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

NATIONAL INSTITUTES
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2 VOLUME

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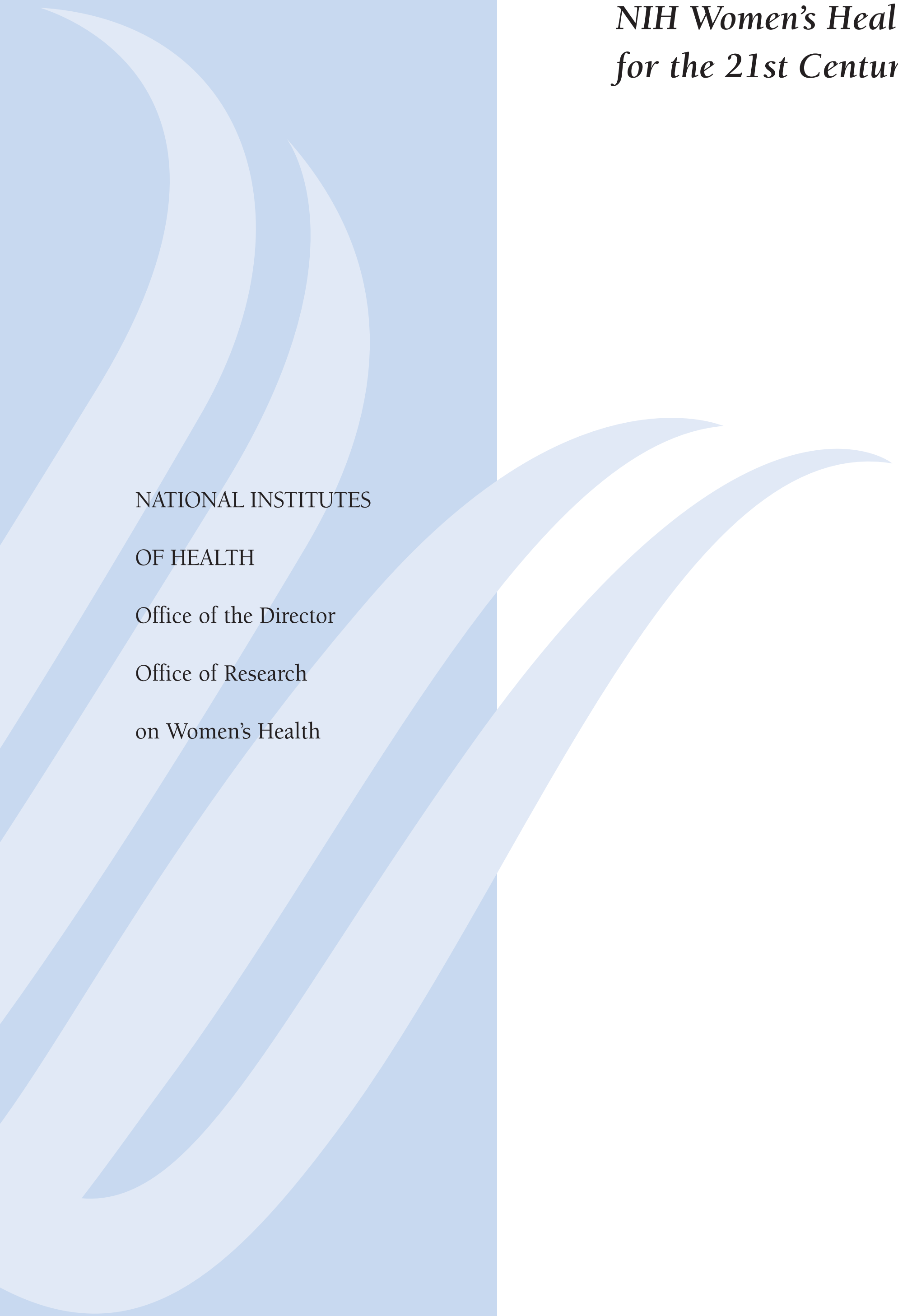

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on Women's Health

2 VOLUME

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, DC

SEP 25 1996

MESSAGE TO THE PARTICIPANTS AT THE MEETING BEYOND HUNT VALLEY: RESEARCH ON WOMEN'S HEALTH FOR THE 21ST CENTURY

I wanted to be with you today for this first regional meeting to update the current biomedical and behavioral research agenda on women's health. You have my best wishes for a productive and fruitful exchange of ideas.

The agencies of the Department of Health and Human Services share the common goal of improving the health of all citizens. And research on women's health is an important priority for this Department and for the agencies of the Public Health Service, including the National Institutes of Health (NIH).

The NIH, through its Office of Research on Women's Health (ORWH), under the very capable leadership of Dr. Vivian Pinn, spearheads the effort to accomplish this goal through research. By continually identifying emerging needs for scientific knowledge, the ORWH and the NIH are insuring that the agenda on women's health research remains viable and relevant to the health needs of women in the 21st century.

The multidisciplinary approaches and perspectives represented at this meeting will greatly enhance the ability of the Department to broaden its research agenda. I look forward to learning about your deliberations.

My best wishes.

Donna E Shalala
Donna E. Shalala

FOREWORD

On 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 over 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 role that culture, ethnicity, race, socioeconomic background, geographic location, and other social and economic factors have as important contributors 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 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 *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 the 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 under its permanent director, Dr. Vivian Pinn, whose appointment was announced at the September 1991 meeting.

Over the past 7 years, the Office of Research on Women's Health at the National Institutes of Health 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, it is clear that the guiding principle regarding women's health research at the National Institutes of Health 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)

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MOTION PASSED BY THE ADVISORY COMMITTEE ON RESEARCH ON WOMEN'S HEALTH

National Institutes of Health
November 16, 1998

MOTION

Taking seriously the strategic planning charge to the Office of Research on Women's Health (ORWH) in the National Institutes of Health Revitalization Act, this report entitled, Agenda for Research on Women's Health for the 21st Century summarizes progress to date and research challenges for the next millennium. The Advisory Committee to the Office of Research on Women's Health strongly recommends acceptance of this report.

The Advisory Committee commends: Dr. Vivian Pinn for the all inclusive and collegial approach to data gathering that shaped this project; Ms. Joyce Rudick for her people-oriented administrative abilities; Dr. Donna Dean and Dr. Marianne Legato, Task Force Cochairs, who demonstrated in their vision and organization just how creative and comprehensive collaboration between the National Institutes of Health and the academic community can be; the Task Force on the NIH Women's Health Research Agenda for the 21st Century for recognizing that a national agenda must be mindful of regional concerns; and the more than 1,500 women and men who participated in the public hearings and scientific workshops for ensuring that the community at large was front and center in this process.

The Advisory Committee also recommends broad dissemination of this report, implementation of the regent with the collaboration of the NIH Institutes and Centers, and encourages Dr. Harold Varmus to support the Office of Research on Women's Health in this endeavor, particularly in the work of moving the research agenda forward within the National Institutes of Health. The Advisory Committee recognizes that women's health research has substantially gone "beyond Hunt Valley." Not only have many of the special concerns of girls and women been studied since the first research agenda was constituted through the Office of Research on Women's Health, but girls and women are no longer being automatically treated as a monolithic group now that the research focus is increasingly mindful of the interface between the behavioral and the biomedical sciences. This growing awareness of the complexities of human experience bodes well for better understanding of the human experience in the 21st century.

We move that the Advisory Committee accept this report, commend those people involved, recommend broad dissemination of the report and that this process be repeated five years from now in 2004.

The motion was passed unanimously.

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PREFACE

During 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 the 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 policy makers, 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 in order 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 the NIH's agenda for research on women's health. In this process, NIH has benefitted 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. She is a noted author on cardiovascular diseases of women and has recently established the Partnership for Women's Health at Columbia University.

In addition to those who served on the Task Force, the ACRWH, and the 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 the 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 benefitted from the support and interest of many members of the United States 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.

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

ACKNOWLEDGMENTS

The Office of Research on Women's Health wishes to acknowledge the many 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. ORWH wishes to thank:

- *Ruth L. Kirschstein, M.D., Deputy Director, National Institutes of Health*
- *Task Force on the NIH Women's Health Research Agenda for the 21st Century*
- *Advisory Committee on Research on Women's Health*
- *Coordinating Committee on Research on Women's Health*
- *Working Group Cochairs of the meetings of Beyond Hunt Valley: Research on Women's Health for the 21st Century*

    Philadelphia, Pennsylvania
    New Orleans, Louisiana
    Santa Fe, New Mexico
    Bethesda, Maryland

- *More than 1,500 men and women who participated in the Public Hearings and Scientific Workshops.*

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BEYOND HUNT VALLEY:
RESEARCH ON WOMEN'S HEALTH FOR THE 21ST CENTURY

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BEYOND HUNT VALLEY:
RESEARCH ON WOMEN'S HEALTH FOR THE 21ST CENTURY

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BEYOND HUNT VALLEY:
RESEARCH ON WOMEN'S HEALTH FOR THE 21ST CENTURY

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INTRODUCTION

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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 the 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 which 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."[1]

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*.[2] In a later 1987 version of the NIH Guide, a policy encouraging the inclusion of minorities in clinical studies was first published.[3]

In 1990, the Congressional Caucus for Women's Issues requested that the United States 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 lacking, the implementation was slow and not well communicated, gender analysis was not implemented, and the impact of policy could not be determined.[4]

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 Institutes and Centers (ICs). ORWH was announced at an NIH roundtable meeting with representatives of the Congressional Caucus for 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:

. . .The 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 IC's 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, one year later, in September 1991, ORWH held public hearings and a scientific workshop at Hunt Valley, Maryland, to set the NIH 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*,[6] 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 cross-cutting areas of science. These included:

Life Span

Birth to Young Adulthood
Young Adulthood to Perimenopausal Years
Perimenopausal to Mature Years
Mature Years

Cross-cutting 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 NIH Revitalization Act.[6] Women's health research at NIH is a partnership between ORWH and the NIH institutes and centers. Over 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, 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,[7] 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.*[8] From nearly 70 testimonies, nine 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. These are:

- 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
- 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 Coordinating Committee for Research on Women's Health, 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,*[9] 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 included: 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 the 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, 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 pubic health policymakers 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 under represented 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 the NIH 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.
- 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 three regional meetings
- Special populations of women
- Factors that affect different populations of women
- Sex and gender issues
- Normal processes, developmental biology, and aging
- 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.

Over 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 your assistance, as we enter the 21st century, the Office of Research on Women's Health 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.

REFERENCES

1 U.S. Public Health Service. Women's Health: Report of the Public Health Service Task Force on Women's Health Issues. Vol. 1, no. 1 (January-February 1985) 1:76.

2 National Institutes of Health. Division of Research Grants. *NIH Guide for Grants and Contracts.* January 23, 1987.

3 National Institutes of Health. Division of Research Grants. *NIH Guide to Grants and Contracts.* September 25, 1987.

4 Nadel, MV. National Institutes of Health: Problems in Implementing Policy on Women in Study Populations. Washington, D.C.: U.S. General Accounting Office, June 1990.

5 National Institutes of Health. Report of the National Institutes of Health: Opportunities for Research on Women's Health. NIH Pub. No. 92-3457. Bethesda, Md.: September 1992.

6 National Institutes of Health Revitalization Act of 1993 (Public Law 103-43), 107, Stat. 22 (codified at 42 U.S.C. 289.a-1), June 10, 1993, at 486(d) (4) (D).

7 U.S. Department of Health and Human Services. National Institutes of Health. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research; Notice. *Federal Register*, 59:14508-15413 (March 28, 1994).

8 National Institutes of Health. Women in Biomedical Careers: Dynamics of Change. NIH Pub. No. 95-3565A. Bethesda, Md.: 1994.

9 Sumaya CV, Pinn VW, Blumenthal SJ. Women's Health in the Medical School Curriculum: Report of a Survey and Recommendations. Health Resources and Services Administration, National Institutes of Heath, Department of Health and Human Services, 1996.

OVERVIEW AND PERSPECTIVES OF THE TASK FORCE COCHAIRS

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The 7 years since the Office of Research on 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 record keeping, 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 for 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, the 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 the 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, the 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 that we 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 investigation, 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 $625,000,000 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. Over 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 the entry into and retention of women 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.[1] Because of the lack of a tracking system to monitor inclusion in 1990, that Committee had difficulty, in fact, 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/gender, did not perform any sex/gender analyses of study results, and did not recruit adequate numbers of women to support conclusions regarding the impact of sex/gender on the observations made.

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

- 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 which have been tested primarily in men. For example, one study reports that the treatment of mild to moderate hypertension in white women increased the all-cause death rate by 26 percent, while lowering all-cause mortality in men by 15 percent.[2] Another study (SWORD trial on sotalol in the treatment of postmyocardial infarction arrhythmias) was discontinued because of the increase in mortality of the women in the trial.[3]

- 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)[4] 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 following chapter on the use of sex and gender terminology.

BASIS OF REPORT RECOMMENDATIONS

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/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 extensively explored by cardiovascular experts over 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 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 HIV 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 (4) 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, 50 to 79 years of age, in the United States, has three components: (1) a randomized controlled clinical trial (67,000 participants) which 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. The 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 underway, including special programs promoting cardiovascular health for Latinos, and in treatment of hypertension and dyslipidemia for blacks. Inducements to increase the interest of women and under represented minorities in research careers are under way as part of NIH's increasing efforts in outreach 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 the ORWH regional scientific workshops in Santa Fe, which addressed health issues as they relate to women at all stages of life — prenatally, during 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/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 over the next millennium in women's health research.

REFERENCES

1 Mastroianni AC, Faden R, Federman D, editors. Women and health research. Ethical and legal issues of including women in clinical studies. Volume I. Division of Health Sciences Policy, Institute of Medicine. Washington, D.C.: National Academy Press; 1994.

2 Anastos K, Charney P, Charon RA et al. Hypertension in women: what is really known? The Women's Caucus, Working Group on Women's Health of the Society of General Internal Medicine. *Ann Intern Med* 1991; 115:287.

3 Lehman MH, Hardy S, Archibald D, Quart B, MacNeil DJ. Sex difference in risk of torsade de pointes with d,l-sotalol. *Circulation* 1996;94:1535-41.

4 Office for Protection from Research Risks. Protection of Human Subjects, 45 CFR 46, Subpart B, Additional Protections Pertaining to Research Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization. March 8, 1983.

THE USE OF "SEX" AND "GENDER" TO DEFINE AND CHARACTERIZE MEANINGFUL DIFFERENCES BETWEEN MEN AND WOMEN

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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/GENDER DISTINCTION

To understand the tenets of the sex/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."[1-9]

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.[10] 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. Over the past 25 years, use of the sex/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.[11,12] 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/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.[13] 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" that "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."[15] 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."[16] 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.[17] 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/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/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.[18-20] 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.[19,21-23] 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 which 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.[24-26] 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.[18,27]

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 (and male) 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 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 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 your 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/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.[28–30] 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 towards sex difference in clinical trials demonstrates the complexities and problems attending to sex difference. The human subjects guidelines have changed to require the inclusion of women in clinical trials, yet the question remains of how similarities and differences between men and women will be explored, studied, and compared.[28–32]

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.[33] It is here that the sex/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.[34,35] 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.[36]

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.[10] 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.[10] 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.[10,37,38] 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 which 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.

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REFERENCES

1 Barrett M. *Women's Oppression Today: Problems in Marxist Feminist Analysis*. London: NLB, 1980.

2 Bem SL. The measurement of psychological androgyny. *J Consult Clin Psychol* 1974;42(2):155-62.

3 Chodorow N. *The Reproduction of Mothering: Psychoanalysis and the Sociology of Gender*. Berkeley: University of California Press, 1978.

4 Dinnerstein D. *The Mermaid and the Minotaur: Sexual Arrangements and Human Malaise*. New York: Harper & Row, 1976.

5 Martin MK, Voorhie B. *Female of the Species*. New York: Columbia University Press, 1975.

6 Oakley A. *Sex, Gender and Society*. London: Maurice Temple Smith, Ltd., 1972.

7 Rapp R, ed. Toward an Anthropology of Women. New York: *Monthly Review*, 1975.

8 Rosaldo M, Lamphere L, eds. *Women, Culture, and Society.* Stanford, CA: Stanford University Press, 1974.

9 Unger RK. Toward a redefinition of sex and gender. *Am Psychol* 1979;34(11):1085-94.

10 Krieger N, Fee E. Man-made medicine and women's health: The biopolitics of sex/gender and race/ethnicity. *Int J Health Serv* 1994;24(6):82-122

11 Lewin RRJ. Sex: An imperfect marker of gender. *Schizophr Bull* 1994;20(4):777-8.

12 Pearson GA. Of sex and gender. *Science* 1996; 274(5286):328-9.

13 Heston TF, Lewis LM. Gender bias in the evaluation and management of acute nontraumatic chest pain. The St. Louis Emergency Physicians' Association Research Group. *Fam Pract Res J* 1992;12:383-9.

14 Fletcher DE. The eternal battle of sex vs. gender [letter]. *JAMA* 1991; 266(20):2833.

15 Iverson C. The eternal battle of sex vs. gender [reply]. *JAMA* 1991; 266(20):2833.

16 Vickers S. Use of gender and oxygenation as synonyms for sex and oxidation [letter]. *Drug Metab Dispos* 1995;23:1007.

17 Miles S, Parker K. Men, women, and health insurance. *N Engl J Med* 1997; 336:218-21.

18 Clarke AE. *Disciplining Reproduction: Modernity, American Life Sciences, and the Problems of Sex.* Berkeley: University of California, 1998.

19 Dreger AD. *Hermaphrodites and the Medical Invention of Sex.* Cambridge: Harvard University Press, 1998.

20 Fausto-Sterling A. *Myths of Gender: Biological Theories about Women and Men*. New York: Basic Books, 1985.

21 Chase C. Hermaphrodites with attitude—Mapping the emergence of intersex political activism. *J Lesbian Gay Studies* 1998;4:189-211.

22 Kessler SJ. The medical construction of gender — Case management of intersexed infants. *Signs* 1990;16:3-26.

23 Kessler SJ. *Lessons From the Intersexed*. New Brunswick: Rutgers University Press, 1998

24 Jordanova L. *Sexual Visions: Images of Gender in Science and Medicine between the Eighteenth and Twentieth Centuries.* Madison: University of Wisconsin Press, 1989.

25 Jordanova L. Gender and the historiography of science. *Br J Hist Science* 1993;26:469-83.

26 Russett CE. *Sexual Science: The Victorian Construction of Womanhood*. Cambridge: Harvard University Press, 1989.

27 Oudshoorn N. *Beyond the Natural Body: An Archeology of Sex Hormones*. New York: Routledge, 1994.

28 Johnson T, Fee E. Women's participation in clinical research: From protectionism to access. In: Mastroianni AC, Faden R, Federman D, eds., *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* (Vol. 2, Workshop and Commissioned Papers, pp. 1-10). Washington D.C.: National Academy Press, 1994.

29 Mastroianni AC, Faden R, Federman D. Executive summary. In: Mastroianni AC, Faden R, Federman D, eds., *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* (Vol. 1, pp. 1-26). Washington D.C.: National Academy Press, 1994.

30 Sherwin S. Women in clinical studies: A feminist view. In: Mastroianni AC, Faden R, Federman D, eds., *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* (Vol. 2, Workshop and Commissioned Papers, pp. 11-17). Washington D.C.: National Academy Press, 1994.

31 Gamble VN, Blustein B. Racial differences in medical care: Implications for research on women., In: Mastroianni AC, Faden R, Federman D, eds., *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* (Vol. 2, Workshop and Commissioned Papers, pp. 174-91). Washington D.C.: National Academy Press, 1994.

32 Rosser S. Gender bias in clinical research: The difference it makes. In: Dan G, ed., *Reframing Women's Health: Multidisciplinary Research and Practice*. Thousand Oaks: Sage, 1994.

33 Weismann MM, Olfson M. Depression in women: implications for health care research. *Science* 1995; 269(5225):799-801.

34 Nikelly AG. Drug advertisements and the medicalization of unipolar depression in women. *Health Care Women Int* 1995;16(3):229-42.

35 Williams JB, Spitzer RL, Linzer M, Kroenke K, Hahn SR, deGruy FV, Lazev A. Gender differences in depression in primary care. *Am J Obstet Gynecol* 1995;173(2):654-9.

36 Pfeffer N. The hidden pathology of the male reproductive system. In: Homans H, ed., *The Sexual Politics of Reproduction*. Aldershot UK: Gower, 1985, pp. 30-44.

37 Williams DR. The concept of race in health services research: 1966 to 1990. *Health Serv Res* 1992;29(3).

38 Williams DR, Lavizzo-Mourey R, Warren RC. The concept of race and health status in America. *Public Health Rep* 1994;109(1):26-41.

SCIENTIFIC CHAPTERS

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

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BACKGROUND

The association between mental health and alcohol and other drug use was addressed during public hearings and workshop proceedings at the regional workshop, “Beyond Hunt Valley: Research on Women’s Health for the 21st Century,” held in Philadelphia, Pennsylvania. The report that resulted from these activities contains a summary of recent findings related to body and mind including addictive disorders and a series of research recommendations.

For the “Beyond Hunt Valley” national workshop held in Bethesda, Maryland, ORWH recommended development of independent reports on mental health and alcohol, tobacco, and other drug use to ensure a wider range of discussion. This resulted in the formation of two working groups: (a) Mental Disorders and (b) Alcohol, Tobacco, and Other Drug Use, Disorders, and Consequences.

The study of women’s health has been formalized through the efforts of ORWH. Inclusion of women and minorities in study populations has increased research attention on issues related to alcohol and drug use among these groups. Clinical studies now use research designs that include the development of more sensitive data collection instruments. Furthermore, women are recognized as a heterogeneous group. Research has expanded to examine life span and lifestyle issues. Studies have been encouraged that focus on alcohol and drug use among postmenopausal women, lesbians, pregnant women, women with disabilities, women of lower socioeconomic status, and other underrepresented and understudied populations. A wider range of variables such as menstrual and endocrine status has been included in research designs.

To ensure that effective research programs address alcohol and other drug use among women, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and National Institute on Drug Abuse (NIDA) have expanded their research and training programs during the past 6 years. From basic to applied science, studies have been supported that examine the sexual and gender differences and similarities among men and women. These studies focus on gender differences and similarities in biology, psychology, and response to environmental factors. Moreover, a major new emphasis has been placed on the family as the unit of analysis.

Alcohol Abuse

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. An estimated 6 percent of women consume two or more drinks daily. Women in the United States continue to use alcohol as a drug of choice. The National Longitudinal Alcohol Epidemiological Survey (NLAES), conducted in 1992, found that a third of American women aged 18 and older were current drinkers and 21 percent were former drinkers. The *Diagnostic and Statistical Manual*, Fourth Edition (DSM-IV), reports that nearly 4 million women (4.1 percent of American women) were alcohol abusers and/or alcohol-dependent.

Men continue to outnumber women in terms of alcohol consumption — women consume a smaller quantity and overall have fewer alcohol-related problems and symptoms of dependency than do men. In the case of women who are heavy drinkers, however, the number and types of problems associated with, and resulting from, alcohol consumption may equal or surpass those of men. Alcohol-dependent women frequently experience greater physiological impairment, with earlier onset, once they begin to drink heavily. Such patterns appear later in the drinking careers of men who use alcohol heavily. Women who are alcoholics develop associated liver disease, alcoholic cardiomyopathy, and brain disorders earlier in their drinking careers than do men, and do so despite their lower quantity of alcohol consumption. Proportionally, more alcoholic women die from cirrhosis than do alcoholic men. Once the onset of alcohol abuse is established, however, women do enter treatment programs sooner than do men.

Tobacco Use

Tobacco use is responsible for more than 500,000 deaths in the United States each year, and nearly a third of these deaths occur among women. It is still the most preventable cause of death in this country. Although tobacco smoking prevalence has declined among men by 84 percent over the past three decades, smoking rates among women declined only 21 percent during this same period.

Adolescents are initiating smoking at younger ages. Forty percent of white, 33 percent of Hispanic, and 12 percent of black female high school students report that they are current smokers. The increase in smoking rates among adolescents, particularly females, has been linked to the tobacco industry's advertising and promotion campaigns.

