supplementation.
- Examine the relationship and effectiveness of vitamin D receptor sites to peak bone mass formation.
- Explore the societal pressures that discourage girls from drinking milk (e.g., dieting).
- Establish a working group on bone and musculoskeletal disorders to continue exploration of the above research questions.

### ***Diet and Physical Activity***

- Measure poverty and its relationship to healthy behavior; for example, when a family cannot afford fresh food or has no access to organized sports or accessible playground facilities.
- Measure available income and recognize the family member in control of total family income; for example, studies in developing countries have shown that children fare better when the mother has control over family spending.
- Investigate the interrelationship between menarche, self esteem, and decreased physical activity.

### ***Tobacco, Alcohol, and Other Drug Abuse***

- Conduct further research exploring within-group variations in the substance use of various ethnic groups.
- Devise effective prevention interventions for these abuses.
- Refine effective prevention and treatment strategies, as new information is generated, for tobacco, alcohol, and drug abuse.

### ***Childhood Maltreatment***

- Study all forms of abuse in the context of the social, cultural, and economic environment in which they occur.
- Assess abuse for a generational and cultural component.
- Explore ethnic and cultural definitions of child maltreatment.
- Examine the relationship of child maltreatment to the development of adolescent- or adult-onset mental illness.

- Review lifelong effects, both physical and psychological, of underreported incidence of all types of childhood maltreatment.
- Develop instruments and techniques to obtain accurate statistical data.
- Examine the relationship of child maltreatment to later development of learning disabilities, failure to thrive, and drug use.
- Develop instruments that measure both prevalence and effects of child maltreatment.
- Measure the relationship between child sexual abuse and early consensual sexual relations, pregnancies, and substance abuse.
- Continue multidisciplinary, multiagency collaborative efforts such as the effort between NICHD, NIMH, and OBSSR that investigates precursors to abuse.

### ***Normal Growth and Development***

- Develop a greater understanding of normal physical and behavioral development, including knowledge of the pharmacologic differences between males and females and among different age and ethnic groups of children.
- Investigate why certain diseases and conditions are more common in female infants and children and among certain ethnic groups.
- Examine how the catchup growth lag differs based on gender.
- Study how cell growth and differentiation are different between sexes.
- Investigate why girls injure differently than boys during exercise.
- Conduct research on the critical periods of development in organ systems, particularly the brain.

- Explore how the lack of a nurturing environment affects emotional resilience.
- Examine how the impact of the psychosocial environment of female children impacts nervous system development in childhood.
- Investigate how the physiology of the brain differs between girls and boys.
- Study the biochemical markers in childhood of chronic disease in later life.
- Understand how molecular biology can be used to identify and understand the influence of human genes on childhood development, diseases, disorders, and conditions.
- Explore how research can best make use of the human genome to improve child health.
- Investigate whether the most commonly used children's drugs are equally efficacious and safe in children of different ages, genders, and races.

#### ***Interaction Between Girls and Their Parents***

- Investigate the impact on children who come home from school without the benefit of parental or other adult supervision.
- Study the effect of maternal depression on girl children.
- Examine how decisionmaking authority differs among ethnic, racial, social, and economic groups, in order to target specific interventions.
- Establish the correlation between quality of the parental relationship and learning disabilities, neglect, failure to thrive, and drug use.

#### ***Hormonal Influences***

- Examine the relationship of testosterone to male aggression and how it can ultimately lead to abuse of females.

- Investigate the effect of cerebral serotonin levels and serotonin receptors on depression and suicidal behaviors and ideations.
- Study the effect of cerebral serotonin levels and serotonin receptors on impulse control and thrill-seeking behaviors.
- Conduct research on the effect of estrogen and exercise on development of peak bone mass.
- Research the relationship of unopposed progesterone to halted bone density development.
- Explore the reason girls of short stature receive clinical diagnosis and treatment less frequently than boys with the same diagnosis.

#### ***Environment***

- Study the influence of livestock hormonal supplementation on children's conditions.
- Examine the environmental influence of schools, where children spend much of their day.
- Research the impact of infectious agents by age and gender.

#### ***Asthma***

- Study asthma in relation to the child's age and onset of disease.
- Examine the relationship, if any, between the menstrual cycle and exacerbations of disease.
- Investigate the relationships between environmental toxins, air, genetic predisposition, carpet, mold, cockroaches, and schools to the development of disease and exacerbations of asthma.

#### ***Mental Health and Depression***

- Investigate whether drugs that are not approved for pediatric use (e.g., Zoloft and Prozac) are safe for use in children.



- Study whether depression in children is actually increasing and, if so, why.
- Uncover the relationship between female self esteem and drug use, eating disorders, and early sexual activity.
- Determine the source(s) of resilience in children.
- Investigate the incidence of mental health problems in children.

### *Oral Health*

- Initiate a study to develop interventions that are effective in eliciting donning of protective head gear in females.
- Institute a study that addresses the effect of dental anomalies on growth and development, nutritional consumption, enamel dysplasia, and self esteem.

## ADOLESCENT YEARS

The specific focus of this working group was to explore the differences in populations (cultural, ethnic, socioeconomic, rural and urban, and disabilities) with respect to female adolescent health issues. The group acknowledged that most of the health problems in this age group are behavioral and community based.

### RESEARCH

### RECOMMENDATIONS

- Study normal growth and development for the diversity within the adolescent female population, studied at physiological, psychological, and sociological levels as expressed in the diverse populations. Examples of areas to be studied under this topic include:
  - breast development, hair growth, and development of genitalia;
  - race and ethnic differences and an acknowledgment that “average” is not necessarily “normal”;
  - effect of sexual abuse on physical and social development and the impact of assaults on normal development;
  - onset of menarche and population differences;
  - longitudinal work to determine normal growth and development; and
  - normal development of sexual identity from infancy on and how that plays out in young females’ lives and sexual orientation.
- Examine health-compromising behaviors, individually and in constellation, including risky sexual behaviors; drug, alcohol, and tobacco use; and delinquency and victimization.
- Study risk factors, looking at the causes and subsequent consequences, including:
  - poverty,
  - victimization,
  - racism and marginalization,
  - school failure,
  - disability,
  - dietary and physical activity patterns that are antecedents of adult disease, and
  - childhood behavior problems.
- Focus research on understanding the disorders of adolescence: gynecological disorders, including endometrial and menstrual, and mental disorders, including depression, anxiety disorders, eating disorders, and suicide.

- Sequence-base, target appropriately, and evaluate prevention, identification, and treatment, including research on:
  - physical and sexual assault prevention,
  - new treatment modalities and prophylaxis for STDs,
  - oral one-dose treatments,
  - oral-administered partner treatments,
  - science-based, female-adolescent-specific research targeted appropriately, and
  - longitudinal studies to evaluate long-term impact.

## REPRODUCTIVE AND MIDDLE YEARS

**M**ore research is needed in many areas for women in their reproductive and middle years, including contraception, infertility, osteoporosis, chronic pain, and cancer. Investigations need to examine the effects of ethnicity, culture, sexual orientation, socioeconomic status, and disability on the health of women.

### RESEARCH RECOMMENDATIONS

#### *Women of Color*

- *Access and screening* — Study the impact of managed care on health outcomes of different subgroup populations. Determine why health care delivery systems make reproductive health care increasingly inaccessible to racial and ethnic minorities and rural women.
- *Fitness and health* — Identify the mechanisms and etiological factors for obesity impacting chronic diseases, with particular attention to exercise, prevention of cardiovascular disease, and prevention of diabetes.
- *Contraception* — Research development of effective, culturally sensitive prevention interventions for different populations and culturally appropriate modifications of safe-sex messages for different populations.
- *Infertility* — Identify the relationships between environmental factors and infertility among women of color who are differentially exposed to greater levels of environmental toxins than Caucasian populations.
- *Birth outcomes* — Discover a possible connection between a pregnant woman's diet and fetal loss and, if this connection exists, determine if this connection is similar in all racial and ethnic groups.
- *Low birthweight* — Increase research on explanatory factors for low birthweight, such as obesity and insulin resistance.
- *Infant mortality rates* — Identify the cultural factors that are predictors of low infant mortality rates among different populations and how this can be transferred to other populations.
- *Premature labor* — Investigate its prevention rates and identified causes in different populations.
- *Infectious diseases and STDs* — On different ethnic populations with HIV, full-blown AIDS, and STDs, augment research to determine how the symptoms manifest and responses to treatment. More research is needed especially for populations of women expected to be at low risk for AIDS.
- *PMS* — Examine the family history of depression and the cultural aspects of PMS and their impact on different populations.