Women who smoke experience early menopause, which may place them at higher risk for coronary artery disease. Smoking rates among higher income white and black women decline as a function of income, whereas Hispanic women have slightly higher rates of smoking as income rises. Black women are less likely to stop smoking than other groups of women. Moreover, black women are more likely to smoke higher tar and nicotine brands, which places them at increased risk for coronary artery disease, cancer, and cerebrovascular disease.

Drug Abuse

In 1995, the National Household Survey on Drug Abuse reported that an estimated 12.8 million Americans ages 12 and older used an illicit drug during the past 30 days. Furthermore, 4.3 million women of childbearing years reported using illicit drugs in the past month. Although fewer women than men use drugs, the potential consequences of drug abuse are often different for women. The National Pregnancy and Health Survey conducted in 1992 found that 221,000 women used illicit drugs while they were pregnant. The National Comorbidity Survey, conducted between 1990 and 1992, found that 6 percent of American women between the ages of 15 and 54 years met the criteria for lifetime drug dependence. This illicit drug use in women has been associated with other comorbid disorders.

Studies have reported that many women who have psychiatric disorders may be predisposed to drug abuse once physician-directed pharmacologic therapy is initiated. Psychiatric disorders, particularly depression, have been identified as a predisposing factor in the use of crack cocaine. Familial associations have also played a role. For example, it has been demonstrated that women who have conflicted relationships and a diminished psychological attachment to their mothers may be at risk for drug use. The same is true of women who have been the victims of crime. Anorexia nervosa, bulimia, and other eating disorders have been correlated with substance abuse, and present indications are that the more severe the diet or binging behavior, the more likely a woman will meet the criteria for substance abuse and/or dependency. Additionally, such eating disorders appear to increase the chance that the consequences of drug and alcohol use will be negative. Profiles demonstrate that many women who are potential drug users have low self esteem, are single mothers who may have limited parenting skills, are often school dropouts with few marketable job skills, and have been exposed at least once to a sexually transmitted disease. Such women may associate themselves with men for protection and support, but frequently do so with men who are themselves involved with drug use. Furthermore, a growing body of evidence suggests the existence of a gender difference in the effects of drug abuse and addiction; women proceed more rapidly to drug dependence than do men once they begin using drugs.

One of the most dangerous and potentially life-threatening consequences of illicit drug use is the risk of HIV infection. AIDS is now identified as the fourth leading cause of death among women between the ages of 15 and 44 years. By the middle of 1997, more than 96,075 cumulative cases of AIDS were reported among women, and 63 percent of these AIDS cases could be related to intravenous drug use. AIDS may be a factor in a woman's health even if she does not use intravenous drugs. Heterosexual contact with an intravenous drug user has been found to be a significant component in the transmission of this virus. Most of the women involved are young, use crack cocaine, and trade sex for drugs or money. Statistics indicate that 72 percent of AIDS cases in women may be attributed to intravenous drug use and 28 percent of cases to heterosexual contact with injection drug users. In men, 22 percent of AIDS cases are related to intravenous drug use and only 1 percent to heterosexual contact with intravenous drug users. Fifty-four percent of pediatric AIDS cases have been related to either the mother's use of intravenous drugs or her sexual contact with men who are injection drug users.

> *"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

Recommendations from the 1991 Working Group on Mental Health and Addictive Disorders

The 1991 Hunt Valley Working Group recommended attention to the following:

- Comorbidity among mental illness, substance use, and physical illness. Identification of certain subgroups of women at risk (genetically, by psychosocial history, chronic stress) for comorbid illness could prove useful for preventive treatment efforts.
- Genetic and environmental factors contributing to mental and addictive disorders through genetic epidemiology, to develop promising prevention strategies.
- Significant gender differences in prevalence of mood, anxiety, and personality disorders.
- Biological and psychological gender-related variables related to the development, onset, course, treatment, and relapse of mental and addictive disorders, including early developmental history and the role of sexual and physical abuse.
- Gender differences in cognitive and/or personality variables that may influence onset or recurrence of disorders.

- Psychological and biological factors linked to gender in suicide attempts and completions across the life span.

- Gender differences in grief reactions and depression following bereavement.

- Gender differences in the development of phobic avoidance for social and specific phobias and agoraphobia.

- More refined behavioral and pharmacologic interventions for alcohol and other substance use disorders that consider issues unique to women, including demands of caregiving for children and other family members.

Summary Recommendations from Beyond Hunt Valley (September 26-27, 1996)

- *Mental and Addictive Disorders Across the Life Span.* Encourage research on the interactions among biological, psychological, and social factors related to mental and addictive disorders across the life span of women.

- *Gender Differences in Brain Function.* Stimulate research on gender differences in brain function, specifically the effect of gonadal hormones on the developing brain and their relationship to the formation of sexually dimorphic brain structures and processes and how these distinctions could be related to gender differences observed in persons affected by mental and addictive disorders.

- *Long-term Effects of Violence and Victimization.* Encourage and support research on (a) psychological and biological effects of sexual assault in childhood and (b) intervention research designed to prevent and/or treat the long-term mental health effects of experiencing abuse and violence.

- *Gender Differences in Etiology and Consequences.* Conduct basic research (both human and animal) as well as epidemiological and longitudinal research directed at identifying gender differences in the etiology and consequences of alcohol and other drug use, abuse, and addiction.

- *Antecedents, Pathways, Risk Factors, and Protective Factors.* Conduct research on antecedents, pathways, risk factors, and protective factors involved in alcohol and other drug abuse by girls and women, with emphasis on early identification and a full spectrum of prevention interventions.

- *Co-existence with Mental Disorders.* Conduct research on the co-existence of alcohol and other drug dependence with psychiatric disorders, especially depression, posttraumatic stress disorder (PTSD), anxiety disorders, and eating disorders.

- *Alcohol and Other Drug Abuse Treatment Models.* Expand research examining the development and effectiveness of alcohol and other drug abuse treatment models that are specific to the unique needs of women. Such models should include treatment for addiction as well as any co-existing psychiatric disorder (e.g., depression, anxiety, PTSD, eating disorder). These models must also be culturally relevant.

- *Women and Alcohol.* More research is needed to:

  - ascertain mechanisms of gender differences in alcohol metabolism;

  - determine the causes and mechanisms of differential susceptibility of women to alcohol organ damage;

  - explain and quantify the relationship between alcohol consumption, and bone density and osteoporosis;

  - examine the long-term consequences of consuming alcohol while on estrogen replacement therapy;

  - determine if the relationship between alcohol consumption and breast cancer is causal and, if so, by what mechanism(s); and

  - determine optimal treatment methodologies for women alcoholics.

- *Address Diversity in All Research Studies.* Many measurement tools used today were normed on white male reference groups. These tools need to be re-examined and validated for use with female and diverse ethnic groups. Similarly, there is a 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 racial, religious, socioeconomic status, and sexual orientation.

- *Integrate Cross-disciplinary Research, from Molecular Level through Societal Level.* Mental disorders and alcohol and other drug abuse are complex problems that involve mutually interactive biological, behavioral, and societal factors. Research is needed that integrates across these levels of analysis to understand this complexity and provide comprehensive solutions. Given that researchers typically receive training in only one of these levels, cross-disciplinary collaborations are needed to develop more integrated programs of research. Prime topical areas for such cross-disciplinary collaborations in women's mental health and addiction include HIV/AIDS, physical and sexual abuse, posttraumatic stress disorder, and depression.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Gender as a Research Variable

Researchers are now paying significant attention to gender differences in the analysis and reporting of epidemiologic data. For example, gender differences in body water and body fat were taken into consideration in the analyses of the groundbreaking NLAES. This national epidemiological survey of nearly 43,000 people was designed to ascertain prevalence estimates of alcohol and other drug use disorders.[1] Another landmark national probability sample survey focused on alcohol and other drug use among women.[2,3] There was also a significant increase in comorbidity studies and in gender analysis. In addition, studies are beginning to examine the role of the menstrual cycle in patterns of alcohol and other drug use. Consideration of the variations in gonadal hormone levels across the menstrual cycle will lead to a better understanding of their influences on variations in alcohol metabolism across the menstrual cycle.[4,5]

Study Design Issues

Progress in study design includes the following:

- A movement from single toward bivariate and multivariate study designs.
- New strategies and research methods, including oversampling, have resulted in improvements in the recruitment into clinical studies of minorities, older women, lesbians, women of lower socioeconomic status, women with disabilities, and other underrepresented and understudied populations.
- Recognition of the importance of effective dosage, with minimal side effects, when prescribing medications for female subjects (patients).
- Recognition and focus on polydrug/alcohol use/abuse.
- 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. This has led to recognition that abused women need comprehensive services that may go beyond drug and alcohol treatment. This is especially true since there is now a better recognition that improved data on women's drug and alcohol use will result in better prevention and treatment programs through the inclusion of basic biological, epidemiologic, and etiologic study findings.

Genetic Studies

Since 1991, studies have examined the genetic basis of alcoholism in women.[6-10] The results of these studies do not lead to definitive conclusions concerning the role of inheritance in alcoholism among women, but they do permit tentative conclusions that can be applied to future research. Studies demonstrate that alcoholism can be genetically transmitted from generation to generation regardless of the gender of the offspring. Studies with twins have indicated that familial similarities may result from both genetic factors and shared environmental factors. In the case of women alcoholics, a lack of consistent findings makes interpretation of data from twin studies difficult. McGue and Slutske believe the inherited component of alcoholism in women is less markedly expressed in women than in men.[11] Despite the strong evidence for an environmental influence on the etiology of alcoholism, there has been no systematic study of environmental factors and their influence on alcohol use in terms of gender.[11] Heath and colleagues have identified several possible behavioral pathways that may interact with genetic influences on alcoholism.[12] Prescott and colleagues report that personality characteristics and parental psychopathology are important indicators of problem drinking and alcohol dependence in women.[9]

Psychological and Psychiatric Functions

Women, like men, may be divided into two populations based on their measured patterns of psychological and psychiatric functioning. The first population is characterized by negative emotionality and internalized psychiatric disorders such as anxiety states and depression. The second population exhibits poor behavioral control and externalizes psychiatric disorders through substance abuse and antisocial personality disorder.[11] Limited data support the hypothesis that the biological markers found in men alcoholics are also found in women. While there is evidence for some shared biological markers, some markers could not be used to differentiate high-risk women from low-risk with a degree of statistical significance.[13]

Reproductive Physiology

Many women of childbearing age (15 to 44 years) experience reproductive health problems as a result of alcohol and drug use. Even social drinkers may experience disruption of the menstrual cycle. Heavy or long-term use may result in abnormalities in the neuroendocrine system that may then impair fertility.[14] Moreover, studies have shown that spontaneous abortion is a frequent concomitant of alcohol and cocaine abuse. In addition to reproductive consequences, biochemical gender differences between alcohol and drug effects and female hormones may contribute to an increase in liver toxicity.[15]

Biochemistry and Physiology

Women have less total body water volume than do men of comparable weight and height. Ingested alcohol diffuses uniformly into all body water regardless of whether it is intra- or extracellular. Women can achieve higher blood alcohol concentrations (BACs) than can men who consume identical amounts of alcohol. Research indicates that less gastric alcohol dehydrogenase (ADH) activity in women may further contribute to a gender difference in BAC as well as the heightened physiological responses to alcohol. Initial metabolism of alcohol in the stomach by ADH decreases the availability of alcohol to the body. The lesser gastric ADH activity in women relative to men allows more alcohol to diffuse throughout their bodies.

Fluctuations in hormone levels during the menstrual cycle may further affect the rate of alcohol metabolism. This would make women more susceptible to elevated BACs at different times in the menstrual cycle.

Osteoporosis

Alcoholics are known to be at increased risk for osteoporosis. In postmenopausal women, paradoxically, low levels of alcohol consumption appear to increase bone density.

Another study indicates possible deleterious effects on other health outcomes when even small amounts of alcohol are consumed during estrogen replacement therapy. When postmenopausal women taking oral estrogen consumed half a drink, the levels of blood estrogen nearly doubled; after three drinks, levels nearly tripled. Other large epidemiologic studies have demonstrated that alcohol consumption at levels as low as one to three drinks per week is associated with an increased risk of breast cancer. The demonstrated elevation of blood estrogen levels associated with alcohol consumption has led to the suggestion that alcohol intake during estrogen replacement therapy may contribute to a possible mechanism for breast cancer.

Violence and Victimization

Epidemiological studies have shown that victimization (e.g., physical and sexual assault and natural disasters) of women and children is associated with alcohol and drug abuse. Longitudinal data from a representative national sample of women have shown that crime victims were 9.7 times more likely to have major alcohol-related problems and 17 times more likely to have major drug abuse related problems than nonvictims. Women who had reported being raped were 13 times more likely to have multiple alcohol-related problems and 26 times more likely to experience multiple drug-related problems. The implications from this and other related studies are that women who have been victimized may need special ancillary treatment such as long-term counseling related to victimization to increase the probability of a successful alcohol and other drug treatment outcome.[16]

Childhood sexual abuse has been associated with drug abuse in women in several studies.[17,18] For example, a study of women in drug abuse treatment found that 70 percent of the women reported histories of physical and sexual abuse, with victimization beginning before 11 years of age and continuing on a serial basis.[18] The path by which substance abuse develops following childhood sexual abuse experiences in women is unclear, and further research is needed to understand the etiology of this strong correlational finding.

Women who abuse drugs may be more vulnerable to victimization than men. A recent study of homicide in New York City found that 59 percent of white women and 72 percent of black women had been using cocaine prior to their death compared with 38 percent of white males and 44 percent of black males. Although cocaine is used by more men than women, its use is a far greater risk factor for victimization for women than for men.[19]

Nicotine

In a study of nicotine withdrawal in female twins, three subclasses were identified that represent a continuum from mild to severe nicotine withdrawal. Women from the severe withdrawal class were characterized by reported hand tremors and depression. Reported lifetime alcohol dependence rates were a function of severity class of nicotine use. Among smokers from the most severe nicotine use class, elevated rates of major depression, conduct disorder, and anxiety disorder were also reported. These findings may have a significant effect on the development of more efficacious treatment interventions.[20]

Behavior

To study pathways to alcohol and drug use and risky sexual behavior, researchers used behavioral, psychiatric interview, and self-report measures to index behavioral dysregulation, negative affectivity, childhood victimization, antisocial behavior, and affiliation with adult males. The research showed that behavioral dysregulation, negative affectivity, and childhood victimization were positively correlated with alcohol and drug use and risky sexual behavior. Age of menarche was correlated with association with risky sexual behavior. Implications for prevention and treatment include the potential use of behavior modification techniques typically used with conduct-disordered adolescents.[21]

Interrelationships among alcohol use, aggressive behavior, and episodes of acute alcohol-related aggression have been examined. Prior aggressive behavior and alcohol use predicted later episodes of acute alcohol-related aggression. Early aggressive behavior predicted later alcohol use. Research results have shown that the interaction of gender and alcohol was significant, such that prior alcohol use was a better predictor of alcohol-related aggression in females, and prior aggression was a better predictor for males. These data suggest that gender is the best predictor of the direction of the relationship between alcohol use, aggression, and alcohol-related aggression over time.[22]

Treatment

In a study of residential treatment outcomes in cocaine-abusing women, the presence of their children during treatment enhanced retention in care. Other benefits may be improvements in the mother-child relationship and postdischarge treatment outcomes.[23] In a study of postpartum women in outpatient drug abuse treatment, retaining custody of the infant was a strong predictor of retention in intensive day services, particularly for voluntary clients.[24]

A recent national study of individuals in drug abuse treatment programs between 1991 and 1993 (the drug abuse treatment outcome study or DATOS) showed that women who had at least 28 days of treatment (with at least 14 days in short-term inpatient care) had sharp reductions in their use of illicit drugs, HIV risk behavior, and illegal activities. For instance, at intake 84 percent of the women who were admitted to long-term residential treatment programs admitted using illegal drugs every day or at least once a week. Twelve months after treatment, only 28 percent continued to abuse drugs. Short-term inpatient treatment women also showed significant reductions in illegal drug use a year after their treatment with 86 percent admitting use at intake and 32 percent reporting use after one year.

Women who abuse drugs face a variety of barriers including barriers to treatment entry, to engagement in treatment, and to long-term recovery. Barriers to entry include a lack of economic resources, referral networks, women-oriented services, and conflicting child-related responsibilities. Because women have many specific needs, a number of components of treatment have been found important in attracting and retaining women in treatment. These include the availability of female-sensitive services, nonpunitive and noncoercive treatment that incorporates supportive behavioral change approaches, and treatment for a wide range of medical problems, mental disorders, and psychosocial problems. One research study showed that treatment of drug-dependent women was more likely to be successful if it was provided in a mutually supportive therapeutic environment and if it addressed the following issues: psychopathology (e.g., depression), a woman's role as mother, interpersonal relationships, and the need for parenting education.

Animal Studies

Animal studies have shown that fundamental gender differences may exist in the reinforcing and stimulus properties of abused drugs. On several measures of stimulant-induced activity, females exhibit more responsiveness than males; moreover, this responsiveness varies with the estrus cycle. Gender differences have also been reported in self-administration of cocaine. When cocaine infusions were made contingent upon increasing numbers of bar presses, female rats made substantially more presses than males, and their level of cocaine self-administration varied as a function of the estrus cycle.

Etiology – Drug Abuse

The progression or developmental stages of drug involvement appear to differ according to gender. In the progression from legal drug use to illicit drug use, for example, cigarettes seem to play a major role for women; for men alcohol alone is sufficient.[25] With regard to initiation into illicit drugs, data suggest that women are more likely to begin or maintain cocaine use in order to develop more intimate relationships, while men are more likely to use the drug with male friends and in relation to the drug trade.[26]

Comorbidity – Opiates and Cocaine

Studies of comorbid psychiatric disorders in opiate and cocaine abusers have reported findings consistent with the epidemiology of these disorders in the general population, specifically, a higher percentage of affective and anxiety disorders in women than in men. The rate of co-occurring substance abuse disorder and PTSD is relatively high for women. Data from a study on female crime victims, for example, indicate that those suffering from PTSD were 17 times more likely to have major drug abuse problems than nonvictims. Furthermore, it has been shown that individuals with a trauma history and PTSD symptoms utilize substance abuse inpatient services more frequently than do their non-PTSD counterparts. This has led researchers to speculate that the co-occurrence of substance abuse and PTSD often predicts a more severe course than would ordinarily be present with either disorder alone.

GAPS IN KNOWLEDGE

Among the gaps in women's health research on alcohol, tobacco, and other drug use are:

- Alcohol and other drug use and associated disorders in female populations by race, ethnicity, socioeconomic status, sexual orientation, age group, and other variables.
- Studies of genetic, physiologic, psychiatric, psychosocial, and behavioral antecedents of alcohol and other drug use including risk and protective factors, particularly replication studies.
- Prevention research expanded to include interventions based on female-specific antecedents, pathways, and risk and protective factors.
- Well-designed theoretically based treatment models that address female-specific issues.
- Gender differences in the etiology and consequences of alcohol and drug use, abuse, and dependence.
- Hormonal factors in alcohol and drug use, abuse, and dependence.
- Mediators of a genetic influence on alcohol and other drug use, abuse, and dependence.
- Identification of barriers to treatment seeking and entry.
- Life span issues.
- Increase in career opportunities including multidisciplinary training.
- Gender-specific behavioral, biological and medical effects of alcohol and drug abuse.
- Gender-specific biological and behavioral mechanisms that underlie alcohol and drug abuse.
- The role of dieting and eating disorders in alcohol and drug etiology.
- Factors that may result in over prescription and abuse of psychotherapeutic agents.

RESEARCH RECOMMENDATIONS

The following recommendations are not listed in priority order.

Reproductive Physiology

Examine basic biological processes across the menstrual cycle. This research should include animal studies on all phases of menstruation and should be developed with regard to cross-species generalities and new animal models. Such research should result in development of better pharmacokinetics data related to specific phases of the menstrual cycle and a description of the role of hormones in the metabolism of alcohol and drugs.

Drug Use Patterns and Treatment Models

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. These should include gender-based studies of drug interactions (e.g., steroids and brain/opiate receptors).

Developmental Effects

Examine effects of maternal alcohol and drug use on children's use of alcohol and drugs. Included should be a study of developmental neurochemistry as affected by pharmacologic agents and alcohol.

Predisposition to Mood, Eating, and Anxiety Disorders

Further examine 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

Study sexual abuse during childhood, and the interaction of other sexual or violent victimization of women and their use of alcohol and drugs. These studies should seek to clarify the correlations between the occurrence of alcohol and drug use with these experiences and explore psychosocial and biological mechanisms.

Biological and Physiological Gender Differences

Detail gender differences in health consequences that occur across a spectrum of consumption and use levels. Research should be designed to reveal gender differences in the sensitivity of specific organ and biological responses to alcohol and drug use that will lead to a better understanding of mechanisms (e.g., first-pass metabolism). This should include additional basic animal and human studies to investigate gender-based biological and physiological differences.

Descriptive Studies in Special Populations

Examine special populations as defined by race, ethnicity, socioeconomic status, sexual orientation, age group, and so on. Furthermore, there is a need for additional studies of alcohol and drug using women who successfully recover.

Multidisciplinary Research

Develop collaborative research programs between NIAAA and NIDA. Furthermore, multidisciplinary research should be fostered that examines biological effects, gender differences, psychosocial, behavioral, cognitive, psychiatric, general health, family, and legal consequences as well as specific sexually transmitted diseases and reproductive effects and their relation to alcohol and drug use. Emphasis should be placed on factors that affect the conduct of multidisciplinary research, particularly the development of strategies that overcome barriers to such research.

Gender-sensitive Surveys

Construct a survey tool that is designed to capture developmental data specific to women. NIH should further the development and standardization of existing and experimental gender-sensitive assessment tools. Better measurement and survey methods should be encouraged so as to more carefully characterize drug and alcohol use and other women's health factors.

Prevention Strategies

Develop counseling techniques for adolescent and adult females who may have a genetic risk of alcohol and drug use and/or abuse. Prevention strategies should also be developed to account for the role of childhood violence and sexual abuse in adolescent and adult females' use of alcohol and drugs and studies should be related to appropriate intervention. Additionally, prevention designed to reduce individual and social environmental risk factors should be undertaken with an emphasis on early intervention with girls and adolescents. Interventions should be based on etiology and pathway findings for females versus males. Implementation strategies should be developed with well-controlled evaluations for alcohol and drug use in pregnant women and women of childbearing age.

Media and Advertising

Examine further the influence of the media and advertising on a woman's use of alcohol and drugs including tobacco.

Gender-based Treatment

Examine the role of ethnic and gender variation in how alcohol and drug users perceive the need for treatment. These studies should examine the motivators and barriers that may affect treatment-seeking behavior as well as the role of co-occurring problems such as history of physical and sexual abuse, and serious affective and anxiety disorders on treatment outcome and the development of appropriate therapies.

Longitudinal studies from childhood through adulthood should be aimed at investigating gender differences in the nature and extent of drug-using behaviors; gender differences in the pathways and determinants of initiation, progression, and maintenance of drug use; and gender differences in the basic behavioral mechanisms underlying drug dependence, vulnerability, and protective factors.

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). Gender similarities and differences in the recovery process should be explored in these studies. Additionally, gender differences and pharmacotherapeutic effectiveness and other effects on women's health (e.g., fertility) should be noted. Other factors to be investigated include treatment-sensitive life span stages, clarification of "gender sensitivity," and exploration of what is required in the therapeutic process to increase efficacy.

Inclusion of Gender as a Research Variable

Develop an integrated strategy to include women in all phases of addiction research, including both biological and biomedical studies. This effort should include the introduction of females in animal models research through such mechanisms as modification of existing NIH guidelines for animal studies.

Training and Career Development

Encourage career opportunities for women in alcohol and drug research through the development of new program announcements.