- *Substance abuse* — Study antecedents, risk, and protective factors for substance abuse; trauma for different ethnic and racial groups; and the resulting consequences of substance abuse. Study the linkages between substance abuse, mental health, and co-morbidity and trauma and how these are culturally mediated.
- *Osteoporosis* — Research the prevalence, bone loss from age 25, and techniques for enhancing bone mass among different ethnic and racial groups.
- *Mental health* — Study the efficacy of traditional approaches to mental illnesses, including alternative treatment interventions that work for certain populations. More research is needed on mental health for other groups as well as their responses to different treatment modalities.
- *Study pharmacodynamics*, drug efficacy, and side effects for different populations of women.
- *Investigate postpartum depression* among different racial and ethnic groups.
- *Cancers* — Research the relationships between nutrition and chronic disease.
- *Violence* — Identify and define abuse (physical, verbal, and sexual) among different racial and ethnic populations and how specific cultures contribute to abuse.
- *Endometriosis, fibroids, and hysterectomies* — Conduct new research on the causes and prevalence of endometriosis and fibroids in these populations. Explore racial differences in efficacies of alternative treatments.
- *Chronic pain* — Identify the major reasons for chronic pain among different ethnic groups.

### **Poverty and Urban Health**

- Develop and test measures of social class, for clinical and population-based health research, that are most reliable and valid for populations of women that differ by race and ethnicity, sexual orientation (or type of partnership), and age — at individual, household, and neighborhood levels.
- Describe social class heterogeneity in patterns of risk, disease, health, and mortality within racial and ethnic groups by gender.
- Investigate the interrelationship of social class and race and ethnicity for different types of cancers to determine why the gender-cancer relationship is direct for some cancers and inverse for others.
- Determine how the lifetime trajectory of social class and socioeconomic position affect health, disease, and mortality among women, and whether there are age, period, and cohort differences.
- Investigate how the interplay of genetic and environmental (including socioeconomic) factors affect women's health during the reproductive years.
- Evaluate to what extent migration and generation in the United States confer a protective effect on women, independent of socioeconomic position.

### **Women with Disabilities**

- *Body image* — Determine the impact of acquired or continuing disability on body image and self esteem, and which interventions will prevent social isolation and withdrawal from health-maintenance activities.
- *Lesbians with disabilities* — Document the health care experiences of lesbians with disabilities. Eliminate heterosexual presumptions from medical history-taking and research instruments. Provide funding to develop relevant educational materials that address specific health issues of lesbians with disabilities.

- *Contraception* — Evaluate the choices of contraceptions for immobilized patients (ruling out thrombotic risk) and women with MS, lupus, cardiovascular conditions, and stroke. Investigate adverse reactions of conventional contraceptive options for women with disabilities and develop possible interventions to make these options safer.
- *Urinary tract infections (UTIs)* — Conduct research on interventions to prevent recurrent UTIs in women with neurologic dysfunction, on low-dose prophylaxis, on anticholinergics, and on diet modification. Prevent UTIs in women who use catheters, such as women with spinal cord injury and spina bifida.
- *Infections (STDs)* — Research prevalence of chlamydia and gonorrhea (and undiagnosed sequelae), concentrating on altered manifestations in sensory-impaired women.
- *HIV* — Investigate the prevalence of HIV in women with disabilities and whether manifestations are different in women with disabilities.
- *Pregnancy* — Investigate prenatal and pregnancy-related issues for women with disabilities:
  - How disability interacts with pregnancy;
  - Mobility adjustments related to pregnancy;
  - The pressure points with wheelchairs;
  - Whether bladder dysfunction is exacerbated by pregnancy;
  - Ways to manage pyelonephritis;
  - Alternative monitoring for contractions in women with sensory impairment — the effectiveness of home uterine monitoring;
  - How the induction of labor affects neurologic conditions;
- Appropriate anesthetic agents for women with STI, MS, and CP — whether an epidural has lasting neurologic consequences;
- Increased risk of C-section — whether there is a true need for it or whether a C-section is performed because of the doctor's anxiety;
- Management of autonomic dysreflexia — how soon to intervene and what parameters to use;
- How women with disabilities prepare for parenting;
- What adaptive strategies and techniques are successful and what adaptive equipment (disability-specific) is useful; and
- How mothers with disabilities adjust to the transition from pregnancy to postpartum — weight changes, independence issues, need for additional assistance, and incidence of postpartum depression.
- *Fitness and health:*
  - Target research at the long-term benefits of exercise for women with disabilities.
  - Explore the effects of exercise and fitness on secondary conditions, including prevention and intervention.
  - Conduct further research regarding the impact of exercise by severity of disability.
  - Research the attitudes of women with disabilities toward participation in physical activity, and the attitudes of individuals who provide services to them.
  - Study and overcome the barriers to adequate nutrition for women with disabilities.
  - Promote better weight management for women with disabilities.

- Determine ways to help women with disabilities manage stress.
- *Secondary conditions* — Target research at basic epidemiology of secondary conditions. Develop multifaceted interventions to prevent secondary conditions, considering the regular monitoring of women's health status and the availability of appropriate assistive technology and community support.
- *Bowel and bladder management* — Research new technology, external collection devices, biomaterials for bladder and sphincter reconstruction, physiological consequences of disability, pelvic floor muscles, changes over long time periods, bowel irritation, stretching of the urethra, and renal stones.
- *Violence* — Investigate the incidence and prevalence of abuse among women with disabilities. Identify risk factors that contribute to violence and abuse against women with disabilities and develop effective interventions to reduce the risk of abuse. Train health care providers to recognize the signs of abuse among women with disabilities.
- *Substance use and abuse* — Determine the interaction between substances such as tobacco, alcohol, and other drugs, and various disabilities. Develop methods to prevent and treat substance abuse among women with disabilities.

### *Pharmacokinetics*

- Support studies on the bioavailability and drug delivery from a social and biophysical point of view for various racial and ethnic groups.
- Among women of different populations, study the pharmacokinetics and pharmacodynamics of folic acid for the prevention of neural tube birth defects.

## PERIMENOPAUSAL YEARS

**T**he menopausal transition is one of the unique aspects of a woman's middle years. However, there is a lack of knowledge about the fundamental biologic processes involved in menopause. More research is also needed on the perimenopausal experiences of women from differing socioeconomic, ethnic, sexual orientation, and disability groups.

### RESEARCH

### RECOMMENDATIONS

- Investigate lifelong developmental and contextual influences on the perimenopausal transition, including physiological (e.g., endocrine, immune, genetics), socioeconomic, cultural, ethnic, and lifestyle (e.g., diet, activity) dimensions.
- Study basic biological processes across the menopausal transition.
- Investigate experiences of symptoms such as hot flashes and bleeding and how women make meaning of them as a basis for self care or seeking health care.
- Examine mental health problems (especially depression) that can appear or continue into this period and the biological impact of the menopausal transition on mental health.
- Study relationships between cognition, emotion, and immune response (psychoneuroimmunology) during the menopausal transition as a basis for understanding how culture, lifestyle, and behavior affect immune response and chronic health problems.
- Investigate fertility management spanning pregnancy prevention, pregnancy care, and fertility enhancement.
- Explore the life cycle course of health behaviors, such as nutritional intake and exercise patterns, and cumulative environmental exposures, including workplace exposures as they are modified by pregnancy, birth, breastfeeding, and menopause.
- Examine environmental exposures, such as endocrine disruptors and workplace stress, and their consequences for midlife health.
- Conduct research on genetics and specific health problems such as cancers (particularly breast cancer).
- Explore midlife women's experiences of HIV/AIDS and the menopausal transition.
- Study midlife women's experiences of violence and models of violence prevention.
- Investigate health care needs of special populations within this transitional period.
- Enhance information dissemination and exchange for consumers and providers through the following efforts:
  - Identify information appropriate for special populations.