REFERENCES

1 Dawson DA, Grant BF, Chou PS. Gender differences in alcohol intake. In: Hunt WA, Zakhari S, eds. Stress, gender, and alcohol-seeking behavior. NIAAA Research Monograph No. 29. Washington. D.C.: U.S. Government Printing Office, 1995.

2 Wilsnack SC, Wilsnack RW, Hiller-Sturmhofel S. How women drink: epidemiology of women's drinking and problem drinking. *Alcohol Health Res World* 1994;18(3):173-81.

3 Wilsnack SC, Wilsnack RW. Alcoholism. In: Galanter M, ed. *Alcoholism and Women*. New York: Plenum Press, 1995.

4 Gavaler JS. Alcohol effects on hormone levels in normal postmenopausal women and in postmenopausal women with alcohol-induced cirrhosis. In: Galanter M, ed. *Recent Developments in Alcoholism*, Vol. 12. New York: Plenum Press, 1995.

5 Gavaler JS, Rosenblum ER. Alcohol effects in postmenopausal women. In: Watson RR, ed., *Drug and Alcohol Abuse Review*, Vol. 5. Humana Press, 1995.

6 Cook BL, Wang ZW, Crowe RR, Hauser R, Freimer M. Alcoholism and the D2 receptor gene. *Alcoholism: Clin Exp Res* 1992;16:806-9.

7 Devor EJ, Cloninger CR, Hoffman PL, Tabakoff B. Association of monoamine oxidase (MAO) activity with alcoholism and alcoholic subtypes. *Am J Med Genet* 1993;48:209-13.

8 Gelernter J, Goldman D, Risch N. The A1 allele at the d2 dopamine receptor gene and alcoholism: a reappraisal. *JAMA* 1993;269(13):1673-7.

9 Prescott CA, Neale MC, Corey LA, Kendler KS. Predictors of problem drinking and alcohol dependence in a population-based sample of female twins. *J Stud Alcohol* 1997;58(2):167-81.

10 Pickens RW, Svikis DS, McGue M, Lykken DT, Heston LL, Clayton PJ. Heterogeneity in the inheritance of alcoholism. *Arch Gen Psychiatry* 1991;48:19-28.

11 McGue M, Slutske W. The inheritance of alcoholism in women. Women and alcohol: issues for prevention research. National Institute on Alcohol Abuse and Alcoholism Research Monograph. No. 32. Washington, D.C.: U.S. Printing Office. 1996. p. 65-91.

12 Heath C, Slutske WS, Madden PAF. Gender differences in the genetic contribution to alcoholism risk and to alcohol consumption patterns. In: Wilsnack RW, Wilsnack SC, eds, *Gender and Alcohol: Individual and Social Perspectives.* New Brunswick, NJ: Rutgers Center of Alcohol Studies, 1997.

13 Hill SY, Steinhauer SR. Assessment of prepubertal and postpubertal boys and girls at-risk for developing alcoholism with p300 from a visual discrimination tasks. *J Stud Alcohol* 1993;54:350-8.

14 Mello NK, Mendelson JH. Cocaine's effects on neuroendocrine systems: clinical and preclinical studies. *Pharmacol Biochem Behav* 1997;57:571-99.

15 Mello NK, Mendelson JH, Kelly M, Diaz-Migoyo N, Sholar JW. The effects of chronic cocaine self administration on the menstrual cycle in rhesus monkeys. *J Pharmacol Exp Ther* 1997;281:70-83.

16 Wilsnack SC, Vogeltanz ND, Klassen AD, Harris RT. Childhood sexual abuse and women's substance abuse: national survey findings. *J Stud Alcohol* 1997;58(3):264-71.

17 Boyd C, Gutherie B, Pohl J, Whitmarsh J, Henderson D. African-American women who smoke crack cocaine: sexual trauma and the mother-daughter relationship. *J Psychoactive Drugs* 1994;26(3):243-7.

18 Miller BA, Downs WR, Testa M. Interrelationships between victimization experiences and women's alcohol/drug use. *J Stud Alcohol* 1993;Suppl 11:109-15.

19 Tardiff K, Marzuk P, Leon AC, Hirsch CS, Stajic M, Portena L, Hartwell N. Homicide in New York City: cocaine use and firearms. *JAMA* 1994;272(1):43-6.

20 Madden PAF, Bucholz KK, Dinwiddle SH, Slutske WS, Bierut LI, Statham DJ, Dunne MP, Martin NG, Health AC. Nicotine withdrawal in women. *Addictions* 1997;92:889-902

21 Mezzich AC, Tarter RE, Giancola PR, Lu S, Kirisci L, Parks S. Substance use and risky sexual behavior in female adolescents. *Drug Alcohol Depend* 1997;14(44):157-66.

22 White HR, Hansell S. The moderating effects of gender and hostility on the alcohol aggression relationship. *J Res Crime Delinquency* 1996;33:451-72.

23 Hughes PH, Coletti SD, Neri RL, Urmann CF, Stahl S, Sicilian DM, Anthony JC. Retaining cocaine-abusing women in a therapeutic community: the effect of a child live-in program. *Am J Public Health* 1995;85:1149-52.

24 Strantz IH, Welch SP. Postpartum women in out-patient drug abuse treatment: correlates of retention/completion. *J Psychoactive Drugs* 1995;27:357-73.

25 Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *J Stud Alcohol* 1992;53(5):447-57.

26 Boyd C, Blow F, Orgain L. Gender differences among African-American substance abusers. *J Psychoactive Drugs* 1993;25(4):301-5.

OTHER RESOURCES

Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 1995;7(no 1):10.

Hill SY, Steinhauer SR, Lock J. P300 amplitude decrements in children from families of alcoholic female probands. *Biol Psychiatry* 1995;38(9):622-32.

Hudson JI, Weiss RD, Pope HG Jr, McElroy SK, Mirin SM. Eating disorders in hospitalized substance abusers. *Am J Alcohol Abuse* 1992;18:75-85.

Lukas SE, Sholar M, Lamas X, Kouri E, Wines JD, Kragie L, Mendelson JH. Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. *Psychopharmacology* 1996;124(4):346-54.

McGue M, Pickens RW, Svikis D. Sex and age effects on the inheritance of alcohol problems: a twin study. *J Abnorm Psychol* 1992;101:3-17.

Mitchell JE, Pyle R, Echert ED, Hatsukami D. The influence of prior alcohol and drug abuse problems on bulimia nervosa treatment outcome. *Addict Behav* 1990;15:169-73.

Ninth Special Report to the U.S. Congress on Alcohol and Health from the Secretary of Health and Human Services. June 1997. Bethesda, MD: U.S. DHHS, NIH Publication No. 97-4017.

Vogeltanz ND, Wilsnack SC. Alcohol problems in women: risk factors, consequences and treatment strategies. In: Gallant SJ, Keita GP, Royak-Schaler R, editors. *Health care for women: psychological, social and behavioral factors.* Washington, D.C.: American Psychological Association, 1997.

BEHAVIORAL AND SOCIAL SCIENCES

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BACKGROUND

Definitions

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."[1] This definition not only expresses the interrelatedness of mind, body, and social context — well represented by George Engel's biopsychosocial model[2] — but also stresses the positive meanings of health. The Working Group on Behavioral and Social Sciences approached its topic in the same encompassing way.

A similar approach informs the definitions developed by the NIH Office of Behavioral and Social Science Research (OBSSR), which has identified these cross-cutting 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.
- A focus on both the social and biological context of behavior.

The OBSSR report[3] states that "for the purposes of this definition, the term 'behavioral' refers to overt actions; to underlying psychological processes such as cognition, emotion, temperament, and motivation; and to biobehavioral interactions. The term 'social' encompasses sociocultural, socioeconomic, and sociodemographic status; biosocial interactions; and the various levels of social context from small groups to [the societal influences of] complex cultural systems . . . ."

These definitions suggest that looking at the behavioral and social dimensions of women's health means looking not only at women's actions, cognitions, and emotions but also at contextual factors including socioeconomic status, race, ethnicity, age, functional status (degree and type of disability), employment, geography, social roles, power relationships, and sexual preference — as well as at the interaction of each of these with biological factors. To take one example, a woman's adherence to medical advice to reduce the risk of osteoporosis by taking calcium is a behavioral issue with physical consequences, and it cannot be understood without considering her financial ability to pay for the calcium supplements and other social factors.

Behavioral and Social Dimension in Previous ORWH-sponsored Meetings

Although the Bethesda gathering was the first ORWH-sponsored meeting to convene a working group on behavioral and social sciences research, it was not the first to consider the behavioral and social dimensions of women's health. At the 1991 Hunt Valley meeting, they were an explicit part of the discussions of each phase of the life span and of the analyses and recommendations of the cross-cutting science groups. For example, the 1991 report discusses the ways in which economic and cultural conditions limit women's health choices, the realities of violence and abuse for many women, the disproportionate disease burden borne by women of color, the role of social and behavioral risk factors in the development of disease, and the significance of social supports for mental and physical health.

In the 1996 Philadelphia meeting, the topic of behavior was paired with neuroscience and brain study in the working groups, thus focusing on the biological determinants of behavior. Broader behavioral and social themes continued in the meeting as a whole. Two working groups are of particular note. First, the Working Group on Research Design: Multidisciplinary Perspectives recommended, among other things, the structuring of NIH funding and review processes to encourage multidisciplinary research and new research designs; the convening of multidisciplinary conferences; rewards for multidisciplinary research within academic institutions; and multidisciplinary training and mentoring for researchers. Second, the Working Group on Racial, Ethnic, and Cultural Diversity in Clinical Research offered a host of recommendations for ways in which NIH can "involve and benefit diverse communities of women in research projects."[4]

The report of the 1997 New Orleans meeting is filled with observations and recommendations about behavioral and social dimensions of health in each stage of the life span — perhaps most notably in the section on adolescence. For example, the Working Group on Adolescence called attention to the health outcomes of adolescent risk behavior, including increasing violence and smoking among girls, and the effects of body image and self concept on health behaviors and outcomes. ORWH Director Vivian Pinn, M.D., also sounded several behavioral and social themes in her introductory remarks. She said the forthcoming Santa Fe meeting would focus on "factors that contribute to differences in health status and health outcome among different populations of women, including biologic, genetic, race, culture and ethnicity, psychosocial and behavioral factors, educational influences, traditional and alternative practices, environment, poverty and socioeconomic status, access to health care, and [occupation]."[5]

The Santa Fe meeting picked up the challenge, as can be seen in a few examples. The Working Group on the Prenatal Years noted the need for information about what issues study populations, not just researchers, believe are important. The Working Group on Infancy/Childhood recommended the use of racial and socioeconomic demographic indicators in all research, and urged cultural sensitivity and flexibility. The Working Group on Adolescence stated that "the major causes of morbidity among female adolescents are largely . . . related to their behaviors," and it highlighted seven social and behavioral risk factors in need of investigation. The report of the Working Group on Reproductive and Middle Years includes extensive recommendations on women of color and on poverty and urban health. A section on women with disabilities in this age group recommends research on body image, fitness, and violence, among other things. And the list could continue.

Major Themes in the Bethesda Working Group Discussion

The Behavioral and Social Sciences Working Group that met in Bethesda in November 1997 had the task of pulling together this immense set of issues and identifying the activities that would most advance this critical and cross-cutting area of knowledge about women's health. Participants agreed that behavioral and social science research on women's health could best be facilitated by basic and methodological research and some key policy changes. The discussion generated a set of process and policy objectives that members felt would create more favorable conditions for behavioral and social science research on women's health. Most, but not all, of these objectives related to NIH policy and programs, with the chief aim of reinforcing and extending the progress already made by ORWH and OBSSR. The overall goals are greater consistency among the institutes and more overlap between women's health and behavioral and social science research.

The working group members stressed the importance of learning from and joining in partnerships with others with shared priorities, particularly those who have previously dealt with similar issues. Several examples were cited, notably the AIDS community, which has stimulated new research paradigms and modeled collaboration among researchers, providers, consumers, and the support community. Another is the Centers for Disease Control and Prevention, which has shown a strong commitment to behavioral and social science research. In another vein, the Pan American Health Organization and the World Bank have developed training programs and materials for institutional leaders on gender analysis and used them in many countries.[6] Of direct relevance are two conferences convened in 1994 and 1996 by the American Psychological Association (APA), with ORWH as a cosponsor, on the research agenda for psychosocial and behavioral factors in women's health. APA has published the recommendations from the first meeting.[7]

Working group members expressed urgent concern about the impact of current welfare-to-work policies on the health of low-income women. The rapidly changing policies require immediate attention to the effect on women and their health. Members suggested the possibility of using existing study populations of welfare recipients to look at the health impacts of the withdrawal of financial support. Finally, violence was another concern that received considerable attention during the discussion.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

As has been noted, this was the first ORWH meeting to convene a working group expressly and exclusively devoted to behavioral and social science research. Therefore, progress since 1991 cannot be assessed in terms of a specific set of recommendations. Nevertheless, there is a good deal of progress to be acknowledged — much of it due to the efforts of two relatively new NIH offices, the Office of Research on Women's Health and the Office of Behavioral and Social Sciences Research. These program offices within the Office of the Director at NIH have identified and highlighted areas that, with increased attention, would advance the knowledge about women's health. They have also taken steps to increase the research activities in those areas. On a very basic level, as has been documented above, the ORWH-sponsored workshops on women's health research have made important strides in articulating behavioral and social issues and weaving them into the agendas of every sector of women's health research.

Research Design

Increased awareness and knowledge of gender and behavioral and social factors have led to changes in the way research is conducted. In this decade, policymakers and health researchers, along with the general public, have become more aware of the significance for health and disease of both gender and behavioral and social factors. As a result of this awareness 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.

The way research is conducted and reviewed also reflects this awareness. 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. In addition, behavioral scientists and women's health experts more routinely sit on review panels and study sections. Some review panels even include consumers.[8]

Behavioral Methodologies

Behavioral methodologies are becoming a standard part of health-related research. Health researchers on health topics are increasingly using the methods developed by behavioral and social scientists. A common tool is focus groups, which use professionally facilitated discussion among carefully chosen samples to gather information on attitudes and behaviors. More broadly, 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. These approaches are helping to challenge and change basic notions about what constitutes "good research," inevitably pointing the way to multidisciplinary research.

Increased Knowledge

More research leads to more knowledge about specific behavioral and social factors. Over this decade, there have been significant advances not only in attitudes toward gender and behavioral and social factors, but in scientific knowledge about them. Attention to these factors in health-related research has moved forward in many fields since 1991 through the efforts of Federal and State Governments, academic institutions, and private foundations. A few examples follow:

- 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,[9] the consequences for women,[10] and the development of effective treatments.[11,12] Both The Commonwealth Fund and the National Academy of Sciences, Institute of Medicine, studied violence against women and its health implications and released reports on the subject in 1996.[13,14]

- 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. The pattern differs from men in that cardiovascular disease occurs at older ages among women, and this may have contributed to the relative lack of research in women. Since 1991, a number of studies have been and are being conducted to fill in gaps in knowledge about the disease in women (e.g., the Nurses Study, PEPI, the Women's Health Initiative, SWAN). These studies are carefully examining behavioral factors, such as exercise, diet, stress, and social support and their relationships to cardiovascular health outcomes.

- The rapidly advancing world of genetic research is leading to the availability of genetic screening for an increasing number of diseases. The discovery of BRCA1 was an important step forward for women in helping to prevent a disease that may affect as many as one in nine women during their lifetimes. However, there are many misconceptions about what it means to have or not have BRCA1. 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.[15] The work going on in the area of breast cancer risk and counseling is the leading edge of a field that will gain in importance as the genetic bases of more diseases are discovered.

GAPS IN KNOWLEDGE

During its deliberations, the working group concentrated on institutions and practices that are responsible for developing knowledge. Thus, many of the observations below address underlying systems contributing to gaps in knowledge.

Basic Knowledge

Basic behavioral and social knowledge are needed to build "a science of women's health" that encompasses biological, behavioral, social, and environmental factors. Basic research questions include:

- How do women make decisions about health — including the adoption and maintenance of healthy behaviors?
- How do gender roles affect health decisions and behaviors?
- What are the effects of culture, including race and ethnicity, on health decisions and behaviors?
- What are the effects of social factors — socioeconomic status, housing, employment, education, and so on?
- How can current knowledge be used to encourage health-promoting changes?

Methodology

Strong methodology is the foundation of all good research. Strengthening behavioral and social science methodology in women's health research would substantially advance the state of knowledge about women's health.

- Behavioral and social terms are used and operationalized in varied ways by researchers, partly due to the lack of widespread agreement about standard definitions and measurements. Research could benefit by having clear and commonly agreed upon definitions and explicit details about how terms are to be operationalized and how, if at all, definitions and measurements differ from those used by others. Examples of terms that need to be operationalized more consistently: adolescent, power differential, role, violence.
- Measures often fail to reflect the realities of women's lives — for example, the types of physical activities that women routinely engage in and women's employment status.
- Data-gathering techniques and strategies often do not involve the people and communities on whom the data are being gathered.
- Although women are included in studies and surveys, the study populations and samples often do not reflect the range of racial, ethnic, and economic groups and the diversity of women's roles. Segments of the life span are underrepresented, for example, pregnant women, elderly women, adolescents. Moreover, the retention rate for women is poor in many studies.
- Gender sometimes is considered only in objective or quantitative terms, and studies fail to apply a gender analysis that recognizes the implications of gender for social roles, power, and other factors — and, in turn, their influence on health.

Balanced, Consistent Multidisciplinary Efforts

The working group perceived a varied level of commitment among the NIH institutes to the inclusion of behavioral and social sciences components in their research. Improvements could be made at each of these stages of the process:

- Attention to behavioral and social factors (e.g., recruitment of a diverse population, retention issues) in research design.
- Inclusion of behavioral and social questions in RFAs.
- Higher budgets for multidisciplinary research in recognition of its potential cost effectiveness.
- Inclusion on research teams of behavioral and social scientists who also have women's health expertise.
- Inclusion in review panels and study sections of behavioral and social scientists who also have women's health expertise.

Health Professional Education and Training

Behavioral and social information and theory are not consistently or adequately incorporated into health professional education. There is no mechanism for updating the information that is included. Generally, students and trainees are not tested on their knowledge in this area, making students unaccountable for what they learn and educators unaccountable for what they teach.

Knowledge Gaps of Special Concern

- Behavioral interventions: What works, with whom, and why?
- Physical activity: Little is known about the maintenance of positive behaviors.
- Violence: Knowledge is spotty, with many gaps across the life span.

RESEARCH RECOMMENDATIONS

Basic Behavioral and Social Science

- Study decisionmaking processes — adoption and maintenance of health behaviors.
- Investigate gender roles.
- Study culture.
- Study social context.

Collaborative, Multidisciplinary Research that Incorporates Behavioral and Social Science into Biomedical and Clinical Studies

- Explore preventive factors.
- Study treatment.
- Investigate the care and caregiving experience.

Methodological Research

- Determine innovative measures that reflect women's lives.
- Devise innovative data gathering strategies including qualitative and community-based approaches.
- Explore effective methods of recruiting and retaining women in studies.

Funding and Training/Institutional Policy

- 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 RFAs in every institute.

The institutions that educate and train health professionals should:

- Integrate behavioral and social science relevant to women into health professional curriculum.
- Develop a process for integrating new advances.
- Devise ways to test students on their knowledge in this area.

Special Initiatives

- Conduct clinical trials related to behavioral interventions.
- Explore physical activity.
- Study violence.

Behavioral and Social Themes in the Recommendations of Other Bethesda Working Groups

Eleven other working groups referred to behavioral and/or social factors in their recommendations, as listed below.

- *Alcohol, Tobacco, and Other Drug Use, Disorders, and Consequences*: Effects of abuse; parenting as an environmental factor; gender-sensitive psychosocial treatment.
- *Bone and Musculoskeletal Disorders:* Quality of life issues.
- *Cancer:* See sections on outcomes and overarching issues.
- *Cardiovascular Diseases:* References to obesity, behavioral determinants.
- *Digestive Diseases:* Target behavioral therapies; fund multidisciplinary research on biopsychosocial factors.
- *Immunity and Autoimmune Diseases:* Environmental influences include diet, stress, lifestyle.
- *Mental Disorders:* Lifestyle and well being included in outcomes; prevention studies include caregiver roles; cross-cultural studies recommended.
- *Neuroscience:* Stress noted as a factor in interactions among systems; social environment noted as a dimension.
- *Oral Health:* See section on women and the health care system; also mentions of violence and abuse.
- *Pharmacologic Issues:* Drug compliance and drug access.
- *Reproductive Issues:* See section on general considerations.

REFERENCES

1 The First Ten Years of the World Health Organization, Geneva, WHO, 1958.

2 Engel G. The clinical application of the biopsychosocial model. *Am J Psychiatry* 1980 May:535-43.

3 A Definition of Behavioral and Social Sciences Research for the National Institutes of Health. Bethesda, MD: Office of Behavioral and Social Science Research.

4 Interim proceedings of the public hearing and scientific workshop. Philadelphia, PA: Office of Research on Women's Health, 1997. p. 104.

5 Interim proceedings of the public hearings and scientific workshop. New Orleans, LA: Office of Research on Women's Health, 1997. p. 26.

6 See, for example, Facilitator's Guide, Workshop on Gender, Health and Development, PAHO, 1997.

7 Research agenda for psychosocial and behavioral factors in women's health, Washington, D.C.: American Psychological Association, 1996.

8 As the result of advocacy by the National Breast Cancer Coalition, Congress mandated that breast cancer survivors be included on the review panels of breast cancer research funding being overseen by the U.S. Army Medical Research and Materiel Command. Consumers have participated on the panels since 1992.

9 Resnick H, Kilpatrick DG, Dansky B, et al. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J Consult Clin Psychol* 1993;61:984-91.

10 Kessler R, Sommega A, Bromet E, et al. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995;52:1048-60.

11 Foa EB, Olasov Rothbaum B, Riggs DS, Murdock TB. Treatment of posttraumatic stress disorder in rape victims: a comparison between cognitive-behavioral procedures and counseling. *J Consult Clin Psychol* 1991;59(5):715-23.

12 Resick PA, Schnicke M. Cognitive processing therapy for sexual assault victims. *J Consult Clin Psychol* 1992;60(5):748-56.

13 Plichta S. Violence and abuse: implications for women's health. In: Falik MM, Collins KS, eds. Women's Health: The Commonwealth Fund Survey. Baltimore: Johns Hopkins University Press, 1996. p. 237-70.

14 Institute of Medicine Panel on Research on Violence Against Women. Understanding violence against women. Washington, D.C.: National Academy Press, 1996.

15 Lerman C, Lustbader E, Rimer B, et al. Effects of individualized breast cancer risk counseling: a randomized trial. *J Natl Cancer Inst* 1995; 87(4):286-92.

BONE AND MUSCULOSKELETAL DISORDERS

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BACKGROUND

Bone 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 (see Figure 1). Many of these conditions are more prevalent in women than men and have gender-specific manifestations, etiology, impact, and possible outcomes of treatment. The initial focus and efforts in women's health have been appropriately on the diseases with acute mortality or female specificity, for example, heart disease and breast cancer. 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.

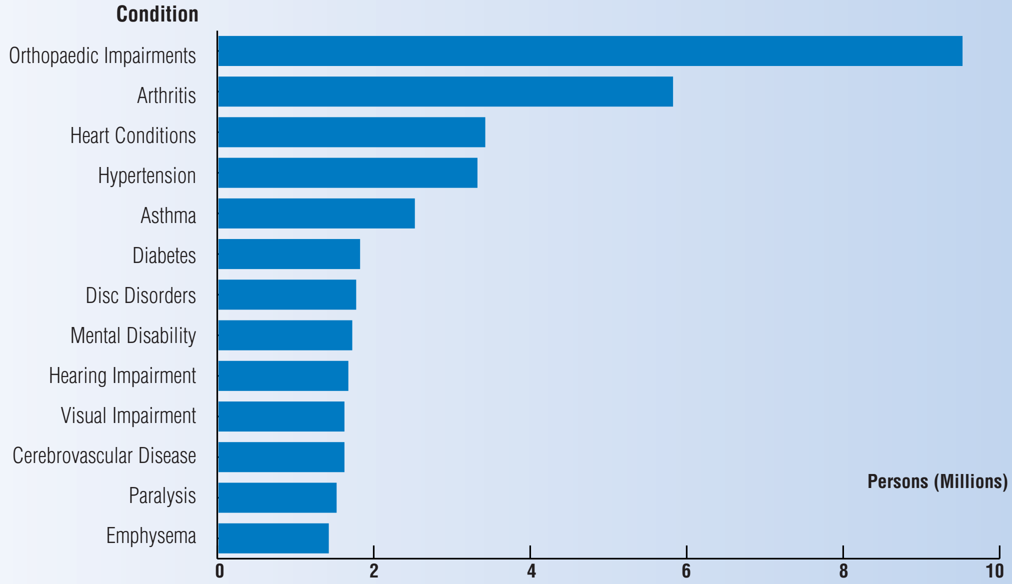
The Bone and Musculoskeletal Disorders Working Group addressed the disorders in three general categories: arthritis and musculoskeletal disability, osteoporosis and fractures, and orthopaedics and physical activity.

The term arthritis refers to more than 100 different illnesses and conditions. The forms of arthritis more prevalent in women include the most common, osteoarthritis, which affects about 16 million Americans. Rheumatoid arthritis, affecting 2.1 million, is 3 times more common in women, and systemic lupus erythematosus affects 9 to 10 times more women than men.[1] Arthritis is currently the most prevalent chronic condition reported by American women.[2] As shown in Figure 1, it is also a leading cause of limited activity in the United States and represents the third leading cause of bed disability. In the National Health Interview Survey, arthritis is more commonly reported by women than men and is more likely to result in limitations of activity (Figure 2). Nevertheless, recent studies indicate that exercise can play a very positive role in arthritis care and management.[3] The toll of arthritis includes not only the costs of medical care but also the consequences of arthritis pain — inability to work, difficulty in performing activities of daily living, difficulty in exercising, and the resulting adverse psychological effects.[4] Moreover, projections indicate that the number of people affected will continue to grow as the population ages. Self-reported arthritis in women involved 22.8 million women in 1990, and projections indicate that this number will grow to 36 million by 2020.[5]

Women are less likely to undergo restorative procedures than men. Gender differences may influence decisions regarding utilization and timing of elective total joint replacement surgery in patients with moderately severe osteoarthritis of the hip or knee. Men and women differ in their willingness to accept continued functional decline, risks of surgery, and disruption of usual role.[6]

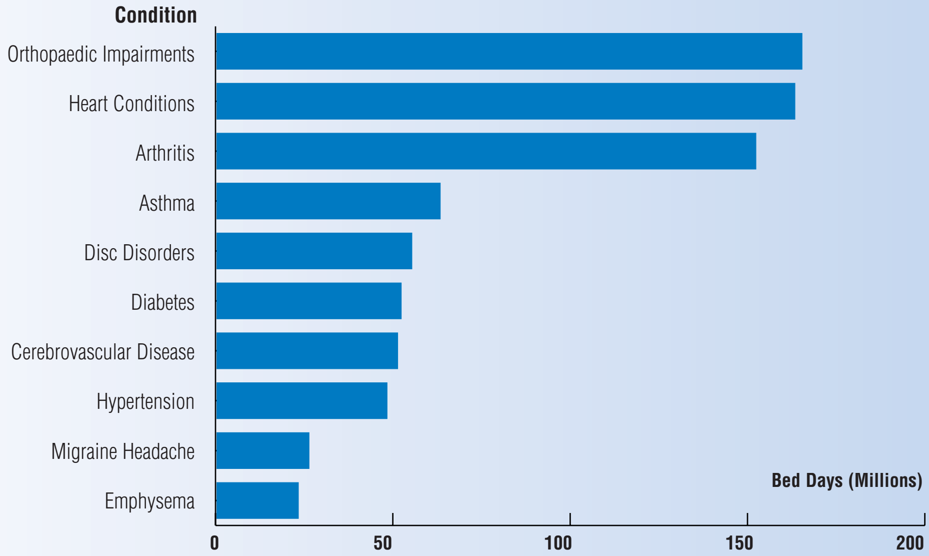
Older women have higher rates of overall disability than men of the same age. This is because women survive longer with disabilities. In individuals over 85 years old, 55 percent of women either require help at home or live in a nursing home, compared with 37 percent of men. Even though white women live an average of 7 years longer than white men, they spend twice as many years disabled.[7] Clearly, a focus of the women's health agenda should be to prevent and delay the onset of disabilities in older women and to postpone the loss of independence and the need for nursing home admissions.

FIGURE 1a. Prevalence of leading chronic conditions causing limitation of activity, U.S., 1990-92.



Source: National Center for Health Statistics, National Health Interview Survey; National Heart, Lung, and Blood Institute, NHLBI FY 1996 Fact Book.

FIGURE 1b. Leading chronic conditions causing bed disability, U.S., 1990-92.



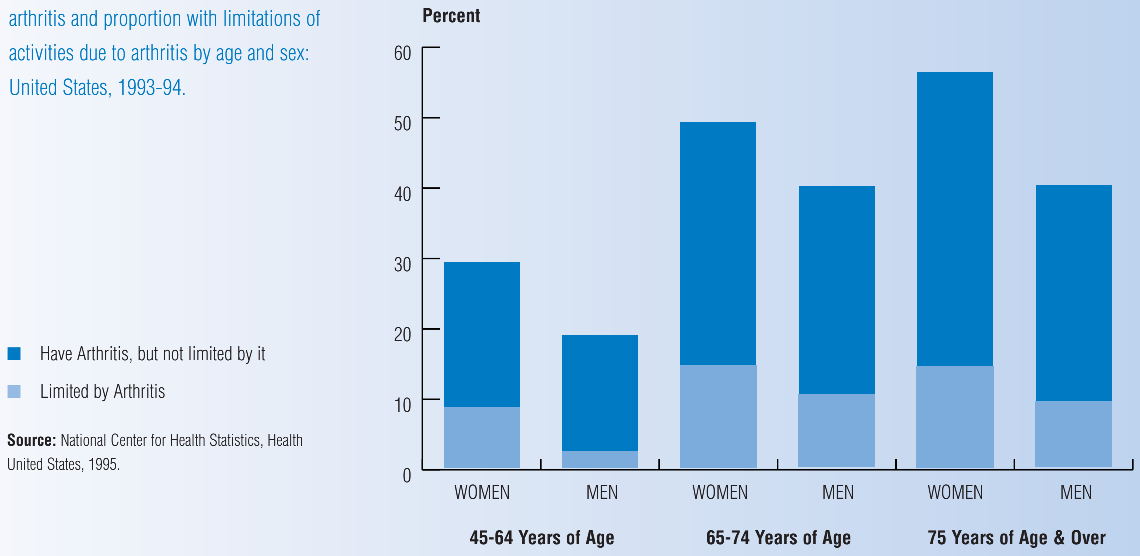
Source: National Center for Health Statistics, National Health Interview Survey; National Heart, Lung, and Blood Institute, NHLBI FY 1996 Fact Book.

Osteoporosis is a condition involving low bone mass and microarchitectural deterioration of bone that leads to an increased risk of fracture. The World Health Organization has developed a quantitative definition of osteoporosis, with less severe bone deficits referred to as osteopenia. The definitions are based on comparison of an individual's bone density with that of young normal individuals. Those whose bone density is 2.5 standard deviations below normal have osteoporosis and a markedly increased risk of fracture. Low bone density is more prevalent in women than men because women accumulate less bone at skeletal maturity and experience increased bone loss due to estrogen deficiency at menopause. Estimates indicate that in women over 50 in the United States, 13 to 18 percent, or 4 to 6 million, have osteoporosis, and 37 to 50 percent, or 13 to 17 million, have osteopenia.[8] The percentage of women in the population with osteoporosis increases with each decade of life after age 50 (see Figure 3). The decreasing bone density in these women is highly predictive of future fractures, especially at the hip.[9] Health expenditures attributable to osteoporosis have been estimated to be $11 billion in older women annually in the United States.[10]

> *"Today, no national system exists which can provide comprehensive information about injury and illness patterns in physically active women."*
>
> Marjorie J. Albohm,
> M.S., A.T.C.
> The National Athletic
> Trainers Association

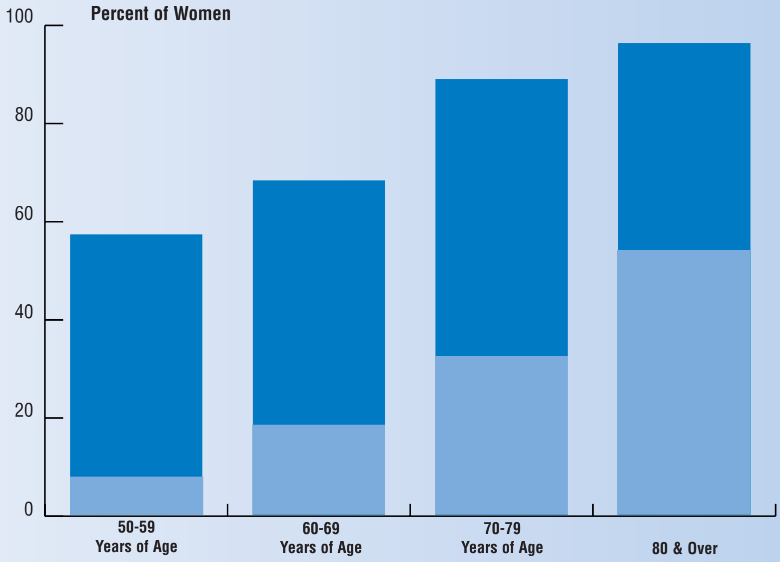
Orthopaedic problems represent the primary cause of bed disability in the United States and, in addition, are a top cause of limited activity (see Figure 1). In the United States, musculoskeletal impairments occur at a rate of 124 per 1,000 persons. Back or spine conditions are the most common, accounting for 52 percent of the impairments. Over a 10-year period, a woman 65 years old has a 40 percent chance of being hospitalized for a musculoskeletal condition.[11] According to the National Center for Health Statistics, women made more than 20 million visits to physicians for musculoskeletal conditions in 1995.[12]

FIGURE 2. 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.

FIGURE 3. Prevalence of reduced hip bone density among women 50 years of age and over by age and severity: United States, 1988-91



NOTES: Osteopenia is defined as a bone mineral density 1-2.5 standard deviations below the mean of white, non-Hispanic women 20-29 years of age as measured in NHANES III (Phase 1); osteoporosis is defined as a bone mineral density value of more than 2.5 standard deviations below the mean of young white, non-Hispanic women (WHO expert panel).

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

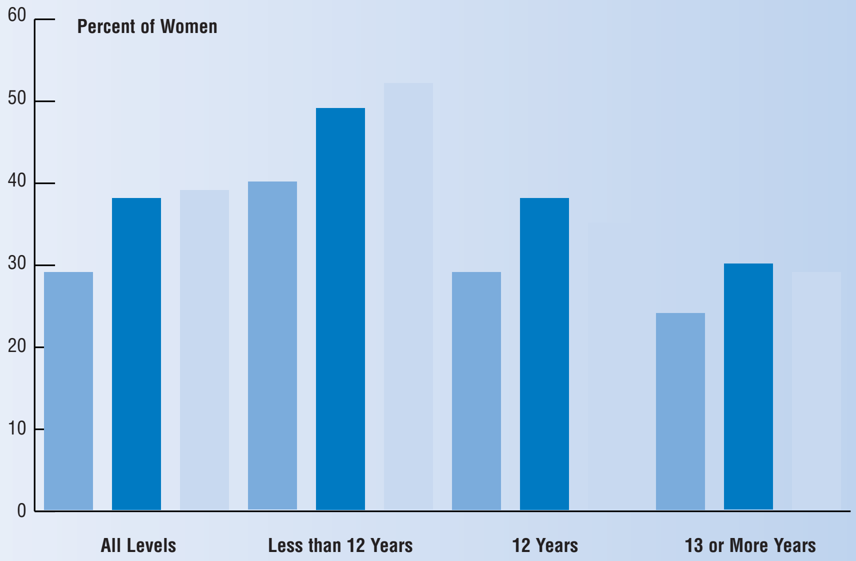
Lack of appropriate physical activity throughout life may potentially underlie some of the physical impairments manifesting with increasing age in women. Unfortunately, a sedentary lifestyle is common in the United States. Women engage in less exercise than do men, according to the Centers for Disease Control and Prevention (CDC), with 30 percent of women sedentary versus 25 percent of men.[13] The percentage of individuals engaging in no leisure-time physical activity is higher among minority women and women with less education, putting them at higher risk of many chronic diseases and disabilities (Figure 4). Physical activity can, however, lead to sports injuries. With the onset of legislation 25 years ago to provide equal opportunity for young girls and women to participate in sports (Title IX), female participants in intercollegiate sports increased from 300,000 in 1972 to more than 2.25 million participants today. Educators and researchers need to focus on the impact of sports on the female body and mind. The many special advantages to participation in organized sports are clear, but some cautionary notes need to be applied to the generic message to "get moving." Excessive exercise can lead to a pattern described as the "female athlete triad," characterized by disordered eating, amenorrhea, and osteoporosis.[14] Certain sports injuries are now found to be more common in women, including lower-extremity injuries such as stress fractures in the pelvis and hip and knee ligament injuries.[15]

During its deliberations, the working group noted a critical lack of data on the prevalence and incidence of many bone and musculoskeletal disorders in women, and particularly on treatment outcomes. Such information is basic to successful care and management of chronic conditions and for goal setting. Finally, the working group stated that effective information dissemination to both health care providers and patients would improve total patient care tremendously.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Progress over the last few years in the basic science, treatment, and management of bone and musculoskeletal disorders has been remarkable. The working group noted the following advances.

FIGURE 4. Prevalence of sedentary lifestyle among women 25 years of age and over by race, Hispanic origin, and years of education: United States, 1991.



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

Arthritis and Musculoskeletal Disability

Basic science related to the pathophysiology of arthritis has been advanced in the last several years. In addition, 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 the following:

- The discovery of some of the effects of genetics and genetic mutations on arthritis.
- Better understanding of cartilage cell physiology, matrix factors, and enzyme cofactors.
- Improvements in joint replacement surgery.
- Increased understanding of modifiable and nonmodifiable risk factors.
- The discovery that self care works and enhances self-efficacy.
- 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.
- Studies showing that weight loss improves osteoarthritis.
- Reliable and validated tools for assessing functional capacity, activity limitations, psychological status, and quality of life.
- Programs monitoring longitudinal outcomes in arthritis.

Osteoporosis and Fractures

During the last 6 years, there have been huge advances in understanding the biology of bone remodeling and functions of various cells in the skeleton. In addition, new treatment options and sophisticated assessment technologies are now available. Recent progress in understanding how calcium and physical activity affect bone health includes (a) an NIH Consensus Development Conference in 1994 on optimal calcium intake; (b) new dietary guidelines for calcium intake;[16] (c) the role of exercise and fall prevention in preventing osteoporotic fractures; and (d) the relationship between calcium intake, physical activity, hormonal balance, and bone mineral density in adolescents. Following are additional examples of advances in our knowledge of osteoporosis and its treatment and management:

- Biochemical markers of bone formation and resorption to identify fast "losers" and to monitor therapy.
- Ongoing prospective trials of large populations to identify risk factors and treatment effects. These include the Study of Osteoporotic Fractures, a prospective observational study of the risk factors for fractures, and the Women's Health Initiative, a large clinical trial testing the effect of hormone replacement therapy and diet on cardiovascular, cancer (breast and colon), and fracture outcomes.
- Diagnosis of osteoporosis and the assessment of fracture risk including (a) a new generation of bone mass measurement devices: dual-energy x-ray absorptiometry (DXA), ultrasound, quantitative computed tomography (QCT), and peripheral computed tomography; (b) the World Health Organization criteria for evaluating results of bone mineral density tests to diagnose osteopenia and osteoporosis; and (c) development of more diverse normative databases, particularly the availability of the NHANES bone mineral density data.
- New pharmaceutical agents for prevention and treatment — women now have choices other than HRT, including bisphosphonates, selective estrogen receptor molecules, nasal calcitonin, and others on the horizon.
- Recognition that many new therapies for other diseases have long-term consequences on bone.
- Better understanding of the role of falls in fracture. Preventing falls and reducing the impact energy of a fall can prevent hip fractures in the elderly.

Orthopaedics and Physical Activity

Total joint replacements have provided enormous relief from pain and disability for individuals with end-stage joint disease. Similarly, improved fracture fixation techniques and surgical techniques for soft tissue injuries have returned people to work and sport activity quickly. Following are some examples of advances in our knowledge and treatment of orthopaedic problems.

- Development of arthroscopic (less invasive) procedures.
- Bioengineering — repair of soft tissue and cartilage with biological materials.
- Distal radius fractures: (a) better recognition of the importance to patients of post-injury function and (b) more aggressive treatment to improve results.
- Recognition of carpal tunnel syndrome and some of the factors that may predispose to this condition.
- Improved technology and techniques for surgical repair for spinal deformity reducing the need for casting.
- Better recognition of the progression of osteoarthritis of the hand, which is much more common in women.

GAPS IN KNOWLEDGE

The advances of the last several years encourage renewed focus on the gender-related issues of bone and musculoskeletal disorders.

Arthritis and Disability

Gender Differences. Research is needed to better understand why arthritis is more common in women. The most significant gap in research about arthritis in women is the role of genetic makeup and hormones in a woman's autoimmune system and in the progression of inflammatory arthritis. In addition, greater scrutiny is warranted for gender-related structural and biomechanical factors that predispose to osteoarthritis in women.

Biological and Mechanical Factors. Biological and mechanical factors that influence the onset and progression of arthritis should be studied, including (a) biologically and socially indicated gender differences; (b) mechanisms of tissue destruction, assessment, intervention, and treatment; and (c) putative prevention or amelioration of symptoms. Such investigations should encompass the cellular, tissue, and organ levels, include all joint components, and use the latest technological advances in assessment.

Repair Processes. Research should address the possible early biological repair process in osteoarthritis with attention to the role of growth factors, among others, that would prevent late changes that lead to joint replacement. Prospective clinical trials should be conducted for various surgical procedures designed to stimulate repair of osteoarthritic joints.

Risk Factors. Modifiable risk factors should be a target for research initiatives. What is the relationship of weight, diet, and lifestyle to the development of osteoarthritis? The environmental impact on development of osteoarthritis should be investigated as well.

Racial Differences. Racial as well as socioeconomic differences in osteoarthritis prevalence need study. Poor socioeconomic status and female gender lead to late treatment, which in turn increases the morbidity of arthritis.

Quality-of-Life Issues. Research must be done to develop outcome measures that have meaning for women with a chronic disease such as arthritis and must include a measurement of functional status and an assessment of their quality of life. Depression is common in women with arthritis, for example. These outcomes must be realistic and relevant to women's lives. The role of self-management in outcomes, methods to maintain patient function, and the art of long-term care are all important subjects for study. The techniques developed for self-efficacy in arthritis care and management could be applied to other chronic conditions such as low back pain.

> *". . . 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."*
>
> Lauri Tosi, M.D.
> American Academy of
> Orthopaedic Surgeons

Exercise. The role of exercise in arthritis pain management is important. Science should be applied to exercise prescriptions with regard to behavioral modification to enhance adoption and maintenance by patients.

Treatment and Rehabilitation. Federal support needs to be applied to answer questions about alternative and complementary therapies for arthritis. Patients spend a great deal of money on untested therapies. Several alternative therapies for arthritis have become popular, such as cartilage transplants, injectable lubricants (hyaluronic acid), acupuncture, and oral glucosamine and chondroitin sulfate, which are advertised as the "arthritis cure."

Arthritis of the Basilar Joint of the Thumb. The major thrust, to date, has been in treating the underlying condition rather than prevention or better understanding of the basis of the disorder. More research efforts need to be directed at understanding the pathophysiology: (a) initial causes of the disease (i.e., why is this joint so lax that it deteriorates?); (b) identification of women who could benefit from early (presymptomatic) treatment; and (c) continued examination of surgical treatment options, that is, better soft-tissue arthroplasties or total joint replacements so that rehabilitation is less difficult.

Other Arthritic Conditions. Less common arthritis conditions need further study. Chronic fibromyalgia is poorly diagnosed, misdiagnosed, and overdiagnosed. Musculoskeletal manifestations of Lyme disease can be better diagnosed and treated. Temporomandibular disorders in women during the reproductive years need investigation with regard to their central nervous system component.

Osteoporosis and Fractures

Peak Bone Mass Development. Factors that affect attainment of peak bone mass in young women need to be studied, including diet, exercise, hormonal, and environmental factors. Many young women are misinformed about their likelihood of developing osteoporosis. The effects of physical activity, calcium, delayed menarche and menstrual cycle irregularities, dieting and eating disorders, pregnancy, and smoking and alcohol consumption must be investigated. Recent retrospective studies indicate a positive correlation between milk consumption and calcium intake during adolescence and young adulthood and bone density in middle-aged and older women; thus, lifelong prospective studies need to be conducted to determine the effects of childhood calcium intake on peak bone mass. Questions relating to the role of skeletal osteopenia during the growth spurt in contributing to the rising incidence of bone fragility fractures during puberty need to be addressed. Finally, factors leading to development of peak bone mass in different sexes, races, and under different conditions require study.

Perimenopause. Women's age at onset of bone loss needs further study. Is there significant bone loss in the perimenopausal years? Bone "losers" need to be characterized and the causes determined. Do genetics or lifestyle contribute to early bone loss? Ways to maintain bone mass during the premenopausal years need to be identified. Should hormone replacement therapy start earlier to offset this?

Therapy with Pharmaceutical Agents and Hormones. The working group addressed a number of research needs in osteoporosis therapy:

- Effect of combination therapies on prevention and treatment. We need human research on the 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.

- Continued development of new selective estrogen receptor molecules (SERMs).

- Determination of optimum vitamin D status. Will optimizing vitamin D status reduce the fracture burden? How much vitamin D do typical adults normally produce in their own skin every day — summer and winter? What is the interaction between vitamin D status and dietary calcium? An inexpensive, reliable, and effective vitamin D preparation is needed. Studies should be conducted in minority groups to determine the extent of vitamin D deficiency and osteoporosis.

- Development of fluoride formulations that are safe and effective to manage patients who already have osteoporosis and to rebuild bone mass of individuals who are osteopenic but have not yet fractured.

- Clinical trials of current approved interventions on women of various races, ethnicity, ages, and estrogen status; explore the impact of ethnic differences in lactose intolerance on calcium balance and fracture risk.

- Development of anabolic agents to rebuild bone connectivity as well as density.

- Better understanding of long-term effects of new therapies on bone. Better understanding of the effects of drugs that stabilize bone mass by limiting bone resorption or enhancing bone formation.

- Pain and deformity management.

- Absolute and relative rates of bone formation and bone resorption may vary across individuals. Which treatment options are best for patients presenting with various combinations of these factors?

- Improved methods of bone fixation following osteoporotic fractures.

- Use of mechanical and electromagnetic forces in stimulating increased bone mass.

- Role of progesterone in skeletal development and maintenance.

- Development of growth factor strategies to enhance fracture repair.

Exercise. Research should be conducted to study the effects of exercise on bone and muscle health across the life span. Exercise may have a critical role in the development of peak bone mass by providing optimal mechanical stimulation. In addition, exercise in childhood and early adulthood may set up good behavioral patterns for life. Research is required to optimize behavioral strategies to encourage exercise. Research to determine how specific forms of exercise affect the risk of fracture would be welcome. The effects of exercise are likely to be site-specific and variety is likely to be necessary to optimize positive effects on bone quality. In addition, the role of exercise in attenuating bone loss and the role of physical fitness (strength, balance, coordination) in preventing falls and enabling women to remain active as they age should be studied.

Screening Methods. More reliable and inexpensive densitometry techniques for earlier intervention should be developed to improve patient quality of life. Normative bone density values for children are needed.