- Promote understanding of the relationship between women and their health care providers and factors that enhance trust.
- Develop a clearinghouse on perimenopausal issues that will include evaluation of information through mechanisms such as those used for evidence-based practice and the U.S. Preventative Services Task Force.
- Investigate informed consent and ethics related to the conduct of research with different ethnic and socioeconomic groups.
- Study patient-provider communication patterns and effects on health outcomes.
- Advance understanding of the therapeutic interventions available to women during the perimenopausal period including:
  - use of allopathic and alternative and complementary medicine and their relationship to primary, secondary, and tertiary prevention (e.g., spirituality, vitamin therapy, alternate care providers);
  - use of hormone therapies and interactions with genetics, other systemic conditions, environmental factors, and alternative therapies;
  - patterns of use of hormones and alternative therapies in special populations including their use by women with HIV/AIDS; and
  - understanding of therapies such as SSRIs and evaluation of them with respect to outcomes such as leaving violent relationships and changes in socioeconomic status.
- Study the effects of health care delivery system models that will encompass:
  - training of health professionals,
  - time spent with patients,
  - provider-patient interactions, and
  - women's access to health care and specific services as these are each linked to health outcomes.

# POSTMENOPAUSAL YEARS

**A**s the population of older women continues to grow, it becomes increasingly important to expand the existing scientific knowledge base so that effective strategies can be developed to optimize the health status of postmenopausal women.

## RESEARCH RECOMMENDATIONS

### *Health Status of Special Populations of Postmenopausal Women*

- Examine descriptive epidemiology on occurrence of risk factors and diseases in postmenopausal women of special populations.
- Define characteristics that influence health status and behaviors to reflect the heterogeneity of special populations.
- Inspect the health outcome differences in racial subgroups of postmenopausal women.
- Explore the impact of survivorship of chronic disease on quality of life as perceived through the special population individual's perspective in terms of the physical, emotional, social, and economic changes they experience.

### *Behavior and Health in Special Populations of Postmenopausal Women*

- Investigate the effect of accumulated risks on specific health problems and special populations of postmenopausal women.

- Examine the influence of living in Western societies on the increased rate of breast cancer in Asian women in the United States.
- Investigate the health of women with disabilities in the postmenopausal years, including facilitators and barriers to their optimal health.
- Study the scientific evidence for the role of menopause versus aging in conditions common in postmenopausal years and chronic diseases.
- Investigate differences between postmenopausal women and men in response to surgical and pharmacological treatment interventions.
- Identify differential risk factors for stroke in postmenopausal women and men and in subpopulations of women.
- Examine possible explanations for the differing prevalence of diabetes among subpopulations of postmenopausal women.
- Explore how to improve rates of regular mammography, clinical breast exams, and colon cancer screening, focusing on minority and underserved postmenopausal women through the use of innovative, culturally appropriate strategies.
- Address ways of improving compliance with followup and treatment recommendations following abnormal diagnostic and screening tests in postmenopausal women, including the examination of psychological effects of positive testing.

- Examine the actions of all natural hormones (e.g., DHEA, natural estrogens, melatonin, human growth hormone, natural progesterone, thyroid hormones) in postmenopausal women.
- Compare the effectiveness of different estrogen treatments in postmenopausal women of different subpopulations.
- Explore pharmacologic differences in drug outcomes and drug-drug interactions specific to postmenopausal women.
- Investigate the reasons for drug use and misuse among postmenopausal women of special populations.
- Delineate mechanisms underlying postmenopausal women's and men's differential sensitivity and responsiveness to pain threshold and tolerance measures. Validate measures of pain in subpopulations of postmenopausal women, informed by specific cultural beliefs and practices.
- Explore possible explanations for gender and age differences in mental health effects.
- Identify the effects of racism on the health of postmenopausal women in special populations.
- Explore the mental and physical issues specific to postmenopausal lesbian women.

#### ***Environmental Exposures and Health in Special Populations of Postmenopausal Women***

- Explore the effect of environmental toxins on postmenopausal health.
- Examine the effects of the workplace on postmenopausal low-income service workers (e.g., women who clean offices and hotels).
- Investigate the effects of pesticides on postmenopausal migrant workers.

- Explore the nature and outcomes for postmenopausal women of stressors associated with military life.
- Examine how the stress of war affects postmenopausal women in comparison to men and what interventions, if any, exist to lessen these effects.

#### ***Health Provider and Researcher Interactions with Special Populations of Postmenopausal Women***

- Train health care providers to consider postmenopausal women of different subpopulations in terms of their entire needs — emotional, rehabilitation, social, and financial — when treating illnesses.
- Investigate how to improve health provider and researcher sensitivity, such as how questions are asked and body language.
- Determine the most effective mixture of health care provider types for delivering health care to special subpopulations of postmenopausal women.

#### ***Research Methods in Special Populations of Postmenopausal Women***

- Address the role of incentives for recruitment and retention of special populations of postmenopausal women in studies and to provide allowances for funds in clinical trials for recruitment and retention of participants.
- Coordinate research activities with community hospitals, clinics, and reservations so that postmenopausal special population women can access them.
- Construct new strategies for instrumentation reliability and validity for postmenopausal special populations (e.g., translation issues).

- Increase the use of behavioral research and strategies to accompany medical diagnosis and treatment procedures for special populations of postmenopausal women.
- Fund additional longitudinal studies for special populations of postmenopausal women.
- Establish a clearinghouse for rapid dissemination of research findings to researchers, health care providers, and the public, and an inventory and distribution center for intervention materials that have been proven effective.



# ELDERLY AND FRAIL

## ELDERLY YEARS

**I**n considering the health of older women, the World Health Organization concept of health applies: all aspects of women's physical, social and behavioral, and environmental health are important. Across the diverse and growing populations of older women in the United States, there is a need for adequate access to and coordination of a wide range of health care providers and care givers.

### RESEARCH RECOMMENDATIONS

#### *Biological and Physiological*

- Determine the effects of chronic illness and disability, such as AD and other dementias, cancer, and osteoporosis, on the quality of life for older women and frail elderly women.
- Conduct research that results in applications on the biomechanics of older and frail elderly women.
- Continue research on the longitudinal, multi-generational effects of DES.
- Examine drug action and effects in relation to age, racial and ethnic groups, and gender.
- Study multiple drug, drug-food, alcohol, tobacco, and other interactions.

- Study the impact of natural and synthetic estrogens on different physiological systems, including the immune, endocrine, and cardiovascular systems, and on cognitive and affective processes and on sleep.
- Investigate the impact of oral health on quality of life and the general health of aging women, as well as on specific diseases.
- Conduct research studies on less well-known physiologic conditions in elderly women (e.g., angiodysplasia of colon, vertigo, hiatal hernia).
- Support scientific studies to evaluate the effectiveness, benefits, risks, and costs of alternative and complementary medicine.
- Study the shift from subclinical to clinical conditions in older and frail elderly women.
- Study multisensory impairment in older women.
- Produce a better understanding of the physiological aging processes across racial and ethnic groups of women.

#### *Psychosocial*

- Study the relationship between self efficacy and positive self image and outcomes such as functional independence and self care as mediated by family and social supports.

- Examine the concepts of health (body image), aging, disease, and disability (and causes and consequences of each) as a function of age, knowledge and attitudes about aging, ethnicity, and cultural background.
- Address gaps in information between the end of the working years and the transition to the need for assistance and nursing care.
- Identify the developmental course of aging and functional levels, to allow older people and care givers to know what to expect.
- Study the role of multisensory impairment on personal and social functioning of older women.
- Investigate the living environments — including physical and social parameters — of older women.
- Examine the influences of spirituality on health outcomes in diverse groups.
- In light of growing evidence, conduct research on the causes, consequences, and interventions related to physical and emotional violence, abuse, and traumatic stress in older women.