Racial, Ethnic, and Minority Groups. Several research areas need more attention. Why is osteoporosis more common in the female white and Asian populations, what triggers it, and what role do risk factors play in its progression? Ethnic (genetic) differences in bone mineralization metabolism (genetic, molecular) should be investigated. Bone density norms should be established for minority groups. Effectiveness of therapies should be ascertained for minority groups as well.

Postmenopausal Years. Relationships between osteoporosis and important diseases of postmenopausal women — breast cancer, depression, rheumatoid arthritis, stroke, and coronary heart disease — need to be explored. Also needing study are the variations in absolute and relative rates of bone formation and bone resorption across individuals. Research needs to determine which treatment options are best for patients presenting with various combinations of these rates. Another area of study is the impact of sarcopenia (muscle loss) on aging women and its relationship to falls.

Quality-of-Life Issues. Psychosocial and quality-of-life studies are needed, focusing on loss of family role, fear of falling, pain, and depression.

Fractures. Osteoporosis does not equally affect bones in a given individual or across individuals. Although the major fracture sites are at the wrist, the hip, and the spine, it is not clear why bones are affected differentially in a “systemic” disorder. Some of this may be related to the protective effect of physical activity and loading. Fall prevention and frailty leading to fractures are subjects that need more study. Attempts to identify and analyze the incidence and reasons for falls leading to osteoporotic fractures must be encouraged. Colles’ fracture should be studied as an indicator of osteoporosis and future hip fractures. Although the medical community has begun to recognize that stress fractures may be the first signs of premature osteoporosis, little has been done to establish guidelines for further evaluation, treatment, and prevention of these injuries. Methods of rehabilitation for frail elderly women who have suffered fractures need to be explored.

Compliance. Bone loss can be prevented. Why do women stop taking the medication that can prevent the loss? We need research on behavioral issues surrounding the widespread lack of compliance with well-known preventive and therapeutic measures in osteoporosis.

Prevention. Research is needed to understand how best to educate the public about prevention of osteoporosis and osteoporotic fractures through diet and exercise. Motivational factors for increasing calcium consumption and exercise in all ages (primary, secondary, and tertiary prevention issues) must be sought.

Basic Research. The working group listed the following basic research topics needing support:

- The biology of bone adaptation to mechanical loading, specifically the set point mechanism that senses loading and responds appropriately to control the skeletal adaptive response.
- Relationship between the mechanical stimulation of normal versus osteoporotic bone cells at the cell, tissue and organ level.
- Genetic influences for osteoporosis (receptors for collagen, calcium, estrogen, vitamin D, cytokines). Role of genetics in predisposing women to osteoporosis. Genetic studies on osteoporosis, including but not limited to studies of the genetic linkage to rates of bone loss.
- Role of testosterone in bone remodeling.
- Interaction of metabolic bone disease and depression.
- Role of smoking and alcohol consumption in bone homeostasis.
- Clinical application of biochemical markers.
- Importance of qualities other than quantity of bone in risk for osteoporotic fractures.
- Inefficient repair of bone tissue micro damage.
- Interaction between estrogens and cytokines, including research on estrogen action on bone, and identifying and isolating osteoclast precursor cells.
- The molecular basis for the cell-to-cell interaction that governs bone resorption and osteoblast activity in vivo. Effect of cell matrix interaction in osteoblast and osteoclast proliferation and differentiation.
- Cellular mechanism of the anabolic affects of parathyroid hormones, prostaglandins, and fluoride on bone.
- Transcriptional control of osteoblast differentiation.

Orthopaedics and Physical Activity

Cell Repair and Growth. We need to investigate the molecular signals that control repair and growth in cells of the musculoskeletal system. Whether women and men heal bone and cartilaginous tissues differently should be studied, including the effects of estrogen and other hormones on tissues at the cellular level and on ligament tissues. Other areas in need of study include stimulation of bone and wound healing, particularly the effect of ultrasound, and relaxants that cause changes in cartilage.

Synthetic Tissue Replacements. Biologically based repair procedures should be developed as alternatives to joint replacements. Synthetic replacements for muscle, soft tissue, and bone damaged beyond repair are needed as well.

Criteria for Surgical Repair. The development of arthroscopic surgical techniques should lead to less invasive surgeries and better outcomes. There is a need for studies that demonstrate the advantage of surgical repair on the natural history of the joint.

Feet. Further studies are needed about the relation of poorly fitting shoes to foot problems and deformities. Long-term wear of high heels is a concern. Another goal is to identify the best types of shoes (a) for children and adolescents for long-term foot health and (b) for the elderly so as to prevent falls. The long-term effects on the feet of enhanced participation in athletics and physical fitness among women should be investigated. What are the mechanisms for progressive foot deformity in women with aging. Finally, additional research is needed to better understand the effects of diabetes, rheumatoid arthritis, and pregnancy on the feet.

Stress Fractures. Stress fractures are common in the elderly and in athletes. The genetic implication and etiology of stress fractures need study. How do we improve training techniques to prevent stress fractures and overuse injuries in athletes? How do these injuries differ from stress fractures in the elderly?

Role of Immune System. We need to enhance our ability to manipulate the body's immune system to increase successful transplantation of donated bones and ligaments.

Total Joint Replacement. Total joint implants fail with increasing frequency after 10 to 15 years. Improved implant development is critical for the aging population. Research should investigate how wear particles from total joints affect implant failure. Women receive 60.5 percent of total hip replacements and 62.5 percent of total knee replacements. Gender differences in preference for surgical replacement need further scrutiny. The interaction of bone loss and implant loosening needs further study. Can agents that inhibit bone loss such as bisphosphonates prevent some implant loosening? What is the effect of postmenopausal estrogen use on the stability of joint replacement implants? Bone health after total joint replacement needs further study as well.

Shoulder Instability and Loss of Motion. Prevention and treatment of instability in the shoulder depends on increased knowledge about the biochemical and cellular pathways involved in the development of generalized ligamentous laxity. Researchers need to determine why there is female predominance of multidirectional instability. The role of estrogen balance in the pathophysiology of adhesive capsulitis (frozen shoulder) has yet to be determined. Research should focus on why the condition primarily affects women ages 40 to 60 — its relation to menopause, relation to hormones, and vasculitic etiology. Additional clinical and basic research is needed on the glenohumeral ligaments of the female shoulder and proper rehabilitation.

"Clinical studies are needed to acquire information about the natural history of [Paget's disease], the incidence of fracture, and other complications including the neuropsychiatric manifestations. Also, greater insight into the relationship between the hyperparathyroid process and postmenopausal bone loss is essential."

Charlene Waldman

Breast Cancer and Bone. Two recent prospective studies have indicated that women with high bone density are more likely to develop breast cancer than women with low bone density. One factor that may be common to both is the total lifetime exposure to endogenous estrogen — with high exposure to estrogen promoting optimal bone mass retention but potentially increasing the risk of breast cancer. These observations need clarification and extension. Trading healthy bones for healthy breasts presents a dilemma that must be resolved.

Breast cancer often metastasizes to bone. More research initiatives are needed in the area of orthopedic oncology, including research on complex interactions between tumor cells and host bone cells.

Chemotherapy, radiation, and surgery for breast cancer often result in bone and muscle loss; research into therapies that prevent these losses is needed. Continued progression of research initiatives in the area of biomechanics research revolving around design of implants as well as design of fracture fixation devices is critical to allow optimum recovery of function in patients who have developed fractures or significant metastatic lesions, particularly following breast cancer.

Development of endocrine therapies for treatment of metastatic lesions depends on a better understanding of bone cell metabolism and response of both normal bone cells and tumor cells to these therapies. It will be essential in the future to develop local delivery systems for chemotherapy and radiation sensitizers to improve local benefit while reducing systemic effects of these potentially dangerous but critical modalities. Research into the causes of bone pain and the cellular mechanism of transmission of bone pain will help to reduce and manage bone pain in women with metastatic breast cancer. Studies of the adverse effects of drugs used in treatment of metastatic breast cancer and ways to prevent such adverse effects in the treatment of metastatic breast cancer are critical to prevent injury and to improve function in patients with the disease.

Carpal Tunnel Syndrome. The pathophysiology of carpal tunnel and other repetitive stress syndromes is not clearly understood and deserves further study. This condition should be researched at the cellular and physiologic levels — for example, the reasons for flexor tenotynovium hypertrophy. The relationship of carpal tunnel syndrome to physical fitness and activity should be investigated and interventions developed and tested. Prevention of carpal tunnel syndrome must be a research priority.

Hyperparathyroidism. Greater insight into the relationship between hyperparathyroidism and postmenopausal bone loss is needed. Information is also needed on the course of patients who undergo parathyroid surgery as well as those who are followed conservatively. Additional studies will help to clarify currently accepted guidelines for surgery versus medical management for primary hyperparathyroidism. Also, research is needed to study possible medical therapies.

Wrist Fractures. Distal radius (wrist) fractures have been treated with benign neglect in the past. Orthopedists fail to see them as a warning sign of osteoporosis. Treatment is still imperfect despite SRS (a bone cement injected into the fracture site that enables activity right away). Areas to be improved include better prevention of falls, wider dissemination of treatment advances, and greater efforts to perform osteoporosis workups in wrist fracture patients to vigorously prevent other fractures.

Scoliosis. While mild scoliosis is equally prevalent in males and females, more severe spine curvature is eight times more common in adolescent females. Research is needed to determine the etiologic factors involved in the progression of mild to moderate and severe scoliosis in females. Outcome studies are needed to identify the best treatment strategies. Investigation into the association between scoliosis and osteoporosis is warranted.

Physical Activity. Definitions of exercise are framed around men’s activities. The type, intensity, duration, and frequency of physical activity that is important for musculoskeletal health in women must be researched. The role of physical activity in the development of bone, tendon, ligament, and muscle is poorly understood. What is the interrelationship of mechanical environment and cellular function? We know that increasing load increases bone mass, but what increases cartilage? In addition, we need to study the impact of musculoskeletal fitness on comorbid disease progression.

Leisure-time exercise needs to be compared with household or occupational activities. Is there a difference in hormonal response to recreational versus work-related exercise?

Clear standards for physical activity are needed for various populations. Populations with chronic diseases need special exercise programs. Differences in inactivity and maintenance of exercise in cultural and economic groups should be explained. Advanced, technically assistive, cost-effective devices should be developed for the elderly with musculoskeletal disorders. The role of physical activity in rehabilitation needs more emphasis to prevent disability and institutionalization of those who have fractured hips from falls, for example. Potential intervention with physical activity to prevent decline in these patients should be further investigated.

Muscle Biology. Marked losses of muscle mass occur with aging (and inactivity) and yet little research has focused on the role of muscle in impaired mobility, increased risk for falls and hip fractures, and inability to perform everyday activities. Women have lower muscle mass and higher body fat content than men throughout life. Moreover, aging can be associated with dramatic shifts in body composition, leading to increases in overall body fat and abdominal fat. Such changes in body fat and its distribution are thought to be important in the onset of disorders commonly noted in older persons, such as insulin insensitivity and cardiovascular disease. As the size of the aging population grows, there will be a greater need for ways to reduce or even prevent the physical disabilities and metabolic consequences of decreased muscle mass and increased body fat. Both clinical and animal findings to date indicate that the underlying pathophysiology of physical disabilities and metabolic disorders may range from a sedentary lifestyle to age-related changes in the intrinsic properties of skeletal muscle. To develop optimal intervention programs, further research will be needed on the qualitative and quantitative relationships between changes in muscle and body composition and the functional and metabolic status of older women.

Sports Medicine. The “female athlete triad” is a term describing a condition common in female athletes that combines premature osteoporosis, menstrual irregularity, and eating disorders. This condition needs investigation, including contributing factors such as nutrition, energy expenditure, and stress. Research and education are needed to better train coaches and doctors to recognize the female athlete at risk for developing female athlete triad to enable appropriate modifications to training programs. Exercise preparation and training for sports are based on a male model, and current practices may predispose women to injury. Do women predispose to injuries during different phases of the menstrual cycle? Women athletes need appropriate muscular techniques and endurance throughout life to prevent sports injuries.

The causes of anterior cruciate ligament (ACL) injury and other common injuries of female athletes should be identified to enable development of adequate prevention programs. More research to delineate the physiological differences between female and male knee stabilization patterns during sports movements is critical. It is unknown whether cellular biochemical or physiologic responses to injury and tissue repair differ in men and women, and further research is critical in this area. Because estrogen has a direct effect on collagen synthesis and because neuromuscular performance is also known to vary during the menstrual cycle, it is logical to question whether the female menstrual cycle has an effect on injury rates.

Continued research on devices and surgical technique improvements will enhance patient care and facilitate an earlier return to function. In addition, the basis for gender differences in treatment should be explored: what is effective, why outcomes in men and women differ when receiving the same treatment, and what mechanisms underlie these differences.

Data Needs and Information Dissemination

In discussing and developing the agenda of research gaps and opportunities in bone and musculoskeletal disorders, the working group identified data collection as one overarching area of need. So that we may understand the impact of research initiatives on the specific diseases and conditions under discussion, we must have a way to track progress. To assess the prevalence and incidence of the bone and musculoskeletal conditions, the working group relied on data from national surveys like the National Health Interview Survey and the National Health and Nutrition Examination Survey. These and other national data sets need to expand the questions related to the musculoskeletal system.

Information on Prevalence and Treatment Outcomes. The Behavior Risk Factor Surveillance Survey administered through the CDC's National Center for Chronic Disease Prevention could add arthritis and musculoskeletal conditions to its core set of questions. Comparative arthritis data are needed, including a better understanding of arthritis risk factors, the impact of behavior changes on pain and disability, and the effectiveness of interventions. Better estimates of the economic consequences of arthritis in women — particularly indirect and intangible costs — should be developed. Other prevalence and treatment outcome data are lacking, including:

- Normative range of musculoskeletal changes in aging.
- Impact of socioeconomic status on musculoskeletal diseases.
- Environmental agents' effect on organ system development, long-term consequences.
- Clinically useful outcome measures (not just of accuracy) that acknowledge the validity of patient measures for functional outcomes.
- Effects of cancer and its treatment on muscle mass and bone; how to counteract.
- Effects of transplants on muscle mass and bone; how to counteract.
- Musculoskeletal injuries caused by violence so as to improve recognition by care givers.

Sports Injury Surveillance. With exercise increasingly recommended to prevent or improve a myriad of health problems, doctors are seeing new and worrisome injury patterns. However, there are no data on the prevalence of such injuries that could be used to study their connection to long-term disability. To prevent activity-related injuries, minimize their effect, and ensure a safe participation environment for physically active females, a nationwide injury surveillance system designed to document, track, and monitor the injury and illness patterns of this population must be established. Only when injury and illness patterns are identified can appropriate preventive interventions be developed and implemented. Information relating to injury and illness patterns, prevention, and management is essential to encouraging females to become physically active and to remain committed to a physically active lifestyle.

Instruments to Measure Physical Activity and Outcome. Instruments to measure physical activity in women from childhood through later adulthood should be developed and validated and related to women's functional and health outcomes. Good performance measures are lacking for the musculoskeletal system; such measures should be highly scaled. An understanding of the relationship between structure, function, and ultimate outcome will strengthen prevention efforts. The rehabilitation field needs instruments — preferably questionnaires or personal interviews — for measuring physical activity in disabled women. These instruments should address specific disabilities and correlate multiple objective and subjective factors.[17]

Tracking and Improving Compliance. Methods are needed for tracking and improving compliance with effective therapies. Patient compliance with therapies for bone and musculoskeletal problems is poor, even though patients suffer from these problems universally and complain about them more than any other health problems. For example, women are more aware of osteoporosis than heart disease but do not take action to prevent or counteract it. Investigators should identify effective ways to encourage women to increase exercise throughout the life span. How do we teach physicians to encourage their patients to make lifestyle changes? How can medical prescriptions be incorporated into daily life? The role of the patient in self-management of chronic bone and musculoskeletal conditions must be better described. For example, cancer patients and transplant recipients need education and instruction on how to counteract the adverse effects on muscle mass and bone.

RESEARCH RECOMMENDATIONS

The working group made the following recommendations at the Beyond Hunt Valley meeting in November 1997.

Arthritis

- Investigate the greater prevalence of arthritis in women and its triggers.
- Explore the biological and mechanical factors that influence the progression of arthritis.
- Examine biological repair processes and bioengineering 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, 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 (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 — does leisure time exercise play 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.

- 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.

REFERENCES

1 FDA Consumer, March 1996.

2 National Center for Health Statistics, National Health Interview Survey, National Heart, Lung, and Blood Institute, NHLBI FY1996 Fact Book.

3 Ettinger WH, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, Shumaker S, Berry MJ, O'Toole M, Monu J, Craven T. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). *JAMA* 1997;227:25-31.

4 Callahan LF, Rao J, Boutaugh M. Arthritis and women's health: prevalence, impact, and prevention. *Am J Prev Med* 1996;12(5):401-9.

5 Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep* 1995 May 5;44(17):329-34.

6 Karlson EW, Daltroy LH, Liang MH, Eaton HE, Katz JN. Gender differences in patient preferences may underlie differential utilization of elective surgery. *Am J Med* 1997;102(6):524-30.

7 Guralnik JM, Leveille SG, Hirsch R, Ferrucci L, Fried LP. The impact of disability in older women. *J Am Med Womens Assoc* 1997;52(3):113-20.

8 Looker AC, Orwoll ES, Johnston CC Jr, Lindsay RL, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP. Prevalence of low femoral bone density in older U.S. adults from NHANES III. *J Bone Miner Res* 1997 Nov;12(11):1761-8.

9 Black DM. Why elderly women should be screened and treated to prevent osteoporosis. *Am J Med* 1995 Feb 27;98(2A):67S-75S.

10 Ray NF, Chan JK, Thamer M, Melton LJ 3rd. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997 Jan;12(1):24-35.

11 Praemer A, Furner S, Rice D, editors. Musculoskeletal conditions in the United States. Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1992.

12 National Ambulatory Medical Care Survey.

13 Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey, 1991.

14 Nattiv A, Agostini R, Drinkwater B, Yeager KK. The female athlete triad. The inter-relatedness of disordered eating, amenorrhea, and osteoporosis. *Clin Sports Med* 1994 Apr;13(2):405-18.

15 Teitz CC, Hu SS, Arendt EA. The female athlete: Evaluation and treatment of sports-related problems. *J Am Acad Orthop Surg* 1997;5:87-96.

16 Standing Committee on the Scientific Evaluation of Dietary References, Institute of Medicine Report. Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Academy Press, 1997.

17 Gerber LH, Furst GP. Scoring methods and application of the activity record (ACTRE) for patients with musculoskeletal disorders. *Arthritis Care Res* 1992 Sep;5(3):151-6.

CANCER

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BACKGROUND

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.[1] Cancer is the leading cause of death for 35- to 74-year-old women. It is only after age 75 that heart diseases cause more deaths among women than cancer. Lung cancer continues to be the leading cause of cancer deaths for women, followed by breast and colorectal cancers. (This varies by geographic region; in some regions breast cancer is more common than lung cancer.)

Although outcomes after cancer diagnosis vary widely by age, ethnic background, and socioeconomic status and the survival data for women of color remain poorer than for white women, cancer mortality rates are falling for some populations of women. Long-term medical, sexual, reproductive, and psychological health need to be addressed in women who are cancer survivors.

Since 1991, enrollment in health maintenance organizations and other managed-care organizations has increased dramatically. Cancer patients now report difficulties in gaining referrals to the appropriate specialists, and in gaining access to NCI-sponsored cancer trials, treatment at NCI-designated cancer centers, and programs for cancer survivors. Changes in reimbursement limit investigator time and institutional monies available to support basic and clinical research. These changes, together with the persistence of a large portion of the population without health insurance, are having a major impact on basic and clinical cancer research and the quality of patient care.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

The major development since the conference held on women's health at Hunt Valley, Maryland, in 1991, is the decrease in the U.S. cancer mortality rates. For women, these advances represent primarily a decrease in mortality for breast and colorectal cancers among white women. Lung cancer mortality is decreasing in men, but increasing in women. Very little progress has been made to improve survival from gynecological tumors. In 1991, the Hunt Valley report projected that 22,500 women would die of ovarian, cervical, and uterine cancers. In 1997, this estimate has risen to 28,200 deaths.[1]

In the interval since Hunt Valley, major advances in genetics have improved the scientific understanding of cancer. Genes that account for 5 to 10 percent of cancers of the breast, endometrium, and ovary have been identified and sequenced. These percentages will probably increase as other genetic factors are identified. In addition, the genetic and signaling pathways responsible for the loss of normal cellular control mechanisms have improved our understanding of carcinogenesis in sporadic (or nonfamilial) cancers. Furthermore, similar changes in oncogenes and tumor suppressor genes occur across many cancers, suggesting common mechanisms of loss of cell cycle control.

Identification of specific genes that increase an individual's risk of cancer has occurred faster than protective legislation and advances in screening methods and therapy to improve long-term survival. Persons now identified as having a high risk of cancer face personal uncertainty and potential discrimination in health care coverage and employment. This lack of synchronism in research and medical legislation raises serious medical, social, ethical, and legal questions about screening for genetic abnormalities and demonstrates the need for improvements in screening and treatment.

Since 1991, the links between infection and some cancers have been extended. Associations between Epstein-Barr virus, Burkitt's lymphoma, and nasopharyngeal carcinomas; specific human papilloma viruses and cancers of the cervix and vulva; and hepatitis and hepatoma were already well established by 1991. However, recognition of the relationship of Helicobacter pylori to gastric cancer and of human herpes virus 8 (HHV8) to Kaposi's sarcoma is more recent. The observation that integration of the viral genome into the host DNA is necessary for carcinogenesis in some cancers suggests a mechanism for viral carcinogenesis in cancer etiology.

The idea that cancer may be a preventable disease is coming closer to reality. Recognition that genetics, diet, cigarette smoking, hormones, and the environment all influence cancer rates has led to small and large-scale cancer prevention trials. These have included evaluation of retinoids to prevent skin, cervical, esophageal, lung, and head and neck cancer, and tamoxifen to prevent breast cancer. The COMMIT and ASSIST studies in tobacco cessation have shown strategies at the community level to decrease tobacco use. Prevention strategies raise new questions regarding access to treatment, individual freedoms versus societal good, and acceptable side effects of treatments.

Since 1991, research studies such as the NIH's Postmenopausal Estrogen/Progestin Interventions Trial have shown the benefit of long-term hormone replacement therapy (HRT) in lowering the risk of cardiovascular disease.[2] HRT may decrease risks of osteoporosis, Alzheimer disease, and colon cancer. HRT has also been associated with increased risks of breast and endometrial cancer. Women and their health care providers must carefully weigh the benefits and risks of HRT based on currently available and emerging data.

Women's health researchers now stress the importance of examining gender, socioeconomic, and racial and ethnic differences when studying cancer incidence, mortality, and cancer-related preventive health practices. This information has broadened our understanding of both similarities and differences in subgroups in the population. For example, compared with men, women develop lung cancer after lower doses and shorter intervals of cigarette smoking. Since the Hunt Valley conference, differences in metabolism that affect responses to carcinogens and to treatment have been observed between women and men, between different racial and ethnic groups, and between older and younger individuals. Research has begun to describe the interplay of genetic, environmental, socioeconomic, and other factors that determine whether an individual will develop cancer and whether that cancer will respond to treatment.

In the years since Hunt Valley, consumer advocates have become more involved in cancer research. These groups have focused the nation's attention on critical cancer issues, including prevention, education, screening, treatment, and survivorship, as well as the importance of laboratory research. They have supported their priorities for research and have become involved in the design and conduct of prevention, screening, and treatment trials. Consumer groups and cancer investigators have also strengthened research on quality-of-life issues for those undergoing treatment and for survivors who have completed treatment. The National Cancer Institute (NCI) has established a Consumer Liaison Group in the Office of the Director and the Office of Cancer Survivorship in the Division of Cancer Control and Population Science.

In this report, the working group addresses remaining research priorities for the most common malignancies affecting women, including cancers of the lung, breast, colorectum, ovary, cervix, and uterine corpus.

GAPS IN KNOWLEDGE

Lung Cancer

In 1997, the American Cancer Society estimated, from the NCI's Surveillance, Epidemiology, and End Results (SEER) data, that 83,200 women were diagnosed with cancer of the respiratory system, and that 67,430 women died of respiratory cancer.[3] These deaths represent 25 percent of all cancer deaths among women and an increase of more than 16,000 deaths since 1991.

The incidence of lung cancer varies by gender and ethnicity and follows historical patterns of smoking. In 1994, the incidence of lung cancer per 100,000 individuals was 43 for white women, compared with 48 for black women, 73 for white men, and 111 for black men. Alaska Natives and Native Hawaiian women have the highest lung cancer mortality rates among racial groups, 45 and 44 per 100,000 respectively, compared with 33 per 100,000 for black and white women.[4] Among women and also men, the number of adenocarcinomas of the lung, a type of lung cancer more weakly associated with tobacco smoke than other histologic types, is rising.

In 1987, lung cancer first surpassed breast cancer as the leading cause of cancer deaths in women. More than 80 percent of lung cancer cases are directly attributable to cigarettes.[5,6] Smoking is now the number one cancer killer of American women, causing not only lung cancer but also cancers of the mouth, larynx, pancreas, bladder, kidney, cervix, and vulva. The human toll extends beyond the smoker.[7] It is estimated that 53,000 people die annually from environmental tobacco smoke, about half of them from exposure in the workplace. This issue is of particular concern to women, since resistance to banning smoking in the workplace is particularly strong in restaurants and bars where approximately 80 percent of waitstaff and 53 percent of bartenders are women. A recent study reported that waiters and waitresses have a 50 to 90 percent higher risk of lung cancer than other workers after controlling for active smoking and socioeconomic status.[7]

Recent molecular and epidemiological evidence shows significant gender differences and adds to the overwhelming data linking tobacco smoke with cancer causation. Smokers whose parents had lung cancer are twice as likely to develop lung cancer as the general population of smokers. In addition, men and women appear to respond differently to the carcinogens found in tobacco smoke. Compared with men, women develop lung cancer after smoking fewer cigarettes over a shorter time. Women may be more sensitive than men to nicotine and have slower metabolic clearance of nicotine. Another major gender difference is the use of cigarettes among women and girls for weight control.[5]

Smoking rates, which had previously been falling among adults, are now increasing. In 1994, 48 million adults reported smoking, compared with 46 million in 1993. Twenty-eight percent of men and 23 percent of women smoke. Ninety percent of all smokers report that they began smoking during their teens. Regular smoking among high school students, especially among white girls, is at an all-time high. American Indian youth have an even higher prevalence of cigarette use. Almost three-quarters (71 percent) of high school students have tried cigarettes.[8]

Percentage of High-School Students Who Were Smokers in the Previous Month, 1990-1994[9]

	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

The key to preventing lung cancer in U.S. women is to prevent initiation of smoking among adolescents and young adults. Optimizing prevention efforts targeted to children and adolescents is an urgent priority. Education about the health hazards of smoking beginning in early childhood and repeated into adolescence may be effective. Recognition of the role of peer pressure, self esteem issues, and the urge to rebel against adult authority must be incorporated into educational strategies.

Antismoking messages must counteract the protobacco messages advanced by cigarette advertising and promotions. Tobacco industry advertising that connects smoking with slimness, social activity, and popularity exerts a powerful impact on adolescent girls. Advertising campaigns aimed at young black and Latina women may have sparked recent increased usage among these groups. Such advertising must be challenged in the public forum.

To be effective, antismoking messages must be tailored to a variety of ethnic, racial, and socioeconomic groups. Research to find the optimal form of oppositional advertising must consider the many influences on young women who smoke, including peer groups, school, work site, and the community institutions in which women participate.

Extensive research on smoking cessation will be needed to help the many people who are now addicted to tobacco or become addicted despite our efforts to prevent smoking initiation. Clinical and research findings suggest that social support can play a significant role in successful smoking cessation, particularly for women. Additional research on the role of social support in smoking cessation is recommended.

Public policy initiatives may offer the greatest promise of any strategy for reducing the number of deaths and diseases due to smoking. Three critical public policy areas are the provision of smoke-free environments, the prevention of youth access, and the outright banning of tobacco industry advertising that targets youth and minorities.[7] Legislation such as the recent Food and Drug Administration regulations designed to reduce youth smoking may be an effective deterrent to reducing teen smoking. Litigation, such as medical cost reimbursement suits,[10] also may help by providing market-driven disincentives, that is, by raising the cost of purchasing cigarettes.

Basic research to address genetic and metabolic risks for lung cancer and to support cessation approaches for vulnerable populations remains important. About 70 percent of women who are currently smokers would like to quit. This figure is true across all ethnic groups (American Indians/Alaska Natives – 70 percent, Asian Americans/Pacific Islanders – 65.3 percent, Blacks – 74.9 percent, Hispanics – 79.3 percent, Whites – 72.4 percent).[9] Nicotine, a stimulant that can improve negative emotions such as depression may be particularly important to women, who have higher rates of depression and, as a group, take more mood-modifying medications than do men. Research should examine the interactions among gender, mood modulation, and smoking patterns and their relevance to prevention and cessation interventions.

Development of reliable biomarkers and imaging technologies are urgently needed to improve early detection of lung cancer. Identification of effective screening, followed by large-scale screening approaches for people at risk could have a major impact on death rates. The National Cancer Institute is supporting a randomized study of screening with chest radiography as part of the Prostate, Lung, Colon, and Ovarian Cancer screening trial (PLCO). This study will enroll 73,000 women and 73,000 men. Special efforts are underway to ensure that Hispanic and black women and men have adequate representation on this trial.

Identification of accurate biomarkers and surrogate endpoints may also simplify prevention studies. Preclinical studies to identify potential chemopreventive agents, followed by Phase I, II, and III chemopreventive trials, are also needed to prevent lung cancer. Diets rich in fruits and vegetables appear to lower the risk of lung cancer up to 50 percent. Some evidence suggests that vitamins A, C, and E, and selenium, and other micronutrients may be beneficial in preventing lung cancer. Epidemiology studies of lung cancer may help identify other potential chemopreventive agents and the etiologic agents for pulmonary adenocarcinomas in nonsmokers.

Advances in cancer treatment are urgently needed, because only 13 percent of individuals with lung cancer are alive 5 years after diagnosis.[3] The timely completion of randomized clinical trials evaluating surgery, chemotherapy, and radiation therapy are critical to progress in the treatment of lung cancer.

Breast Cancer

The incidence of breast cancer per 100,000 women rose dramatically between 1980 and 1987, from 85 to 113, but it leveled in 1994 with a rate of 109 per 100,000.[3] The American Cancer Society, based on SEER data, estimated that, in 1997, 180,200 women would be diagnosed with breast cancer, and 43,900 would die of the disease. White women have the highest incidence of breast cancer, followed by Native Hawaiian women. For white females the death rate has fallen slightly, from 28 per 100,000 women in 1985 to 26 per 100,000 in 1994. For black women, however, the death rate has risen, from 26 to 31 per 100,000 women, between 1973 and 1994.[4] Known risk factors include advancing age, family history, early age at onset of menarche, late age at onset of menopause, and first full-term pregnancy after age 30.

Since the Hunt Valley report, NIH has directed substantial effort to breast cancer research, including mammography. In 1994, breast cancer accounted for 20 percent of all NIH research expenditures for women's health issues.[11] In addition, substantial funding for breast cancer research and screening has been provided by the Centers for Disease Control and Prevention and the Department of Defense. This research and privately supported research may be beginning to make a difference. Breast cancer survivors now constitute the largest single group of cancer survivors. Many of them are young, with growing families and productive lives. The many issues of cancer survivorship have particular resonance for them.

Advances in chemotherapy for breast cancer are noteworthy. Fifty-six new drugs for the treatment of breast cancer are in various stages of development, from Phase I through submitted new drug applications.[12] Several new drugs are based on innovative mechanisms. Thus, quality-of-life issues, including secondary malignancies and second primary malignancies, hormone administration to breast cancer survivors, and effects of early cancer on normal aging processes, will become increasingly important.

Important areas to study for breast cancer survivors include ways to optimize quality of life after treatment, to restore a positive body image and sexuality, and to maintain fertility after adjuvant chemotherapy. Do estrogen replacement therapy, birth control pills, or even pregnancy after breast cancer treatment adversely affect outcome? What can be done to relieve the hot flashes, mood swings, and night sweats of early menopause and to prevent osteoporosis and heart disease associated with long-term estrogen depletion?

Questions surrounding the safety of long-term HRT affect all midlife women, not just breast cancer survivors. On one hand, women are urged to take long-term hormone replacement for its benefits against cardiovascular disease, osteoporosis, and possibly even Alzheimer disease. On the other hand, a recent analysis of the large epidemiological study, the Nurses' Health Study, shows an increased risk of breast cancer associated with long-term HRT.[13] New medications with the benefits of HRT and fewer side effects are urgently needed. Pharmaceutical companies are developing "designer estrogen" or "selective estrogen receptor modulators." One, raloxifene, recently received FDA approval.[12] Such research needs to be encouraged. Epidemiological studies that determine what aspect of living in Western societies increases the rate of breast cancer in Asian women in the United States are also needed. If changes in diet are a factor, the evaluation of plant-based phytoestrogens, more prevalent in the Asian diet, could prove useful.

Genetic loci responsible for some cases of familial breast and ovarian cancer have been identified. Tests for two of the most common genetic loci, BRCA1 and BRCA2, are now commercially available. Assuming a BRCA1 or BRCA2 mutation is found, however, the medical community is still profoundly uncertain about the appropriate medical care for these women. How should these women be screened, counseled, and followed? Under what conditions are these tests most helpful and least harmful to women and their families? Models for counseling need to be developed, and legislation that prevents employment and insurance discrimination is necessary.

For women who carry mutations in BRCA1 or BRCA2, until recently research data were not available to evaluate prevention or early detection measures that might reduce morbidity and mortality.[14] Some women have opted for measures such as prophylactic mastectomy. The Breast Cancer Prevention Trial evaluated the administration of a 5-year course of tamoxifen to women at high risk for breast cancer. The important trial, which recruited 13,000 women, was closed prematurely when a 45 percent reduction in breast cancer incidence associated with tamoxifen was observed. Phase I, II, and III trials of new preventive strategies, which are particularly important for women at high risk for breast cancer, should continue. Issues of quality of life and adherence in prevention studies also need scrutiny.

A better understanding of the etiology of breast cancer is critical to developing new prevention, diagnosis, and treatment strategies. Research priorities include the basic biology of the breast, mechanisms of carcinogenesis, and genetic, hormonal, and environmental factors. As the development of breast cancer is better understood, detection of neoplastic lesions at greatest risk for progression to cancer may become more accurate, and the significance and management of these precancerous lesions better understood. New imaging modalities may help to identify persons at high risk for developing breast cancer and identify smaller cancers before metastasis occurs.

Meanwhile, data continue to support the use of routine screening mammography for detecting breast cancer at an early stage. Between 1983 and 1994, the detection of in situ cancer rose by 107 percent in white women under age 50, 166 percent in black women under age 50, 220 percent in white women age 50 years or older, and 232 percent in black women age 50 or older. Studies of minimally invasive and alternative conservative therapies are needed to avoid overtreatment of precancerous and in situ lesions.

Although survival rates have improved overall, fewer black women diagnosed with breast cancer survive than white women. Between 1986 and 1993, 5-year survival rates were 71 percent for black women but 86 percent for white women. A recent study suggests that 75 percent of the difference in survival between black and white women may be explained by late diagnosis, tumor characteristics, concomitant illness, obesity, and social and demographic factors.[15]

The most recent NCI, ACS, and ACR screening guidelines recommend that all women aged 40 years or older obtain mammograms every 1 to 2 years. Data from the 1994 Health Interview Survey show that 56 percent of black and white women aged 50 years or older had a mammogram during the previous 2 years, as well as 53 percent of American Indians, 50 percent of Latinas, and 46 percent of Asian-Pacific Islanders. Poverty and the lack of insurance are the chief factors associated with low utilization. Disabled women also have low rates of breast self-examination and mammography. Improved access to screening and education of patients and health care providers to increase utilization rates for all ages and all racial and ethnic groups is a major priority for lowering breast cancer rates. Psychosocial and behavioral research is needed to identify culturally acceptable interventions to increase use of screening, diagnosis, treatment, clinical trials, and supportive care among medically underserved women.

Treatment issues remain important. Development of refined molecular diagnostics may identify women with breast cancer who may be safely treated with surgery alone, and who would benefit from adjuvant chemotherapy or radiotherapy. The role of sentinel node assessment needs to be evaluated. The effectiveness of tamoxifen in reducing the risk of recurrent or contralateral breast cancer supports further investigation of endocrine therapy for both prevention and treatment. The efficacy of high-dose chemotherapy coupled with hematologic support (stem cell transplant) is currently under evaluation in randomized, controlled clinical trials. New treatment approaches using monoclonal antibodies, tumor vaccines, and angiogenesis inhibitors are in Phase I and II studies. New methodology is required to assess the roles of these agents. Long-term strategies such as weight control, physical activity, and antioxidants should be considered to prevent first or second primary cancers or as adjuvant therapy to prevent cancer recurrence.

Colorectal Cancer

In 1997, an estimated 65,900 women were diagnosed with cancer of the colon or rectum, and 24,300 died of the disease.[1] The highest incidence is among Alaska Native women (52 per 100,000 women), followed by black women (46 per 100,000), Japanese women (29 per 100,000), and white women (27 per 100,000).[4] Although screening tests for colorectal cancer are readily available, recent reports show that many women are not being screened.[16] Prevention efforts must include new strategies to educate both women and their physicians about the benefits of screening women for colon cancer.

Acceptable screening strategies include fecal occult blood testing, sigmoidoscopy, colonoscopy, and barium enema. For those at normal risk, screening should begin at age 50. Individuals at increased risk for colon cancer should begin screening earlier. Further studies are needed to determine the optimal combination of these tests and how best to integrate them into standard clinical practice.[16]

Since the Hunt Valley conference, knowledge about factors that increase and decrease the risk of colon cancer has expanded. Familial adenomatous polyposis coli and hereditary nonpolyposis colon cancer (Lynch II) are the most common familial syndromes identified with colon cancer. Multiple genetic loci for these syndromes have now been identified. Other factors have been associated with a decrease in colon cancer risk, including HRT, nonsteroidal anti-inflammatory agents, exercise, and a low-calorie, low-fat, high-fiber diet. Prospective randomized prevention trials are evaluating these and other agents such as selenium and calcium.

Since the Hunt Valley meeting, several new drugs have shown activity against colon cancer. Many treatment-related questions remain unanswered, however. After primary surgery for stage III colon cancer, the combination of 5FU and leucovorin or levamisole is effective in reducing recurrences and death from colon cancer. Women appear to be more sensitive to 5FU toxicity than men. The mechanism leading to this toxicity needs to be identified and preventive strategies developed. Such strategies might include new chemotherapeutic agents and combinations to improve cure rates and reduce toxicity from adjuvant therapy.

A current intergroup Phase III trial is evaluating laparoscopic surgery in early colon cancer. Neoadjuvant chemoradiation has been effective in preserving normal rectal sphincter function in patients with rectal cancer. Improvements in chemotherapy and radiation therapy may improve long-term survival in patients with locally advanced rectal cancer. Patients with liver metastases can have long survival. Ongoing trials evaluating whether chemotherapy can convert nonresectable to resectable liver disease and prolong survival and whether chemotherapy after surgical resection of metastases is effective in prolonging survival should be continued.

Ovarian Cancer

Ovarian cancer accounts for about 4 percent of all cancers in women and 6.7 percent of all cancer deaths. In 1997, about 26,800 new cases of ovarian cancer were diagnosed in the United States, and 14,200 women died of ovarian cancer.[3] According to the Society of Gynecologic Oncologists, a relative survival rate of 90 percent can be achieved if ovarian cancer is diagnosed early. Unfortunately, in 70 percent of the women, ovarian cancer is detected at an advanced stage, which has an 80 percent fatality rate.[17] Identification of effective screening procedures is critical if survival is to be improved.

No screening test or combination of tests reliably diagnoses early ovarian cancer. Screening tests currently in use include serum CA-125, gynecologic examinations, and transvaginal ultrasound. At present, the sensitivity, specificity, and positive predictive value of these screening tests are inadequate to warrant their use in the general population, even when used together. Timely completion of large-scale Phase III screening trials under way in the United States (PLCO) and Europe will help evaluate the effectiveness of serum CA-125 and ultrasound. Other strategies to screen for ovarian cancer need to be developed and evaluated.

Known risk factors for ovarian cancer include abnormal BRCA1 and BRCA2; advancing age; nulliparity; Northern American or Northern European descent; a personal history of endometrial, colon, or breast cancer; and a family history of ovarian cancer. Protective factors include pregnancy, lactation, and the use of oral contraceptives. The role, if any, of infertility treatment, is poorly understood. A better understanding of the epidemiology, genetics, and biology of ovarian cancer is critical if advancements in treatment and prevention are to occur.

Prevention trials are problematic because the etiology of ovarian cancer is not well understood. Nonetheless, population-based data on the protective effect of birth control pills and preliminary data on retinoids suggest that prevention trials can be designed for high-risk individuals. Some women with BRCA1 or BRCA2 mutations are opting for prophylactic oophorectomy. Unfortunately, data on any effectiveness of this extremely invasive preventive method are few. Collection of such information represents an especially critical research need.

A 1997 study showed that only 14 percent of women with early-stage ovarian cancer received the surgical staging and treatment recommended by an NIH Consensus Panel.[18] In 40 percent of the cases, no pathologic grade was assigned to the cancers removed. New approaches to physician and consumer education, including psychosocial and behavioral research, are needed. Women should be informed of the need to have doctors with the appropriate expertise in gynecologic cancer surgery and pathology available at the time of surgery.

The clinical significance and relation of invasive carcinoma to “borderline” ovarian tumors are poorly understood. Some of these lesions may be overdiagnosed or overtreated. Research on their biology and clinical management is encouraged.

Intraperitoneal therapy, immunotherapy, radiotherapy, and high-dose chemotherapy with hematologic support are current research strategies. In patients with advanced disease, optimal debulking surgery followed by appropriate paclitaxel and platinum-based chemotherapy prolongs survival. The current Phase III trial of high-dose chemotherapy versus standard consolidation therapy should be promoted. Approaches to ovarian cancer are needed, including new chemotherapeutic agents more effective for women with recurrent or persistent ovarian cancer, with survival and quality of life as major ends.

Malignant germ cell tumors of the ovary, although rare in the general population, constitute most ovarian cancers in young women under 20 years of age. Recent therapeutic advances, which produce a high cure rate and can preserve fertility, should be extended.

Cervical Cancer

In 1997, the estimated number of American women with a new diagnosis of cervical cancer was 14,500; some 8,000 women were estimated to have died of the disease.[3] Since 1973, the incidence of cervical cancer has fallen 40 percent among white women and 60 percent among black women, and mortality has fallen 44 percent for white women and 52 percent for black women.[3] Worldwide, cervical cancer is second only to breast cancer in incidence and mortality from cancer in women. More than 471,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing and industrialized nations. In the United States, the highest incidence of cervical cancer is found among Vietnamese women (43 per 100,000), followed by Alaska Native women (16 per 100,000), Korean women (15 per 100,000) and black women (12 per 100,000). The mortality rate for black women (6.3 per 100,000) is more than twice that of white women (2.5 per 100,000).[4]

> *"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

Invasive cervical cancers and precursor lesions are firmly associated with specific strains of sexually transmitted human papilloma virus (HPV). The HPV genes E6 and E7 are integrated into the host genome and inactivate p53 and Rb gene products. The prevalence of infection decreases with increasing age, suggesting that most infections resolve over time through host immune responses.

Several cofactors, including cigarette smoking, may contribute to the development of cervical cancer. Immunosuppressed women, whether due to corticosteroids or HIV infection, are at increased risk for precursor cervical lesions and cervical cancer. The role of immune response in cervical cancer, including growth factors, cytokines, and humoral and cellular immunity, is still under study. Other factors under study include the use of oral contraceptives, number of live births, age at first intercourse, and coinfection with other sexually transmitted diseases.

The primary prevention of HPV infection is a research strategy to reduce the incidence of cervical cancer. Public health efforts to prevent HPV infection must focus educational efforts toward adolescents to encourage the delayed onset of sexual intercourse. Women of all ages and their health care providers must understand the strong causal link between the acquisition of HPV as a sexually transmitted disease and the development of cervical cancer. Development of effective vaginal microbiocides and a prophylactic

HPV vaccine are ultimately needed. Secondary preventive efforts must focus on developing effective antiviral agents to treat HPV, or to prevent transformation by E6/E7, and on therapeutic vaccines to prevent HPV progression.

Squamous cell cervical cancer is an ideal disease for screening because the typically long preclinical phase provides the opportunity for early detection. Use of Pap smears reduces morbidity and mortality from cervical cancer. However, optimal management of patients with certain precursor lesions, atypical cells of undetermined significance, and low-grade squamous intraepithelial lesions, is not established. A large NCI-sponsored clinical trial is currently evaluating the different ways to manage these patients. Research to improve current screening technology also should be encouraged. Liquid-based specimen collection methods and computer-aided screening of Pap smears, recently approved by the Food and Drug Administration, need further evaluation in routine primary screening and in subsequent screening.

Despite the recognized benefits of Pap smear screening, many American women have not been screened or are not being screened at regular intervals. One-half of the women with newly diagnosed invasive cervical carcinoma have never had a Pap smear, and another 10 percent have not had a Pap smear in the past 5 years. Inadequately screened populations include older women, the uninsured, the disabled, ethnic minorities (especially Latinas, certain Asian subgroups, and elderly black women), and poor women, particularly those in rural areas.

Data from the 1992 Health Interview Survey show that one-half of all women 60 years and older have not had a Pap smear in the past 3 years.[19] Older women are screened less frequently, although they have as many recent physician visits as younger women, showing the need to educate older women and their health care providers about the importance of Pap smear screening. Reasons for nonparticipation in screening should be identified and appropriate interventions taken.

New developments in therapy are needed. The development of more accurate imaging studies would improve the definition of the extent of disease at presentation and refine radiation therapy plans. Development in molecular diagnostic markers may help identify those patients with disease confined to the cervix who might benefit from adjuvant therapy after hysterectomy. The optimal adjuvant regimen for patients with disease confined to the pelvis, whether radiation, chemotherapy, or both, has not yet been defined. Clinical trials are also needed to define the role of prophylactic or therapeutic para-aortic node radiation.

Optimal management of HIV-positive women with precursor lesions and cervical cancer remains to be determined. Defining any impact of p53 status and HPV subtypes may allow customizing of treatment strategies. Dose-response relationship, time/dose relationship, improvements in technical instrumentation, and optimization of brachytherapy techniques should be studied further. Predictive assays for tumor and normal tissue radiation sensitivity might allow individualization of radiation prescriptives. Strategies to reverse anemia and tissue hypoxia could improve the radiation responsiveness of the tumor.

Adenocarcinoma and other nonsquamous cervical carcinomas may be increasing in frequency, but the biology of their precursor lesions is poorly understood. Studies are needed to define the epidemiology, biology, natural history, and treatment of nonsquamous cancers and their precursors. Clinical trials are needed to define the benefit of neoadjuvant chemotherapy.

Uterine Cancer

Based on SEER data, 34,900 women were diagnosed with cancer of the uterus in 1997, and 6,000 women died of the disease.[1] The highest incidence rates for uterine cancer are among Native Hawaiian and white women (24 and 22 per 100,000, respectively). Most uterine cancers arise in the endometrial lining of the uterus (endometrial adenocarcinoma); the remainder form in the muscle wall of the uterus (uterine sarcomas and carcinosarcomas). Eighty percent of women with endometrial cancer develop abnormal vaginal bleeding, prompting early evaluation and treatment, usually hysterectomy.