### ***Health Practices and Interventions***

- Study the influence of age, culture, and socioeconomic status on older women's health practices and the receptivity to lifestyle interventions, and the effectiveness of health behavior interventions in different population groups of older women.
- Evaluate elderly and frail elderly women's use of alternative and complementary health care services, focusing on self care and health education preventive services.
- Examine health and life choices as they impact living arrangements (independent, congregant, family, or institutional) and health care decisionmaking.

### ***Effects of Interventions***

- Regarding health behaviors and lifestyles of older and frail elderly women, study the differences in intervention applications for exercise, smoking cessation, and nutrition.
- Conduct research on the effectiveness of interventions on health conditions and health events in the lives of older women and frail elderly women, particularly in regard to:
  - Incontinence,
  - Falls,
  - Depression and anxiety,
  - Cognitive impairment,
  - Sleep, and
  - Traumatic events such as physical and emotional violence.
- Investigate medication use by older and frail elderly women, particularly HRT and polypharmacy.
- Examine patterns of alcohol and substance abuse in the various populations and subpopulations and across the sociocultural spectrum.
- Address the cost of intervention choices for different populations.

### ***Formal and Informal Caregiving***

- Conduct research on formal caregiving that addresses the following issues:
  - Caregiver selection;
  - Training and education given to care givers;
  - Cultural matching between care giver and client;

- Implications of transition from family to paid caregiving, or a mix of both;
- Work conditions that maintain, strengthen, or sustain quality caregiving for family care givers, volunteer care givers, and care givers in institutions; and
- Outcomes measurement — training, effectiveness, client satisfaction, and impact of caregiving on care givers.
- Conduct research on family caregiving that addresses the following issues:
  - Work conditions that maintain, strengthen, or sustain quality caregiving;
  - The multiple caregiving roles and how they are handled by families;
  - Cultural and socioeconomic differences in family caregiving;
  - Intergenerational relationships and family dynamics involved in caregiving; and
  - Role of older women as care givers.
- Investigate the new models for providing care, including research on the effectiveness of alternative caregiving arrangements for long-term care — assisted living options, new ways of providing care in traditional settings (e.g., special care units), and the role of volunteerism to reduce the burden of care givers.
- Understand the factors associated with access to care across age, gender, and ethnicity and on the levels of functioning.

#### ***Provider and Client Interaction***

- Investigate gender, ethnic, and regional influences on health care practices of older persons, especially diagnosis and treatment.

- Examine the interactions among patients and care providers, particularly among different cultures, ages, SES groups, and defined racial and ethnic groups.
- Enhance patient and provider interaction of elderly and frail elderly and the relation to quality of care, patient and provider satisfaction, prescribing patterns, and health outcomes.
- Study characteristics and training of health care providers who provide service to older people.
- Investigate barriers to the receipt of appropriate health care by the homebound and disabled, and of health care to older women in general.
- Conduct research on informed consent and the decision process for participation in health care or research, to help identify barriers to including older women in research studies.
- Explore the impact of changing health care financing and delivery systems on subgroups of older women.

#### ***Methodological Issues***

- Develop measures for nursing home residents that are culturally and ethnically sensitive for quality of life, SES differences, and different levels of cognitive functioning.
- Include the oldest old and institutionalized persons in studies; develop the ability to analyze such data by age and gender. Investigate age in terms of younger elderly (65 to 84) and older elderly (85+), compare outcomes, and differentiate groups by functional status rather than by age groups.
- Develop research strategies to recruit old and oldest-old women, as well as members of all ethnic groups and SES levels, as research participants. Include community organizations and their members as partners in research.



- Determine whether there are circumstances in which it is appropriate to consider age vs. functional status as a criterion for access to care or participation in research.

### *Death and Dying*

- Investigate attitudes toward death as a function of ethnicity, culture, and age.
- Examine end-of-life decisions, including end-of-life care and cultural and ethnic backgrounds and their influence on such decisions.
- Conduct research on managing death and ethnic and cultural differences regarding pain management, family support, place of death, dignity, special needs of women as informal care givers for dying persons, and assisted dying.
- Include quality of dying and ways to improve the end of life for patient and care providers.



CAREER ISSUES FOR WOMEN SCIENTISTS



# CAREER ISSUES FOR WOMEN SCIENTISTS

**I**n November 1997, the working group on Career Issues for Women Scientists met in Bethesda, Maryland, to discuss areas of concern and progress and to develop final recommendations for ORWH.

## *Recommendations and Conclusions*

The following recommendations apply, where appropriate, to the entire educational and career path from grammar school up to and through medical school and the various health science careers. The intent is to include all populations of women, and to foster collaboration among external agencies, associations, academic institutions, and the Federal Government.

## *Data Collection*

- Create a comprehensive database on women scientists by field, a database that should be widely available to university and industry search committees for new laboratory chiefs, division heads, and department chairs.
- Catalog and organize a list of existing databases to include emerging leaders, mentors, and special populations of women.

- Identify new database needs.
- Collect outcome data to determine the effectiveness of specific programs targeted at women scientists.

## *Program Monitoring for Institutional Accountability*

- Evaluate effectiveness of principal investigators in supporting academic careers of women and minority scientists.
- Evaluate effectiveness of institutional programs aimed at enhancing careers of women and minorities.
- Collect statistics on gender gap issues such as salary, tenure, and percentage of women at senior levels.

## *Dissemination*

- Develop mechanisms for disseminating information and data for those with and without Internet access.
- Assist institutions whose faculty are still unable to gain Internet access.
- Expand the ORWH web site for disseminating research information and other data pertaining to women scientists.

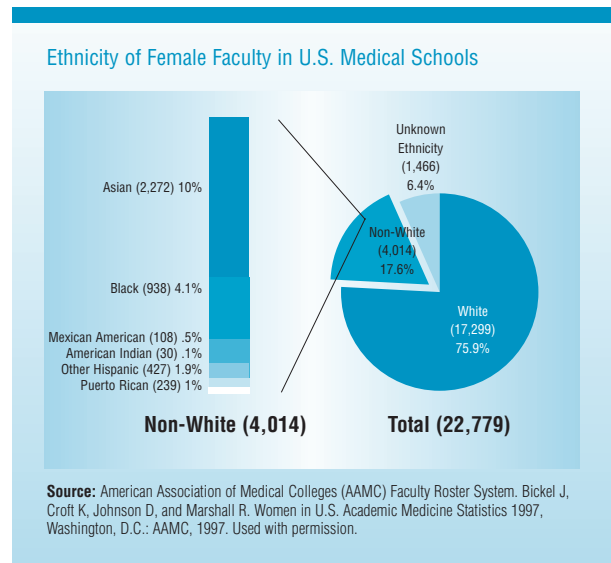
- Link the ORWH web site to other databases and web sites within NIH and in professional societies, biomedical organizations, academic institutions, and community groups.

### ***Institutional Responsibility, Collaboration, and Partnering***

- Encourage each institution to create new programs to address inequities in representation and participation of women and minorities in science and medicine.
- Include in expectations for NIH-funded principal investigators the point that training for investigators should include:
  - Requirements for special attention to recruiting, training, and advancing all underrepresented groups in medicine and biomedical sciences; and
  - Requirements for institutional responses to harassment and discrimination at all ranks, but particularly in training programs.
- Issue a contract from NIH for models of institutional self-study and corrective actions for any practices that hinder or discourage underrepresented groups from full participation in research and training in biomedical research.
- Increase participation of underrepresented groups at all levels in NIH (e.g., study sections, advisory groups, conferences). The same point applies to partnering institutions where appointment to committees, invitations to speak, and travel to conferences all add to the academic maturation of the faculty member.

### ***Education and Training***

- Encourage institutions to increase efforts to introduce science into the education of children from kindergarten through high school.