Mortality from endometrial cancer is highest for Native Hawaiian women (9 per 100,000), followed by black women (6 per 100,000) and white women (3 per 100,000).[3] Although the time from the onset of symptoms to treatment appears similar for blacks and whites, the incidence of carcinomas associated with normal estrogen levels is higher among black women. These tumors are associated with a higher stage at diagnosis, a greater propensity to metastasis, and worse survival.

Risk factors for endometrial adenocarcinoma include anovulation, obesity, diabetes, Lynch II syndrome (hereditary nonpolyposis colon cancer), and estrogen unopposed by progesterone. Elevated estrogen levels may be endogenous (associated with obesity or certain ovarian tumors) or exogenous (from estrogen replacement therapy or tamoxifen). Protective factors include pregnancy, lactation, oral contraceptives, and progestins. Atypical endometrial hyperplasia is a known precursor lesion. The etiology of other histologic subtypes of endometrial cancer is unclear.

Research on the basic biology of endometrial cancers, uterine sarcomas, and carcinosarcomas is critical to develop more effective prevention and treatment programs. Clinical trials aimed at preventing endometrial cancer, particularly for obese or anovulatory women or women on tamoxifen, should be encouraged. The role of ultrasound in screening for endometrial cancer deserves further evaluation.

The association of many cases of endometrial cancer with elevated estrogen levels suggests that progestins or "designer estrogens" might be effective for treatment of atypical endometrial hyperplasia, thus sparing some women a hysterectomy. Ongoing clinical trials, evaluating the role of laparoscopic surgery, adjuvant radiotherapy, and chemotherapy, and also systemic chemotherapy for patients with metastatic disease, should be expanded.

RESEARCH RECOMMENDATIONS

Public Health Research Efforts

- Expand clinical trials evaluating single- and multimodality methods for smoking prevention and cessation.

- Expand trials evaluating the effects of exercise and weight control on cancer risk.

- Identify behavioral issues affecting adherence to recommended guidelines for cancer prevention, screening, and treatment.

- Evaluate the cumulative effects of environmental, exogenous, and endogenous estrogens (including DES, HRT, and oral contraceptives) on cancer risk and support continued epidemiologic research on previously identified cohorts.

- 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 on cancer treatment trials, as a high priority.

- Study how managed care has transformed the delivery and economics of health care and hampered access of cancer patients to optimal treatment, research studies, and cancer centers. Barriers to participation in cancer screening and prevention research programs and barriers that limit access to appropriate specialists, clinical trials, and treatment are unethical and shortsighted. All Americans must have access to optimal cancer treatment, and representation of women and minorities in clinical trials must be a high priority.

Biology and Genetics

- Consider how consumers and all concerned scientific disciplines must work together to facilitate the appropriate use of tissues for research. The ethical and legal implications of research on tissues stored in repositories must be carefully assessed, particularly issues involving consent and confidentiality.

- Define the molecular, genetic, cellular, and physiologic mechanisms associated with cancer initiation, development, and spread. The biology of premalignant lesions remains important. Identification of better biomarkers, including susceptibility to carcinogens, should help to further cancer prevention, early detection, and individualization of cancer treatment.

- Define the cancer risk associated with identified genetic mutations. The social, ethical, legal, and economic effects of the new commercially available genetic tests should be carefully studied, and appropriate counseling models, linked to genetic testing, should be developed.

- Develop medications with fewer side effects (efforts must be by the National Cancer Institute, the pharmaceutical industry, and the Food and Drug Administration).

Interventions

- Ensure adequate funding, efficient management, and timely completion of Phase I and II and randomized trials to examine new prevention and treatment strategies.

Prevention

- Identify effective screening tests for all cancers.

- Continue research on the role of steroid hormones in cancer prevention and causation and translate that knowledge into effective approaches to lower cancer risk.

- Design prevention and screening strategies appropriate to individuals at increased genetic risk for cancer.

- Develop chemoprevention strategies and vaccines against cancer.

- Enhance research efforts to communicate cancer risks and encourage health-promoting behavior in targeted populations.

- Give high priority to communicating the risks of smoking, preventing the initiation of smoking by children, and smoking cessation in children and adults already addicted as our only effective strategy against lung cancer.

- Communicate the risks of early sexual activity and of multiple sexual partners (or of sexual partners who have had multiple partners), and encourage appropriate behavioral changes to decrease the transmission of HPV and HIV to decrease the risk of cervical cancer and HIV-associated lymphoma and Kaposi's sarcoma.

Diagnostics

- Continue to develop and validate diagnostic and screening tests. New imaging algorithms that combine functional, metabolic, and anatomic imaging should be evaluated.

- Define optimal tests for the early detection of cancers and precancerous lesions. Tests should be inexpensive, highly sensitive and specific, and acceptable and available to women of all socioeconomic strata.

Therapy

- Ensure appropriate access to and adequate funding for randomized clinical trials to evaluate new methods and therapies.

- Review existing NIH mechanisms for large, multicenter clinical trials to increase efficiency and more rapid completion.

Outcomes

- Expand psychosocial, sociocultural, and behavioral research of the differing perceptions of risks and benefits between consumers and providers to design better prevention, screening, treatment, and outcomes interventions.

- Expand research on issues affecting cancer survivors, including quality of life, the most effective followup care, and reproduction and fertility outcomes after treatment. Studies of the long-term effects of chemotherapy and radiation are also important.

- Continue studies of gender differences in response to pain and analgesia.

Overarching Issues

- Consider the 41 million U.S. citizens without health insurance and the many more who are inadequately insured. Uninsured individuals often do not have access to prevention or screening programs. Precancerous lesions and early cancers may go undiagnosed and untreated. When patients seek medical care, treatment may no longer be effective. The medical research community must work with policymakers to ensure that adequate access to health care is available to all U.S. citizens and that health promotion becomes part of the activities of daily living.

- Continue research on enhancing adherence to health recommendations.

- Facilitate communication among investigators, clinicians, patients, and the public. Clinicians frequently define observations needing laboratory explanations, while promising laboratory developments need timely clinical evaluation.

- Facilitate evidence-based medicine, disseminate and integrate research results into practice patterns.

- Teach health care providers skills in communicating risks and in encouraging health-promoting behavior to their patients and the public.

- Develop, evaluate, and carry out educational and intervention programs that are sensitive to an individual's cultural and socioeconomic background.

- Collaborate with colleagues from other disciplines to expand and strengthen research into the benefits and risks of steroid hormones in women's health.

REFERENCES

1 Parker SL, Tong T, Bolton S, Wingo PA. Cancer statistics, 1997. *CA Cancer J Clinicians* 1997 (Jan/Feb);47(1):5-28.

2 Williams L. PEPI: reducing risk factors for heart disease. *NIH News & Features* (special issue) Fall 1997:14-15.

3 Ries LAG, Kosary CL, Hankey BF, et al. (eds). SEER Cancer Statistics Review, 1973-1994. NIH Pub. No. 97-2789. Bethesda, Md: National Cancer Institute, 1997.

4 Miller BA, Kolonel LN, Bernstein L, et al. (eds). Racial/ethnic patterns of cancer in the United States 1988-1992. NIH Pub. No. 96-4104. Bethesda, Md: National Cancer Institute, 1996.

5 Erickson M. Smoking and women: a major "disconnect." *JAMWA* 1996 Jan/Apr;51(1,2):7, 18.

6 Blumenthal SJ. Smoking v women's health: the challenge ahead. *JAMWA* 1996 Jan/Apr;51(1,2):8.

7 Scheg KE. Public policy: Effective treatment for tobacco disease. *JAMWA* 1996 Jan/Apr;51(1,2):52-6, 69.

8 Kann L, Warren C, Harris W, Collins J, Williams B, Ross J, Kolbe L. Youth risk behavior surveillance: United States, 1995. *MMWR Morb Mortal Wkly* Rep 1996;45(SS-4).

9 US Department of Health and Human Services. Tobacco use among U.S. racial/ethnic minority groups — African Americans, American Indians and Alaska natives, Asian Americans and Pacific Islanders, and Hispanics: a report of the Surgeon General. Atlanta, Georgia, US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease and Prevention and Health Promotion, Office on Smoking and Health, 1998.

10 Keldner GE Jr, Daynard RA. Tobacco litigation as a public health and cancer control strategy. *JAMWA* 1996 Jan/Apr;51(1, 2):57-62.

11 National Institutes of Health. NIH Support for Research on Women's Health Issues, Fiscal Years 1993-1994. NIH Pub. No. 98-3983. Bethesda, Md.: 1998; p. 30, 34.

12 New medicines in development for women. Washington, D.C.: Pharmaceutical Research Manufacturers Association, October 1997. 31 pp.

13 Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, Rosner B, Fuchs C, Hankinsen SE, Hunter DJ, Hennekens CH, Speizer FE. Post menopausal hormone therapy and mortality. *N Engl J Med* 1997; 336(25):1769-75.

14 Biesecker BB, Brody LC. Genetic susceptibility testing for breast and ovarian cancer: A progress report. *JAMWA* 1997 Winter;52(1):22-7.

15 Eley JW, Edwards B. Racial differences in survival from breast cancer. *JAMA* 1994;272:947-54.

16 Winawer SJ, Fletcher RH, Miller L, et al. Colorectal screening: clinical guidelines and rationale. *Gastroenterology* 1997;112:594-642.

17 Brooks MD. Summary of Testimony, Beyond Hunt Valley: Research on Women's Health for the 21st Century, November 17, 1997.

18 Munoz KA, Harlan LC, Trimble EL. Patterns of care for women with ovarian cancer in the United States. *J Clin Oncol* 1997;15:3408-15.

19 Brown CL. Screening patterns for cervical cancer: how best to reach the unscreened population. *Monogr Natl Cancer Inst* 1996;21:7-11.

CARDIOVASCULAR DISEASES

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BACKGROUND[1-3]

The 1991 Hunt Valley conference, "Opportunities for Research on Women's Health," acknowledged cardiovascular disease as a critical issue because of its prevalence, its importance as the leading cause of death among women, and its disproportionate impact on some racial and ethnic groups. The conference also highlighted differences between women and men with respect to research in cardiovascular disease and to the diagnosis, treatment, and management of symptomatic and asymptomatic disease.

During 1996 and 1997, three regional meetings sponsored by the Office of Research on Women's Health (ORWH) examined progress in research on cardiovascular diseases in women and articulated issues that needed further examination. The conclusion was that many important questions remain unanswered and that there is significant need for further research on the molecular, cellular, physiologic, and behavioral levels.

Cardiovascular disease is the number one killer in the United States. It kills more than 960,000 Americans each year, about 1 person every 33 seconds. The disease also is a major cause of disability. About 13.5 million Americans, including 6.6 million women and men under the age of 60, now live with the consequences of heart attack. Approximately 4 million Americans suffer from the consequences of stroke, the main cause of permanent disability in the United States. More than 900,000 of these stroke patients are under the age of 60.

Costs of cardiovascular disease are measured not only in terms of lives lost or affected but also in the dollars needed to diagnose, treat, and manage these diseases. More than one in four Americans has some form of cardiovascular disease, resulting in an estimated cost of $151 billion in 1996. These costs will continue to grow because the disease is being treated with expensive technology, not prevented. Moreover, even more cardiovascular disability will occur in the future because many people who have effective treatment for coronary artery disease and atherosclerosis between the ages of 40 and 60 may develop further cardiovascular disease later in life unless effective prevention methods are undertaken.

Cardiovascular disease is a well-known killer of men in the United States. What is less known is that heart disease has been the number one killer of women for nearly a century. Cardiovascular disease accounts for about 45 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. A postmenopausal woman is 10 times as likely to die from coronary artery disease as from breast cancer.

TABLE 1. Five Leading Causes of Death for Population Groups in the United States; 1995 Mortality, Final Data

WHITES BLACKS	HISPANICS ASIAN/PACIFIC ISLANDERS							
	Female	Male	Female	Male	Female	Male	Female	Male
Total cardiovascular disease	1	1	1	1				
Diseases of the heart and stroke					1	1	1	1
Cancer	2	2	2	2	2	2	2	2
Accidents	5	3	5	4*	4	3	3	3
HIV/AIDS			4	3		4		
Chronic obstructive pulmonary disease	3	4						5
Pneumonia/influenza	4	5			5		4	4
Homicide				4*		5		
Diabetes mellitus			3		3		5	

* Tied ranking.

Source: National Center for Health Statistics: Health, United States, 1995, and the American Heart Association

Women develop heart disease later in life than do men, but, at any age, heart attack is more deadly for women. 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 a year, whereas only about 27 percent of men die within a year. Among women who die suddenly of coronary heart disease, 64 percent have no previous symptoms, compared with 48 percent of men. For black women, the rates are even more ominous. The heart attack death rate for black women between the ages of 35 and 74 is about twice that of white women and three times that of women of other races.

Other cardiovascular diseases are also prevalent in women. For example, stroke, America's number three killer, killed about 158,000 people in 1995. Of these, 61 percent were women. Stroke kills twice as many women as does breast cancer. Less prevalent cardiovascular diseases include rheumatic heart disease, a disease that permanently damages the heart and its valves. Again, mortality from this disease is higher for women (69.9 percent of all deaths) than for men.

Dramatic progress has been achieved against heart disease in recent decades. Declines in overall death rates from heart disease have been spectacular, in both men and women. The rate in men is now about the same as at the turn of the century, and the rate in women is actually 37 percent lower than it was in 1900. Declines in younger age groups have been particularly significant.

However, the prevalence of heart attack and other cardiovascular diseases remains disturbingly high. Risk factors for heart disease in women and men have been known for years, but until recently, heart attack, stroke, and other cardiovascular diseases in women have not been recognized as a serious problem, particularly by women themselves. Significant gaps still exist in our knowledge of the normal development of the cardiovascular system in women; diagnosis, treatment, and management of cardiovascular disease; participation and retention of women in clinical research; and behavioral and lifestyle issues that are important in the development and prevention of cardiovascular disease. Analysis of these gaps provides potential fruitful avenues for research, many of which are described below.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Participants in the 1991 Hunt Valley conference made 14 recommendations dealing with cardiovascular function and disease. These focused primarily on psychosocial and clinical issues. In examining these recommendations and other issues relating to cardiovascular disease, participants at the 1996 and 1997 Beyond Hunt Valley meetings recognized that significant progress has been made since establishment of ORWH. ORWH has made important contributions to the following areas:

- Basic and applied biomedical research funding opportunities in women's health, especially those in cardiovascular research.
- Types of research (health services, cost effectiveness, population-based, community) pertaining to women's health.
- Participation of women, especially diverse groups of women, in clinical studies.
- Cardiovascular treatment regimens in women's health.
- Participation and advancement of women in science.
- Number and outreach capacity of professional societies related to women's health.
- Number of men active in women's health research.

TABLE 2. The Leading Causes of Death in Women, U.S., 1995

CAUSE OF DEATH	NUMBER	PERCENT
Heart Disease	374,849	32.9
Cancer	256,844	22.5
Stroke	96,428	8.5
COPD	48,961	4.3
Pneumonia/Influenza	45,136	4.0
Diabetes	33,130	2.0
Accidents	31,919	2.8
Alzheimer	13,607	1.2
Nephritis	12,287	1.1
Septicemia	11,974	1.1
All Other	214,038	18.8

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

> *"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

GAPS IN KNOWLEDGE

The Cardiovascular Diseases Working Group identified gaps in five key areas.

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

Significant gaps remain in our knowledge of the normal development and functioning of the cardiovascular system in females and of the numerous physiologic, environmental, and behavioral factors that influence the development of cardiovascular disease in women. For example, we need to know more about basic mechanisms of development of the cardiovascular system and how its functioning changes through adulthood into very old age. Other issues where information is needed include:

- Mitral and other valve function in normal populations over different ages.

TABLE 3. NHLBI Major CVD Clinical Trials – History

- First Trial in 1965
- 59 Trials from 1965 to 1997
  - 41 included both men and women
  - 4 included men only
  - 14 included women only

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

- Cardiovascular-related diseases during pregnancy. Pregnancy is a unique time and setting in which several important cardiovascular disease risk factors emerge, such as gestational diabetes, hypertension, and toxemia. Toxemia is an old disease, but despite some emerging knowledge, little is known about its etiology, prevention, and management. A greater understanding of the development of toxemia may shed light on the pathogenesis of cardiovascular disease more broadly.

- Gender differences in effects of medications traditionally prescribed to treat cardiovascular disease.

- Presymptomatic disease, including ways in which detection in asymptomatic women can be improved. Events that trigger the conversion of an asymptomatic, atherosclerotic lesion to symptomatic disease also need to be understood more fully.

Interest is growing in the role of the fetal environment in programming lifelong cardiovascular function. Suboptimal intrauterine conditions may cause a fetus to redistribute its resources to preserve the nutrient and oxygen supply for the brain. This may result in deprivations to the gut, liver, and carcass. If these processes continue, the baby will be born with a small liver and altered vasculature in many vital organs. Ongoing animal studies suggest that these changes predispose to high blood pressure and diabetes in later life.

In keeping with these animal studies, epidemiologic investigations in several countries now indicate that decreased birth weight and altered placental growth are associated with a higher incidence of cardiovascular disease in later life. A clearer understanding of this fetal "programming" is essential to preventing the adverse consequences of a suboptimal period of intrauterine development.

Molecular and Physiologic Mechanisms of Hormone Action in the Cardiovascular System

Given the important protective role that estrogen and other hormones appear to play in cardiovascular disease,[4] the rapidly developing molecular and cellular biology research techniques in this area, and the public debate over hormone replacement therapy, research in the molecular and physiologic mechanisms of hormone action in the cardiovascular system is a high priority.[5-7] We know there are two types of estrogen receptors and that estrogen can cause immediate (nongenomic) and long-term (genomic) effects on the vasculature.[8] However, there are gaps in our knowledge with respect to:

- The distribution of alpha and beta receptors throughout the vasculature, and how this distribution changes with age and disease.

- The cellular events triggered by activation of the two receptors.

- The ways in which manipulation (stimulation or inhibition) of the receptors affects progression of cardiovascular disease.

- The ways in which the relative expression of receptors might be used to identify women at risk for cardiovascular disease.

Cardiovascular Implications of Diabetes and Obesity

Diabetes and obesity and their relationship to the development of cardiovascular diseases pose many unanswered questions. Insulin-dependent diabetes mellitus is an important cause of premature cardiovascular disease among young women and men under 45 years of age. Cardiovascular disease is especially high among premenopausal women who have insulin-dependent diabetes mellitus and smoke cigarettes.

High body mass index, weight gain, and obesity are associated with increased blood pressure, elevated serum lipid levels, and development of type II diabetes, all of which are major risk factors for cardiovascular disease. Obesity is also an independent risk factor for cardiovascular disease. It affects outcomes following a cardiovascular disease event, as well as treatments for cardiovascular disease. Despite the attention directed to obesity, its causes and treatments are poorly understood. Gender differences in obesity also are not well understood. As a health problem, obesity continues unabated and its prevalence is increasing. Research is needed to more fully understand this condition as well as its relationship to cardiovascular disease.

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

An important gap in current knowledge involves prevention, detection, and management of cardiovascular disease in high-risk populations across socioeconomic levels. These populations, who disproportionately experience the effects of cardiovascular disease, include the elderly, women with disabilities, and racial and ethnic minority groups, such as blacks, Latinas, and American Indians.

TABLE 4. 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

Research guidelines now require that a diversity of subjects be represented in clinical studies. Studies directed specifically to these populations are important for two reasons:

- Only research protocols specifically designed to focus on these populations will ensure that sufficient numbers of high-risk women are studied to adequately answer the questions posed by a study.

- Women in high-risk groups may have distinguishing physiologic, behavioral, or environmental characteristics that place them at increased risk for cardiovascular disease and that increase the severity of complications following treatment or invasive procedures. Only through studies designed specifically for these population groups can these characteristics be elucidated and methods devised to address and ameliorate them.

Impact of Patient and Health Care Professional Behaviors on Cardiovascular Disease Development and Prevention in Women

Despite the fact that risk factors for cardiovascular disease have been well known for years, heart attack, stroke, and other cardiovascular diseases in women have not been recognized as a serious problem until recently, particularly by women themselves. Considerable information has been published for the general public and health care professional audiences on heart disease prevention and treatment, but it appears that these audiences are not acting on this information.

There are still significant gaps in knowledge about the determinants of behavior related to cardiovascular disease among patients, the public, health care professionals, and policy makers. Understanding these determinants more fully will permit development of more effective information materials, interventions, and support strategies.

The hope is that these will lead, in turn, to improved preventive behaviors and improved compliance with heart disease treatments.

RESEARCH RECOMMENDATIONS

The consensus of the Cardiovascular Diseases Working Group was that recommendations for cardiovascular disease research should center around the five identified major gaps in knowledge. Furthermore, the research conducted should encompass the biomedical spectrum from basic laboratory research to applied research, and from the individual to the public health level.

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

- Understand the ways in which suboptimal conditions in utero may lead to prenatal programming of cardiovascular function throughout life and the ways in which environmental influences can affect the expression of different genes to result in altered phenotype.
- 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 coactivator and corepressor 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, using molecular, cellular, and animal models, with an emphasis for the latter on transgenic models of estrogen receptor function.
- 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 hormone receptors in the vasculature and their gene targets, including progesterone receptors in the vasculature of women and men, and androgen receptors in the vasculature of women and men.

Cardiovascular Implications of Diabetes and Obesity

- Develop and evaluate strategies to improve the outcome of women with diabetes. This should span the spectrum from the molecular evaluation of insulin and glucose on endothelium and other aspects of blood vessel function to optimizing treatment for women with diabetes.

- Study the interactions between estrogen and diabetes on blood vessels and the heart, and the potential role of estrogen replacement therapy 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 that are important in the expression of a predisposition to obesity, and the development of approaches to alter the environment so as to avoid or address obesity.

- Study the roles that various stages of life play in placing women at increased risk for obesity and the development of ways to address these risks.

- Investigate modifiable societal and community factors that result in increased obesity and ways in which to change these so that they favorably affect the prevalence of obesity.

- Study effective therapeutic modalities to treat obesity, in particular the role of physical activity in reducing or preventing obesity.

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. In recruiting subjects, investigators should cast a broad geographic and socioeconomic net, and should incorporate these variables into the hypotheses to be studied. A critically important element of this area of research should be devising logistics and methods that will improve recruitment and retention into clinical studies of women in these high-risk groups.

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.

- 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, race, and ethnicity of patients.

REFERENCES

1 American Heart Association. 1998 Heart and Stroke Statistical Update. Dallas (TX): American Heart Association, 1998.

2 Hayman LL. Testimony presented on behalf of the American Heart Association at a public hearing at: “Beyond Hunt Valley: Research on Women’s Health for the 21st Century”; 1996 Sep 25; Philadelphia, PA. Hearing and workshop sponsored by the Office of Research on Women’s Health, National Institutes of Health; University of Pennsylvania School of Medicine; Allegheny University of the Health Sciences; and MCP Hahnemann School of Medicine.

3 Lenfant C. Heart disease research in women: A look back and a view to the future. Talk presented at: “Beyond Hunt Valley: Research on Women’s Health for the 21st Century”; 1997 Nov 17-19; Bethesda, Md. Hearing and workshop sponsored by the Office of Research on Women’s Health, National Institutes of Health.

4 Rifkind BM, Rossouw JE. Of designer drugs, magic bullets, and gold standards [editorial]. *JAMA*;279: 1483-85.

5 Iafrati MD, Karas RH, Aronovitz M, Sullivan TR Jr, Lubahn DR, O’Donnell TF Jr, Korach KS, Mendelsohn ME. Oestrogen inhibits the vascular injury response in oestrogen receptor-deficient mice. *Nature Medicine* 1997:3:545-548.

6 Mendelsohn ME, Karas RH. Estrogen and the blood pressure wall. *Curr Opin Cardiol* 1994;9:619-626.

7 Mendelsohn ME, Karas RH. Mechanisms of disease: the vascular protective effects of estrogen. *N Engl J Med* 1999 (in press).

8 Pennisi E. Differing roles found for estrogen’s two receptors [Research News]. *Science* 1997;277:1439.

DIGESTIVE DISEASES

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BACKGROUND

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 other 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. Much work remains to be done, however.