- Encourage NIH to offer competitive funding to increase the ability of individual institutions to develop quality programs to attract able young people into the biomedical sciences.
- Support and expand existing programs that encourage the exposure of women and minorities to science and medicine at the precollege level in order to increase the pool of student applicants from underrepresented groups.
- Expand the NIH Office of Education Scholarship Program for Minority Undergraduates with more vigorous outreach.
- Establish partnerships between NIH and academic institutions, industry, or professional societies to develop programs for enhancing careers of women scientists.

### ***Career Enhancement***

- Expand the ORWH re-entry program. Providing opportunities for women who have already completed their professional training but have taken time off for family reasons will salvage precious talent and encourage women to resume careers in science.

- Develop and fund a national fellowship program to support protected time for academic activities of women junior faculty at those points in their careers when they must teach, conduct research, compete for grants, publish, and practice (if a clinical faculty member) at the same time they are assuming increased family or other responsibilities. Such a program would be particularly valuable for women in science and medicine, but could be made available to men junior faculty if they face similar obstacles.
- Establish collaborative programs with the U.S. Department of Education and Department of Rehabilitative Services.

### **Leadership Training**

- ORWH should support appropriate professional societies and academic institutions in their development of programs to enhance management and leadership skills in women scientists.

### **Professional Visibility of Women**

- Encourage NIH to increase the participation of women and minorities at all levels of NIH (e.g., study sections, advisory groups, conferences).
- Encourage academic institutions to place more women on appointment and promotion committees as well as tenure committees. Ensure that women have visible teaching roles (e.g., lectures, grand rounds presentations).
- Encourage journals to include more women on their editorial boards.

### **Mentoring**

- Define, facilitate, and reward mentoring.
- Require the principal investigator of every funded RO1 grant to make a commitment to mentoring of junior faculty included in the grant.

*“It is our view that it is unconscionable to allow talented women (and men) to wither on the academic vine when a modest amount of support could maintain their academic careers and preserve their capacity to contribute to the research and teaching that are absolutely vital to the future of medicine.”*

Eleanor G. Shore, M.D., M.P.H.  
Harvard Medical School

- Incorporate into the criteria of judging applications for grants and contracts a component of mentoring and outreach.
- Encourage collaboration among NIH, academic institutions, and professional societies to develop programs for training mentors (with NIH support) and to adopt the most successful models of mentoring.
- Encourage NIH to include in its own workshops a session that focuses on development of mentoring skills.

### **Cultural Issues and Social Norms**

- Fund a study of the cultural and sociologic aspects of being a woman in biomedical science careers to see how these beliefs impact on the success of a woman’s career.
- Study the different definitions men and women may use to describe work.
- Encourage NIH and other institutions to recognize legitimacy of different work styles, if the output is identical.

- Develop a survey to document the work styles of men and women and analyze for correlations with advancement in biomedical careers (hours at work vs. productivity).
- Introduce educational programs to educate the scientific community about harassment and discrimination as it affects all women and minority scientists, but particularly trainees.
- Encourage NIH to convene a conference to study how social norms impede the careers of women scientists. This conference would focus on factors that discourage entry or retention of women at all levels in biomedical careers.
- Incorporate enough flexibility in NIH grants to accommodate the transient but compelling needs of women around issues of childbearing.



SELECTED ISSUES IN RESEARCH DESIGN





# HEALTH OF SPECIAL POPULATIONS OF WOMEN

“Special populations” includes, among others, women of different racial, ethnic, and cultural origins; women with disabilities; lesbians; women living in urban and rural settings; and immigrants.

Any one of several data books demonstrates differences in health status and health outcomes among different populations of women. For example, whereas heart disease and cancer are the leading causes of death for all American women, cancer is the leading cause of death for Asian women. Cerebrovascular disease is the third leading cause of death for Caucasian, African-American, Asian, and Hispanic women; for American Indian women, however, the third leading cause is accidents and unintentional injuries. Death rates from

cancer vary among the different populations. For example, the death rate from breast cancer reported for African-American women is 31 per 100,000, whereas American Indian women in New Mexico are reported to have the lowest incidence with a death rate of 9 per 100,000.

Interpretation of the data from the source books and from epidemiologic and other types of research requires an understanding of how special populations are defined. Agreement is needed among researchers on a uniform method, so that sound comparisons can be made. Differences in health status and health outcomes among the different populations are known to correlate with educational, cultural, and behavioral variables;

**Detailed Race and Hispanic Origin of U.S. Women, 1980 and 1990-1993, Numbers in Thousands**

RACE/ORIGIN	1980	1990	1991	1992	1993
<b>All Persons</b>	226,546	248,710	252,177	255,078	257,783
<b>Women</b>					
White	99,835	106,561	107,631	108,584	109,515
Black	14,046	16,063	16,412	16,653	16,925
American Indian and Alaskan Native	718	1,041	1,068	1,081	1,099
Asian and Pacific Islander	1,915	3,805	4,087	4,279	4,444
Hispanic	7,329	10,966	11,460	11,871	12,405

Source: National Center for Health Statistics: Health, United States, 1995.


individual preference; availability of services; differences in treatment of disease; and differences in supplementary services. However, physiologic and pharmacokinetic differences and predisposition to certain disorders may explain some of the differences as well.

### ***Cultural and Behavioral Differences***

The roles of traditional cultural values and sociologic and behavioral factors in health maintenance must be recognized.

### ***Provider Attitude Differences***

One cannot examine differences in health outcomes among special populations of women without addressing physician attitudes and practice. Cultural insensitivity of providers has been implicated as a reason that women of color fail to receive health-promoting care. Attitudinal barriers toward individuals with disabilities remain. Differing practice patterns may relate to patients' race.



*“ . . . my life as a disabled woman will shed some light on this important topic. . . I continue to forge ahead and tackle each day’s challenges and obstacles head on. Yes, there will be detours along the way. That is a given circumstance and also my challenge.”*

Mary Hepburn

# SEX AND GENDER DIFFERENCES IN CLINICAL STUDIES

## *Designing Clinical Studies*

**T**hat women and minorities should be “included” suggests that it is appropriate to design a study with men as the major focus as long as women are included. This concept should be addressed more clearly to promote studies that are initially designed for women or minorities. The point is not just to increase the number of women in clinical trials, or even how to determine if women are eligible for trials; rather, the point is what is being studied, the nature of how the experimental groups are being determined, and how drugs and devices are being tested. There is a lack of studies on healthy people, an area for which research designs must be unique to healthy women.

## *Balancing Research Cost While Asking Clinically Significant Questions*

Adding sex and gender issues to a biomedical study can considerably increase study costs, at a time when pharmaceutical companies and grant agencies are cutting costs. Excluding women from trials would result in inadequate data, which could lead to inappropriate treatment, added risks for women, and increased costs to society. The medical research community is currently examining the role of managed care organizations (MCOs) in women’s health research. Because large numbers of people use the services of MCOs, an extensive pool of data is potentially available to researchers.

## *Recruiting and Retaining Women in Clinical Trials*

Unless the appropriate women, in sufficient numbers, participate in clinical trials, the base of biomedical knowledge about specific conditions and diseases will always have major gaps. Designing research models to include women in clinical studies presents new questions about how to recruit women. The recruitment techniques that are used for men may not be effective for women. Informing the appropriate people is key to recruiting for clinical trials; once informed about a study, whether a woman decides to participate may depend on attitudes toward the medical profession, research team members, and clinical studies in general.

## *Ethical and Liability Considerations*

A major ethical and liability consideration is the inclusion of women of childbearing age in clinical trials. It should be noted that excluding women does not exempt manufacturers from liability risks; the manufacturers are still responsible for knowing how pharmaceutical agents affect women. Although pregnant women have been excluded from clinical trials in the past, they do use drugs during pregnancy.

## *Sex and Gender Differences*

Women and men are obviously different in regard to the presence of hormones. It is vital that investigators determine under what conditions sex

and gender differences manifest and design clinical studies appropriately to examine these situations. Women and men also differ biologically in body composition, size, and metabolism. The design of diagnostic technology and medical devices poses concerns. Research on the aging process should include women; on average, women live 7 years longer than men and constitute the majority of the population over 65.

### ***Longitudinal and Life Phase Research***

Because of the unique role that female hormones play in women's lives, women go through various stages based on hormone support. It is essential to conduct studies that include and describe the different phases of a woman's life, and to classify women by the menopausal stage, instead of by age only. Research designs and study instruments should be developed that describe the menstrual cycle longitudinally and assess hormone differences across menstrual cycles.

## RACIAL, ETHNIC, AND CULTURAL DIVERSITY

To a large extent, a woman's health status may depend on the group or subgroup to which she belongs. Despite statistics that clearly indicate the disparities in health status among various subpopulations of women, clinical research that has included women at all has focused on Caucasian, middle-class, heterosexual, able-bodied women. The percentage of minority groups in the population is increasing and the disparity between the health status of the majority group and that of minority groups is widening.

### *Recommendations*

The working group on racial, ethnic, and cultural diversity recommended the following ways in which NIH can more effectively involve and benefit diverse communities of women in research projects:

- Give peer review groups strict criteria to follow in reviewing grant applications and proposals, specifying requirements as to gender, race, and ethnicity of study participants.
- Diversify peer review groups, ensuring that they include women and minorities.
- Encourage collaborative research with minority institutions, states, and communities.
- Award more grants to minority women investigators.
- Examine the cultural and financial barriers to the participation of low-income populations in research.
- Increase the number of supplemental awards to minority students.
- Meet with journal editors to encourage them to require that clinical studies report data classified by race and ethnicity.
- Encourage researchers to publish their experiences, successful and unsuccessful, in working with minority populations.
- Establish a clearinghouse for the publication of research experiences with minority populations.
- Relax guidelines for inclusion in studies so that potential participants are not excluded from studies because they have some disease or condition that makes them ineligible to participate.
- Encourage a more comprehensive approach to the study of health problems of minority women than the traditional medical model allows.
- Encourage the development of research models that study population assets and resiliencies that prevent disease and promote survival.

The working group also recommended the following ways in which investigators can more effectively involve and benefit diverse communities of women in research projects:

- Report data by gender and racial and ethnic categories.
- Analyze the data for previously published studies by gender, race, and ethnicity, and publish an addendum to the studies.
- Report experiences, successful and unsuccessful, working with participants from diverse racial, ethnic, and cultural groups.
- Design more studies that are homogeneous in terms of ethnic and racial groups in order to find out more about a particular group.
- Collaborate on research projects with researchers who have access to other populations, using the same variables.
- Examine substance abuse and violence in the general population, not only in low-income populations.
- Design more studies to include two groups of women who are now usually excluded from clinical studies: women with disabilities and lesbians.
- Ask women within the community to collaborate on projects by helping to identify the problem to be studied, suggesting appropriate recruitment strategies and methods of data collection, and participating in the analysis and interpretation of study results.
- Include the participants' families in subgroups where family is of great importance.
- Collaborate with community and church groups in planning, conducting, and evaluating research.
- Collaborate with churches on research in minority communities.
- Reach out to those minority women who never enter the health care system or who do so only at a time of crisis.
- Develop culturally appropriate instrumentation and outcome measures.
- Determine what participants themselves want to achieve through participation in the study.
- Examine barriers to health care from the participant's point of view, which may differ radically from the researcher's preconceptions of the barriers.
- Use a qualitative rather than quantitative model of health care so that researchers can understand the health care needs of the community and how well they are meeting those needs.
- Establish community-based centers for research, much like the community centers that have been established for HIV and drug abuse.
- Find ways to give back to the community through providing health care, education and training, and employment.

# MULTIDISCIPLINARY PERSPECTIVES

**R**esearch on women's health provides a unique opportunity to assemble researchers from multiple disciplines. Collaborative research projects on women's health can cut across disciplinary boundaries within the basic and molecular sciences, within medicine, and with other disciplines including, but not limited to, nursing, pharmacy, anthropology, psychology, sociology, health education, social work, economics, and demography. Multidisciplinary research should not replace single-discipline research but should supplement it, thereby enriching understanding and permitting the development of broad-based knowledge.

The working group specifically makes the following recommendations to encourage multidisciplinary research on women's health.

- Encourage multidisciplinary research by appropriately structuring NIH funding.
  - Identify multi-institute issues.
  - Encourage inter- and intra-institute multidisciplinary research.
  - Use RFA and RFP mechanisms to support multidisciplinary research.
  - Establish ORWH as a broker.
- Encourage multidisciplinary research through ORWH funding priorities.
- Establish multidisciplinary coordinating groups.
- Convene multidisciplinary conferences.
- Create core centers to encourage close cooperation, communication, and collaboration among investigators with similar interests.
- Reward multidisciplinary research within academic institutions.
  - Increase the amount of multidisciplinary research conducted on women's health issues by increasing collaboration between NIH and academic institutions.
  - Encourage promotion criteria that stimulate multidisciplinary research.
  - Encourage scientists to learn how to “package” multidisciplinary careers.
  - Encourage NIH funding mechanisms that support multidisciplinary research and training at academic institutions.



- Provide researchers with training in multi-disciplinary research.
  - Establish multidisciplinary training programs.
  - Publicize effective individual and institutional role models.
  - Publish and publicize the process of putting together multidisciplinary teams.
  - Recognize mentors.
  - Encourage and provide funding mechanisms for continuing education in fields other than one's area of primary expertise.
  - Encourage NIH institutes to fund multi-disciplinary training.
  - Develop inter-institute review processes and funding for training awards.
- Multidisciplinary research proposals are often reviewed by single-discipline individuals.
  - Expand the use of ad hoc reviewers on standing committees.
  - Use ad hoc review committees.
  - Solicit reviewers with appropriate multi-disciplinary expertise.
  - Inform applicants how to use existing review structures.
  - Identify and publicize successful models.



SELECTED TOPICS IN HEALTH IMPACT AND HEALTH OUTCOMES



## SELECTED TOPICS IN HEALTH IMPACT AND HEALTH OUTCOMES

**T**hese selected topics in health impact and health outcomes were presented at the Philadelphia regional meeting and the Bethesda national meeting of the Beyond Hunt Valley activities to update the agenda for women's health research for the 21st century. Because of the extent of work required, it may be necessary to pool resources of both public and private sectors. Within the public sector arena, broad interagency collaboration (NIH, FDA, AHCPR, NSF, and CDC) is crucial to develop and implement methodical and uniform processes and systems to enhance the value of clinical data, improve the consistency and interpretation of collected data, and expedite adoption of important research recommendations. Industry must collaborate with academia in this research because these groups sponsor and/or conduct the majority of pharmacological research in this country.

### GENDER CONSIDERATIONS IN THERAPEUTIC ADVANCES

A vaccine offering protection against serious illness, an effective drug treatment for HIV/AIDS patients, a diagnostic test capable of detecting a treatable disease at its earliest stage, and artificial joint replacement devices are examples of therapeutic and diagnostic advances that offer immeasurable benefits for the health and quality of life of all Americans.

But as these "miracles of modern science" are developed and used, important gender-related questions must be asked. Are the side effects of a vaccine the same for men and women? Do men and women react in the same way to new HIV/AIDS drugs? Are the therapeutic products that have become standard clinical care appropriate and advisable for women? Should artificial joint devices be designed differently for male and female patients? The answers to these questions are the essence of this discussion because, in fact, many therapeutic advances are put into use and continue to be used without consideration of gender differences in response to these products.

#### *Concept to Marketplace*

The following recommendations encourage a more deliberate assessment of new therapeutic products as they affect women and call for ongoing assessments that consider women's health perspectives:

- Keep consumers safe. Make gender-specific analysis of safety and efficacy data and identification of outliers a critical element prior to any transfer of new therapeutic products to the marketplace.
- Identify and evaluate therapeutic products that warrant further research based upon the ORWH agenda. Assess, in a systematic way, which therapeutic products are obsolete, not effective, used inappropriately, or warrant dosage reductions in women or in other subpopulations at risk.

## CLINICAL TRIALS

As for all medical technologies, clinical trials are a key stage in the introduction of new therapeutic products. Such trials raise many crucial overarching questions. For example, how can research designs be modified to encourage greater involvement by women (i.e., clinical trial participation)? How can we increase the statistical power to detect meaningful gender differences? Coming up with increased statistical power to analyze the data by gender will involve more than just including women. Current clinical trials are not sufficiently large or of sufficient duration, in general, to detect rare or delayed adverse events, regardless of gender. Which populations of women are not now participating in trials? Which populations of women cannot be analyzed in trials because of a lack of statistical power to separate their safety profile from the average responder? Can new kinds of trials be designed? What ethical and social issues are involved?

*Recommendations to improve the process include:*

- Re-assess the adequacy of current dosage recommendations of approved drug products to optimize dosages for women.
- Improve the quality of study design, data collection, analysis, and re-analysis of the data.
- Establish databases that include analysis of data by gender, hormonal status, age and race, and clinical outcomes.

### ***Identification and Quantification of Risks Associated with Use of Pharmacological Agents***

Current methods to detect adverse events include reviews of case series, qualitative summaries of safety data from clinical trials, voluntary reports, and epidemiologic studies of suspected agents. Scientific research is needed for developing improved methods to monitor, identify, and quantify hazards associated with use of pharmacologic agents. More sensitive methods are needed to identify high-risk subgroups (e.g., variations in risk

*“Outcome measures that have meaning for women with a chronic disease (such as arthritis) must include a measurement of functional status and an assessment of their quality of life.”*

Brenda Crabbs  
Arthritis Foundation

by gender, age, race, concomitant medical conditions) as well as drug-drug and drug-nutrient interactions.

*Limitations of Clinical Trials.* Clinical trials may have sufficient statistical power to detect differences in primary efficacy endpoints but not enough power to detect rare or delayed adverse events. The safe use of a drug or biologic agent may be determined by complex interdependent factors including pharmacokinetics; pharmacodynamics; drug dose; adaptation; demographic characteristics such as gender, weight, age, and race; immune response; and concomitant conditions or medications.

*Lack of Standardized Data Structures.* There is a pressing need to standardize databases to enable analysis, comparison, and merging of data. Prescribers rely on clinical trials as the major source of information on which to base medical decisions, yet tremendous amounts of information in clinical trials remain untapped, including information critical for women's health.

*Voluntary Reports of Adverse Events.* A recent meta-analysis to estimate the incidence of serious adverse drug reactions (requiring hospitalization, permanently disabling or fatal) in hospitalized patients suggests that the problem of adverse drug reactions (ADRs) may be more urgent than previously thought.

Researchers examined four electronic databases and found the overall incidence of ADRs to be extremely high, with serious reactions affecting nearly 7 percent of hospitalized patients. Additionally, on the basis of several studies reporting an increased incidence of ADRs among females, these researchers suggested that women could be at greater risk than men.

*Recommendations for clinical trials include:*

- Develop improved and more sensitive systems for collecting and analyzing adverse events by gender, age, hormonal status, and race.
- Organize a multidisciplinary “think tank” that includes the NSF (an agency experienced in analyzing large databases in real time, such as the visualization of the Mars landing).
- Identify all elements essential for a complete comprehensive data structure. Develop one common language, such as a medical informatics system, to be used in all forms of clinical recordkeeping and reporting from clinical trials, hospitals, HMOs, Medicaid and Medicare databases, case-control studies, large longitudinal databases, and systems for collecting adverse events. This effort should include standardized nomenclature for therapeutic agents. As part of developing such a system, various cost incentives for implementation need to be considered. In order to collect and study clinical outcomes in subpopulations, the common language would have to be sensitive to gender, age, weight, menopausal status, use of hormones, and race and ethnicity.

*Research goals:*

- Develop a common standardized database structure for clinical trial data from research to clinical practice and implement it throughout the health care system to improve the quality of data and to simplify timely data retrieval and signal generation analysis.

- Develop strategies to improve the quality of reporting adverse events.
- Develop population-based record linkage systems that can be used to assess the incidences of adverse drug reactions, compare and evaluate risk factors, and assess the changing prescribing patterns among health care providers.
- Develop systems for analyzing large amounts of data to detect differences by gender, age, and race in rates of serious adverse events caused by therapeutic agents used either alone or in combination.
- Develop tools that will systematically screen and analyze available databases during the postmarketing period (after a drug is approved for use) for identification of “higher than expected” risks associated with the drug combinations.
- Develop data mining techniques that are capable of detecting patterns of associations in large databases to systematically screen these databases for the presence of gender-specific adverse events and for drug interactions.
- Consider a new system and entity for postmarketing surveillance that will (a) foster cooperation among existing postmarketing surveillance programs, (b) develop new methods for carrying out surveillance, and (c) train scientists in the disciplines needed for doing safety analysis of clinical trial data for performing postmarketing surveillance.
- Cause-of-death rankings accounting for ADRs in hospital patients should be assessed with a gender component.
- Implement prospective methods for collecting data on drug use in pregnancy.
- Conduct research to assess potential adverse effects on mother and fetus of dietary supplements taken most frequently by pregnant women.

## COMMUNICATION AND OUTREACH

Communication of therapeutic and diagnostic advances and outreach to health care providers, health professionals, and the public remains an enormous challenge. The best ways to disseminate objective information on therapeutic advances after they reach the marketplace have not yet been found. Practitioners are hard-pressed to keep informed and current on the range and volume of developments in therapeutic advances as well as changes in the standards of care. In addition, translation of technical information into lay terms must accommodate the needs of different audiences, with the role of the media being a significant factor. The interests of those outside the scientific and business worlds need to be taken into consideration and served. Meaningful forums must be developed for the exchange of information between and among scientists, practitioners, and consumers.

*Recommendations to improve these channels of communication include:*

- Establish Internet outreach to consumers and health care professionals on up-to-date safety information, including labeling changes. Link commercial company advertisements to this web site.
- Network with private and academic institutions such as poison control centers and schools of pharmacy and medicine to gather adverse event data efficiently.
- Continue to sponsor dialogs among clinicians, scientists, advocacy groups, managed care providers, insurers, and other parties to improve overall communication on such topics as concepts of safety and efficacy, concepts of risk and benefit, and consequences for both the individual and society.

- Continue to seek input from diverse populations of women regarding their most pressing health needs and concerns to ensure their inclusion in the research agenda.
- Work with health educators to integrate gender-based science into the curriculum.
- Provide patent extension when a firm improves safety profile of the drug.
- Determine the best way to inform health care providers and consumers about risks and side effects.

### *Education of Health Care Providers*

There is a lag between basic scientific research and its application in the health care setting. Training and education programs are needed to ensure that pertinent research results are properly disseminated and integrated into health care practice. Additional education regarding the proper prescribing of medications is needed for nurse practitioners, physician assistants, and pharmacists.

*Recommendation:*

- Develop improved training and continuing education programs for health care providers.

*Research goals:*

- For optimal health care of the patient, it is essential that the following organizations work together to teach health care students optimal safe and effective use of pharmacologic agents: American Association of Colleges of Pharmacy, American Association of Medical Colleges, National League for Nursing, and American Association of Dentistry Colleges.

- Increase continuing education activities and requirements for practicing health care providers to update their knowledge about pharmacologic and biologic agents.

## P A T I E N T C A R E

The cost effectiveness of treatment is an essential part of consideration in clinical care, particularly in the managed care environment. But the question remains: When are technologies advanced enough to gain status for third-party reimbursement? Clinical practice guidelines, which recommend appropriate practices based on existing scientific peer reviewed literature and clinical experience, should incorporate gender as a variable. There is need to define quality and outcome measures that are broader and more sensitive to women's needs and that are better measures of quality of care.

### *Recommendations:*

- Involve a broad constituency in developing professional practice guidelines that have gender-specific components.
- Identify quality and outcome measures that are broader and more sensitive to women's diverse needs.
- Propose improvements to existing technologies and standards of care based on new information on gender differences.

### ***Gender Effects on Drug Compliance and Drug Access***

Research is needed into factors that may be barriers to appropriate care among women.

### *Recommendation:*

- Clarify effect of gender on compliance and access.

### *Research goals:*

- Establish whether gender is a significant factor in compliance and, if not, identify other factors useful as predictors of compliance for women.
- Determine if gender is a factor in successful access to therapeutic agents and, if so, ascertain causes of this phenomenon.
- Investigate factors that may present barriers to appropriate care among women, including physicians prescribing behaviors, ability to pay for medications, educational level, health literacy, age, concomitant medications and conditions, functional limitations, and social support.







CROSSCUTTING ISSUES AND RECOMMENDATIONS



## CROSSCUTTING ISSUES AND RECOMMENDATIONS

The differences to be discovered between men and women in health and disease are not deficits, but provide avenues for new analysis and treatment interventions tailored to the group, the individual, and the circumstances.

### RESEARCH AGENDA RECOMMENDATIONS

#### *Clinical Trials*

Enroll more women in efficacy and safety trials, including pregnant women. This recommendation contains two implications: (1) conduct more clinical trials on women's health issues and (2) enroll more women in clinical trials in which men have previously prevailed in numbers.

- *Subject participation and compliance.* Conduct research on how to increase recruitment and retention in clinical trials and how to enhance compliance with treatment regimens.
- *Clinical trials of treatment protocols.* Undertake well-controlled clinical trials with gender-sensitive models (single vs. mixed gender, mixed gender, gender sensitivity absence or presence).
- *Inclusion of gender as a research variable.* Develop an integrative strategy to include women in all phases of research, including both biological and biomedical studies.

- *Effect of combination therapies on prevention and treatment.* Conduct human research on incremental effectiveness and safety of combination therapies. These combinations include simultaneous administration of calcium, vitamin D, male and female hormones, and bisphosphonates or other pharmaceutical agents.
- *Treatment models.* Expand research examining the development and effectiveness of treatment models, specific to the unique needs of women, for treatment of psychiatric disorders such as depression, anxiety, PTSD, and eating disorders. These models must also be culturally relevant and address developmental life span issues.
- *Stratification of data.* Stratify future and existing data from basic and clinical studies for sex and age of subjects.

#### *Specific Populations of Women with Particular Health Care Needs or Concerns*

Identify the potential differences in each specific population and how these affect health needs, health outcomes, and health behaviors across the life span. Specific populations include medically underserved women (such as homeless women and women living in poverty and in rural areas), women of color, women with disabilities, adolescents, postmenopausal and elderly women, lesbians, women with somatic and/or developmental disorders, and women in jails. These

women have special treatment needs and are at much greater risk than women with greater economic resources, and they may have different etiologies, needs, and outcomes compared to middle-class women from easy-to-reach populations.

- *Diversity.* Address diversity in all research studies. Many measurement tools were normed on Caucasian male reference groups. Re-examine these tools and validate them for use with females and diverse ethnic groups. Similarly, there is need for female-centered models of treatment. In developing these models, researchers need to be cognizant of the variables important in women's mental health, including race, religion, socioeconomic status, and sexual orientation.

### **Multidisciplinary Research**

Collaborate with colleagues from other disciplines to expand and strengthen research; include behavioral and social science components in research.

- *Alcohol and other drugs and biological effects.* Develop collaborative research programs to examine the relation of alcohol and drug use to biological effects; gender differences; psychosocial, behavioral, cognitive, psychiatric, general health, family, and legal consequences; specific sexually transmitted diseases; and reproductive effects.
- *Resource sharing.* Increase sharing of resources among researchers — including sharing of clinical samples, DNA banks, serum banks, animals, and reagents.
- *Collaboration.* Foster interagency and public-private collaboration in order to carry out the full range of research recommended for studying health issues in women, including pregnant women.

### **Information Systems**

Design information systems that allow easier access to archival material on clinical and genetic studies.

## **R E C O M M E N D A T I O N S T H A T S U P P O R T T H E R E S E A R C H A G E N D A**

- *Women's life cycle.* Ensure that research on women's health takes into account the full biological life cycle of the woman and the concomitant physical, mental, and emotional changes that occur. Easily identifiable stages in a woman's life include: prenatal, infancy, childhood, adolescence, childbearing potential, pregnancy, lactation, perimenopause, postmenopause, elderly, and frail elderly.
- *Training and career development.* Develop new program announcements to encourage career opportunities for women in research. Continue to provide supplemental research training and funding opportunities to women who must often interrupt their careers because of family care responsibilities. Establish mentoring programs for girls to encourage them to pursue science courses and careers, including programs linking high schools to universities. Develop research and clinical research training programs targeted for women.
- *Education.* Educate the public and health professionals to optimize the choices of management in reproductive health and diseases. Health care providers need to be fully, yet critically, informed about advances in their fields including risk factors, diagnostic tests, treatment options, and followup strategies, to best advise consumers about their care. Consumers need the information to understand the pros and cons of options available to them, for example in contraception, management of pregnancy and delivery, and menopause, as well as in diagnosis and treatment of infertility and other reproductive diseases and disorders. Develop, evaluate, and carry out educational and intervention programs that are sensitive to an individual's cultural and socioeconomic background.

- *Communication.* Foster improved communication between the lay public and the scientific community, making information readily accessible to researchers, health care providers, and consumers.
  - *Among professionals:* Facilitate communication among investigators, clinicians, patients, and the public. Clinicians frequently define observations needing laboratory explanations, while promising laboratory developments need timely clinical evaluation.
  - *With patients and public:* Teach health care providers skills in communicating risks and in encouraging health-promoting behavior to their patients and the public.
- *Evidence-based medicine.* Facilitate evidence-based medicine; disseminate and integrate research results into practice patterns.
- *Prevention.* Focus research on a continuum of prevention methods, ensuring that prevention messages are culturally appropriate.



# ORDER FORM

**A**genda for Research on Women's Health for the 21st Century is a 6-volume report from four scientific meetings and public hearings to establish an agenda for women's health research for the 21st century. Volume 1 contains the executive summary and volume 2 is a composite report containing recommendations from all four meetings. Volume 3 contains public testimony from the Bethesda, Maryland meeting, and volumes 4, 5, and 6 are reports and public testimony from the three regional meetings and public hearings. To order a single, free copy of each volume, please indicate which publication(s) you would like to receive.

- Volume 1 — *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, Executive Summary; NIH Publication No. 99-4385.
- Volume 2 — *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; NIH Publication No. 99-4386.
- Volume 3 — *Agenda for Research on Women's Health for the 21st Century*, Public Testimony; Bethesda, Maryland: November 1997; NIH Publication No. 99-4387.
- Volume 4 — *Agenda for Research on Women's Health for the 21st Century*, Influences of Sex and Gender on Health; Philadelphia Scientific Meeting and Public Hearing, September 1996; NIH Publication No. 99-4388.
- Volume 5 — *Agenda for Research on Women's Health for the 21st Century*, Sex and Gender Perspectives for Women's Health Research; New Orleans Scientific Meeting and Public Hearing, June 1997; NIH Publication No. 99-4389.
- Volume 6 — *Agenda for Research on Women's Health for the 21st Century*, Differences Among Populations of Women; Santa Fe, New Mexico, Scientific Meeting and Public Hearing, July 1997; NIH Publication No. 99-4390.

Name \_\_\_\_\_

Title \_\_\_\_\_

Affiliation \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_

Telephone Number \_\_\_\_\_ Email \_\_\_\_\_

- Please check here if you would like to be added to the Office of Research on Women's Health mailing list.

Please mail or fax this completed form to: Office of Research on Women's Health, Office of the Director, National Institutes of Health, 1 Center Drive, Room 201, MSC 0161, Bethesda, Maryland 20892-0161; fax: 301-402-1798.







NIH Publication No. 99-4385