Digestive diseases were included for the first time as a separate working group at the November 1997 ORWH conference. This afforded attendees an opportunity to focus on these diseases and how they affect women as well as men. While there was much progress to discuss, significant gaps in knowledge and the pressing need for further research were also identified.

The working group focused its discussions primarily on irritable bowel syndrome, functional bowel disorders, colorectal cancer, gallstone disease, and selected liver diseases. This report also highlights knowledge gaps, issues, and research needs pertaining to peptic ulcer disease, metabolic bone disease, digestive diseases during pregnancy, and women in the field of gastroenterology.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Since 1991, significant progress has been made toward understanding the etiology and mechanisms of many of these diseases and how they affect men and women differently. In the area of irritable bowel syndrome and functional bowel disorders, advances have included an increased understanding of the functions of specific brain peptides, nitric oxide, carbon monoxide, and other factors in gastrointestinal motility, a key mechanism involved in these conditions. Progress has also been made in relating elements such as sensory dysfunction, pelvic floor dysfunction, motor dysfunction, and psychosocial factors, including physical and sexual abuse, to such disorders.

Regarding colorectal cancer, four distinct genes have been identified that, when inherited in altered form, cause increased susceptibility to colorectal cancer at unusually early ages. Some of these gene alterations have been associated with increased risk of colorectal cancer alone, but others have been associated with a higher risk of developing other tumors as well, including pancreatic, small bowel, and endometrial cancers, and possibly ovarian and breast cancers. A further advance has been the identification of a gene associated with familial adenopolyposis. In the area of screening for colorectal cancers, studies have shown that screening with fecal occult blood testing or sigmoidoscopy is associated with decreased mortality from these cancers. As of January 1, 1998, Medicare enrollees receive coverage for colorectal cancer screening. This recognition of the benefits of colorectal cancer screening is an exciting development with the potential to save many lives.

A number of advances have been made that relate to gallstone disease. These include identification in an animal model of genes associated with the disease. This finding may be helpful in determining the genetic inheritance of gallstone disease in humans. The evolution of laparoscopic cholecystectomy as the most common technique for gallbladder removal has been associated with a significant decrease in morbidity and more rapid recovery rates for patients, because surgery is performed through three small incisions and the abdominal cavity does not have to be opened further. Recent work has fostered a greater understanding of the physiological role of the gallbladder in gallstone formation, as well. This increased understanding may lead to better prevention and treatment techniques for this common disorder. A further development in this area has been the discovery that certain drug therapies may prevent the formation of gallstones in patients experiencing rapid weight loss, a group at high risk for this problem.

The identification of a genetic defect that accounts for a large proportion of cases of acute fatty liver of pregnancy may lead to significant reductions in maternal and fetal mortality from this condition. Recent research has also lead to a greater understanding of the mechanisms of nonsteroidal anti-inflammatory damage to the gastrointestinal tract, along with a greater understanding of the mechanism for cytoprotection of the gastric mucosa. Some of the causes and extent of the problem of bone disease in inflammatory bowel disease have also been brought to light by recent work. This has led to the recognition that osteoporosis is common among inflammatory bowel disease patients and has highlighted the need for targeted treatment for such patients.

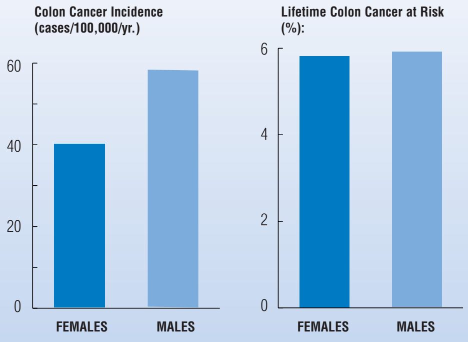
GAPS IN KNOWLEDGE

Colorectal Cancer

Colorectal cancer is the second deadliest cancer in the United States and the third leading cause (behind lung and breast cancer) of cancer deaths in women. Of the 140,000 new colon cancer cases in the United States each year, 60,000 occur in women. (See Figure 1.) Thirty thousand women die each year of colon cancer in the United States. This figure is far greater than the number of cervical cancer deaths each year in this country, yet the general public seems less aware of colorectal cancer.

Hereditary colon cancer accounts for some 15 percent of all colon cancers. Studies of patients with hereditary colon cancer have shown that women are more at risk than men for developing associated malignancies. As noted above, the associated malignancies include pancreatic, small bowel, and endometrial cancers, and possibly ovarian and breast cancers. Further study of families with inherited colorectal cancers may provide valuable information regarding the possible etiology of the associated cancers and why they develop in some cases and not in others.

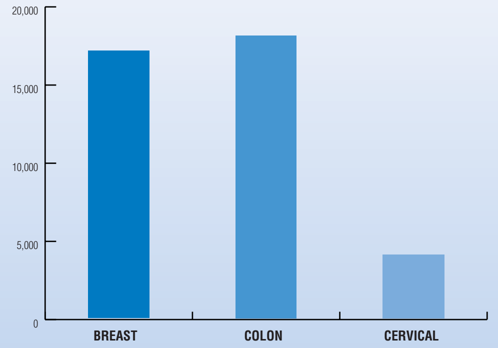
FIGURE 1. Gender Differences in Colon Cancer



Sources: Ries LAG, Hankey BF, et al., eds. SEER Cancer Statistics Review, 1973-1991. National Cancer Institute. 1994.

From a public health standpoint, there is a pressing need to increase awareness of colon cancer and to encourage greater participation in colorectal screening programs. While many women are being screened for breast and cervical cancer, far fewer receive screening for colorectal cancer. The rate of sigmoidoscopy screening is significantly lower for women than for men. This is unfortunate in that early screening for colorectal cancer is highly effective in actually *preventing* new cases of colon cancer because growths can be discovered and removed *before* they become cancerous. Thus, strategies are needed to make the medical community and the public more aware of the importance of screening women and men for colorectal cancer. (See Figure 2.)

FIGURE 2. How Many Cancer Deaths Per Year Could Be Prevented by Universal Screening?



Sources: Ries LAG, Hankey BF, et al., eds. SEER Cancer Statistics Review, 1973-1991. National Cancer Institute. 1994.

Irritable Bowel Syndrome and Functional Bowel Diseases

Irritable bowel syndrome and functional bowel diseases affect 15 to 20 percent of the U.S. population. Two to three times as many women as men suffer from these conditions. Symptoms include abdominal pain, changes in bowel habits, gas, and bloating. Irritable bowel syndrome is estimated to be responsible for some 20 to 50 percent of referrals to gastroenterology clinics. A recent study indicated that individuals with irritable bowel syndrome miss 13.4 days of work per year, compared with the national average of 4.9 days missed. Health care costs for such patients have been found to be significantly higher, as well. Data indicate that irritable bowel syndrome patients are also at greater risk for unnecessary surgery.

Recent studies have yielded epidemiological, physiological, and psychosocial data that have led to an improved understanding of these disorders and their treatment. They are now thought to be biopsychosocial in nature and to involve the interaction of three major mechanisms: psychosocial factors (e.g., life stress, sexual and physical abuse, psychiatric disorders), altered motility in the small intestine or colon, and increased sensitivity to pain and other sensations.

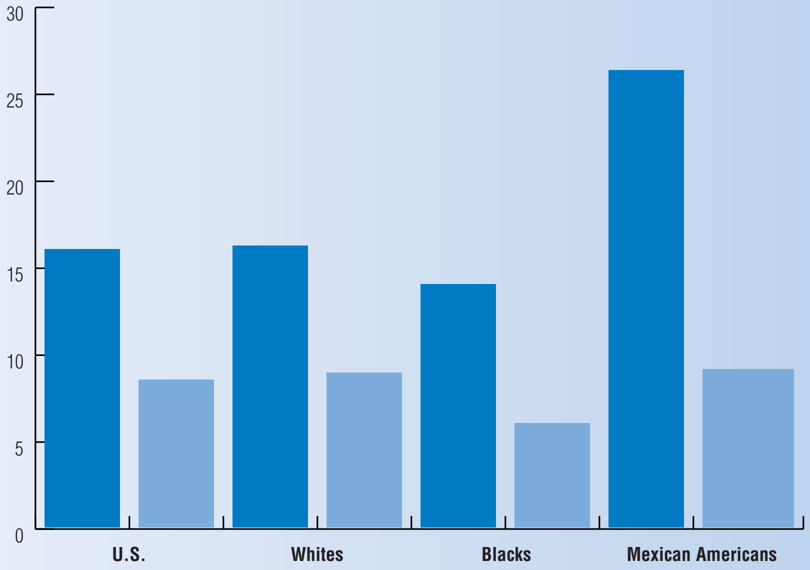
Further studies aimed at clarifying the causes and mechanisms of these disorders are needed so that effective treatment strategies can be developed. Specifically, existing tools need to be standardized and new technologies developed in the areas of evaluating and categorizing patients, identifying disease mechanisms, targeting specific behavioral and medical therapies, and better educating professionals, patients, and the general public.

Gallstone Disease

Gallbladder and biliary tract disease from gallstones are major causes of disease and death in the United States, with some 20 million people estimated to have symptomatic or asymptomatic gallstones. (See Figure 3.) These conditions occur twice as frequently in women as they do in men. (See Figure 4.) More than 500,000 cholecystectomies a year are performed in this country, and gallbladder removal is one of the most common surgeries performed on women. These conditions represent a significant health care expense, totaling more than $8 billion annually.

Three mechanisms are thought to favor the development of gallstones in women: the effect of estrogens on the uptake and metabolism of

FIGURE 3. Age-adjusted Prevalence of Gall Bladder Disease Among Adults According to Ethnicity and Sex



■ FEMALES

■ MALES

Source: Third National Health and Nutrition Examination Survey

cholesterol in the liver, inhibition of gallbladder motility during pregnancy, and increased cholesterol saturation of bile during periods of weight loss, which is more common among women than men. Better understanding of the importance and interactions of these and perhaps other factors will be critical to the development of rational approaches to the prevention of gallstones.

Evidence suggests that gallstone disease may be familial in humans, and further studies are needed to test this hypothesis. Recent studies have identified genes that are responsible for gallstone formation in mice. Additional work is needed to determine whether there is a genetic basis for such disease in humans. Further elucidation of the role played by estrogens and progesterones in the formation of cholesterol stones is also needed, along with a greater understanding of the natural history of the disease in women. Better understanding of the basic biology of the disease and the development of strategies to prevent gallstone formation could contribute greatly toward patient welfare and decreased health care expenditures.

Nonsteroidal Anti-inflammatory Drugs and Peptic Ulcer Disease

High dosages of nonsteroidal anti-inflammatory drugs (NSAIDs) are a known cause of peptic ulcer disease in both men and women. Examples of these medications include aspirin and ibuprofen. Women tend to take more of these medications than do men because they suffer more from degenerative arthritis and pelvic pain. Older women, in particular, use these drugs heavily and are therefore at higher risk for gastrointestinal ulceration and bleeding. Prostaglandin analog (misoprostol) has been shown to decrease the risk of NSAID-induced gastritis and ulcers, but has diarrhea as a major side effect. Further information is needed on how to prevent NSAID-induced peptic ulcer disease in both women and men.

Liver Disease

Autoimmune Liver Disease. The two principal autoimmune liver diseases, primary biliary cirrhosis and autoimmune hepatitis, are much more common in women than in men. Primary biliary cirrhosis

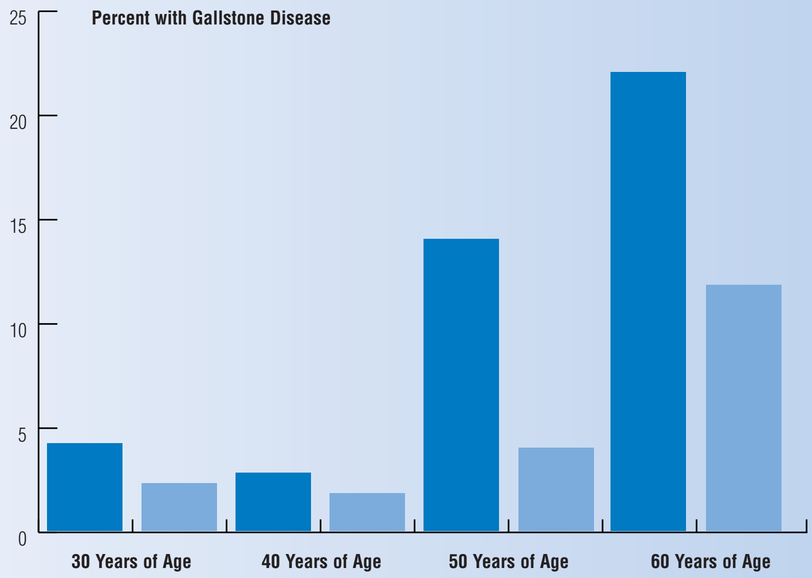


FIGURE 4. Woman Are at Higher Risk of Gallstone Disease

Source: Jorgensen T. Prevalence of gallstones in a Danish population. *Am J Epidemiol* 1987; 126: 912-21.

occurs nine times more frequently in women than men and primarily affects middle-aged women. Although not a common disease, primary biliary cirrhosis causes substantial morbidity from chronic fatigue, pruritus (severe itching), and skeletal fractures. More importantly, primary biliary cirrhosis is a leading cause of end-stage liver disease and is the most common reason for liver transplantation in women. The main autoimmune marker for primary biliary cirrhosis is serum antimitochondrial antibody. Although this antibody is present in 90 percent of primary biliary cirrhosis patients, its pathophysiological importance remains to be determined. Inflammation and subsequent loss of small bile ducts within the liver are the main findings upon liver biopsy. Intense investigation is needed to understand the causes of the bile duct injury and why it progresses to cirrhosis and liver failure. This work will have important implications for this disease and for understanding injury to bile ducts in many disorders. Treatment with the bile acid ursodiol is modestly effective in preventing transplantation and death, but more effective therapy is needed.

Autoimmune hepatitis affects women three to four times as often as it does men. This disease is associated with a number of other autoimmune conditions (such as thyroiditis and Sjögren's syndrome) and with several autoantibodies. However, even less is understood about the causes of autoimmune hepatitis than primary biliary cirrhosis. The hepatitis is often severe and leads to liver failure if left untreated. The mainstay of treatment for many years has been glucocorticoids, which are often required in high doses for extended periods. Because of the complications and occasional ineffectiveness of these drugs, better therapies are needed. Research into the etiology and mechanisms of this disorder could have important implications for understanding the immune response and hepatic inflammation.

Nonalcoholic Steatohepatitis. Nonalcoholic steatohepatitis is an important liver disorder that has been recognized as a distinct entity only within the last 15 years. This disorder has all the histological characteristics of alcoholic liver disease, including large accumulations of fat, acute and chronic inflammation, and fibrosis and cirrhosis. Nonalcoholic steatohepatitis is a common reason for elevated liver enzyme tests and may be the most common cause of liver disease in women. Risk factors are thought to be obesity and non-insulin-dependent diabetes mellitus, which are both disorders of insulin resistance. However, much about the cause, pathogenesis, and natural history of nonalcoholic steatohepatitis remains to be determined. It is quite possible that many of the patients — especially women — who arrive at transplantation with so-called cryptogenic cirrhosis may have nonalcoholic steatohepatitis as an important contributing cause. To date, there is no established treatment. With the increasing prevalence of diabetes and obesity in the United States, particularly among minority women, nonalcoholic steatohepatitis can be expected to become an increasingly important problem.

Metabolic Bone Disease

Osteoporosis, or loss of bone mass, affects both men and women, but advances more rapidly in women, especially after menopause. Some 25 million Americans suffer from this condition, which may result in bone fractures and a loss of skeletal support. In the United States, more than 1 million fractures per year are attributed to osteoporosis. Osteoporosis-related debilitation and death account for $7 to $10 billion in annual health care costs. Maintaining adequate calcium absorption through the intestines is a critical factor in preventing osteoporosis.

Patients with inflammatory bowel disease are at increased risk for osteoporosis, due in part to a decreased ability to absorb calcium as a side effect of the corticosteroid therapy that is often used to treat inflammatory bowel disease, and because of the presence of increased cytokines, which probably have a direct effect on the bone. Hormone replacement therapy has shown some promise in lessening the severity of osteoporosis among these patients. Further work is needed to develop better osteoporosis prevention and treatment strategies for patients with inflammatory bowel disease.

Bone loss is also a common and significant problem among patients with the chronic liver disease, primary biliary cirrhosis. Osteoporosis develops early among such patients, and related spine and hip fractures often contribute to their deaths. Because primary biliary cirrhosis primarily affects women, and women are more susceptible to osteoporosis, this is an important women's health issue. Recent findings indicate that progressive bone loss is halted and sometimes reversed in primary biliary cirrhosis patients following liver transplantation. (Bone loss was found to worsen immediately following transplantation, but then improved. The initial high doses of steroids that are included in immunosuppression therapy may be responsible for this temporary worsening.)

Osteoporosis and osteopenia, conditions that are distinguished by the amount of bone loss involved, accompany other chronic liver diseases, as well. Improved methods are needed to evaluate and treat bone loss in chronic liver disease patients.

Digestive Diseases During Pregnancy

Digestive problems during pregnancy largely fall into two categories: (a) chronic conditions that exist before the patient becomes pregnant and continue during the pregnancy and (b) symptoms and conditions unique to or particularly common during pregnancy. In all cases, the sensitivity of the fetus to the mother's illness and to the diagnostic procedures and medications used to address it must be given high priority.

Chronic conditions that present special problems during pregnancy include inflammatory bowel disease and biliary disease. Inflammatory bowel disease, including ulcerative colitis and Crohn's disease, is common among women of childbearing age. Successful management of these conditions correlates with successful pregnancy outcomes. While some patients' symptoms improve during pregnancy, this is not the case for most patients. The safety of monitoring procedures —

such as ultrasound, endoscopy, MRI scans, x-rays and CAT scans — and medications used to treat these conditions during pregnancy are vitally important. Ultrasound is deemed safe, and endoscopy and MRI scans are thought to be safe, but x-rays and CAT scans are not considered safe for routine use. Only a few medications used to treat digestive diseases have been established as safe for use in pregnancy. Whether the dose response of the medications is the same in pregnancy as in the nongravid state is not known. Continuing efforts and better mechanisms to determine and ensure the safety of procedures and medications used to address these conditions are needed.

Gallstone and sludge formation are common during pregnancy and are thought to be influenced by hormonal changes that affect biliary physiology. Because these conditions can lead to pancreatitis and other complications, careful monitoring and treatment are required. As noted above in the section on gallbladder disease, more information is needed on gallstones formed during pregnancy to develop better prevention and treatment strategies.

Common symptoms such as nausea and vomiting of pregnancy and heartburn can often be treated with safe, conservative measures. Again, the safety of the medications used must be continually monitored. *Hyperemesis gravidarum* is nausea and vomiting during pregnancy that is severe enough to cause systemic effects such as dehydration, electrolyte abnormalities, and weight loss. Hospitalization is sometimes required to control these effects. Few studies of this condition have been conducted.

Recent research has enabled scientists to identify a genetic defect that accounts for a large percentage of cases of acute fatty liver of pregnancy, a rare but frequently fatal disease. In this condition, fat is deposited in the cytoplasm of hepatocytes. With further research, this advance may lead to a significant reduction in the rate of maternal and fetal mortality from this disease and may provide insight into similar diseases such as Reye's syndrome.

> *"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

RESEARCH RECOMMENDATIONS

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 to 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.

Irritable Bowel Syndrome and Functional Bowel Diseases

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

- 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 irritable bowel syndrome and functional bowel disorders.
- Examine the relationship between pelvic floor dysfunction and these conditions.
- Study the effects of the menstrual cycle on irritable bowel syndrome and functional bowel disorders.
- 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 irritable bowel syndrome and functional bowel disorders.

In addition, care should be taken in designing patient studies to address limitations that were present in previous studies. Areas to be addressed include targeting selection criteria for these conditions, grouping patients by the severity of their symptoms, adequacy of sample size, length of treatment and followup periods, and analytical methods used.

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 identify 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

- Understand nonalcoholic steatohepatitis, including (a) ascertaining why women are more susceptible; (b) learning the natural history, including who goes on to cirrhosis; (c) determining the molecular mechanisms and genetic and environmental susceptibility factors; and (d) identifying treatment and prevention strategies.
- Explore pathogenesis, immunology, and therapeutic approaches to primary biliary cirrhosis.
- Explore influences of sex hormones on elements of the immune system related to autoimmune liver diseases.

- 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 primary biliary cirrhosis and autoimmune hepatitis.

Nonsteroidal Anti-inflammatory Drugs and Peptic Ulcer Disease

- Research and develop medications to replace nonsteroidal anti-inflammatory drugs to control pain from arthritis and other disorders because these medications have gastrointestinal ulceration and bleeding side effects. More women than men use these drugs, and therefore studies should 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.

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.

- 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.

Career Issues for Women in the Field of Gastroenterology

- Expand support for mentoring programs for women.

- Encourage improvements in existing mentoring programs, including the inclusion of more female mentors.

- Encourage and provide funding for the formation of special academic tracks for women interested in research careers.

- Encourage academic institutions to revise their tenure and promotion policies in order to accommodate the need for family leave, leaves of absence, flexible scheduling, and the like.

- Encourage institutions to develop programs to prepare more women faculty members for senior administrative positions.

- Support policies that promote the concept of equal pay for equal work.

- Improve NIH support for women who work part-time or interrupt their careers.

REFERENCES

Alexander L, Collman SW, Richard-Davis G. Reproductive/Middle Years. In: Interim Proceedings of the workshop, Beyond Hunt Valley: Research on Women's Health for the 21st Century. Sponsored by the Office of Research on Women's Health, National Institutes of Health; 11-13 Jun 1997; New Orleans, La. p. 37-43.

Amouyal G, Amouyal P. Endoscopic ultrasonography in gallbladder stones. *Gastrointest Endosc Clin North Am* 1995;5(4):825-30.

Bjorkman DJ. Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury. *Am J Med* 1996;101(suppl 1A):25S-32S.

Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995;87(7):517-23.

Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther* 1997;11;3-15.

Camilleri M, Saslow SB, Bharucha AE. Gastrointestinal sensation: mechanisms and relation to functional gastrointestinal disorders. *Gastroenterol Clin North Am* 1996; 25(1):247-58.

Danze PM, Colombel JF, Jacquot S, Loste MN, Heresbach D, Ategbo S, Khamassi S, Perichon B, Semana G, Charron D, et al. Association of HLA class II genes with susceptibility to Crohn's disease. *Gut* 1996;39:69-72.

Diehl AM. Presentation to the Digestive Diseases Working Group on liver diseases at: Beyond Hunt Valley: Research on Women's Health for the 21st Century; 1997 Nov 19; Bethesda, Md. Sponsored by the Office of Research on Women's Health, National Institutes of Health.

Dill J, Hill S, Callis J, et al. Combined endoscopic ultrasound and stimulated biliary drainage in cholecystitis and microlithiasis: diagnosis and outcomes. *Endoscopy* 1995 Jul;27.

Dill J. The gallbladder, the gut, and the brain: connections and implications for women's health. In: Interim Proceedings of the workshop, Beyond Hunt Valley: Research on Women's Health for the 21st Century. Sponsored by the Office of Research on Women's Health, National Institutes of Health; 1997 Jun 11-13; New Orleans. p. 5.

Donovan JM, Syngal S. Colorectal cancer in women: an underappreciated but preventable risk. *J Women's Health* 1998;7(1):1-4.

Donovan JM. Presentation to the Digestive Diseases Working Group on gallstone disease at: Beyond Hunt Valley: Research on Women's Health for the 21st Century; 1997 Nov 19; Bethesda, Md. Sponsored by the Office of Research on Women's Health, National Institutes of Health.

Drossman DA. Chronic functional abdominal pain. *Am J Gastroenterol* 1996;91(11):2270-81.

Drossman DA, Creed FH, Fava GA, Olden KW, Patrick DL, Toner BB, Whitehead WE. Psychosocial aspects of the functional gastrointestinal disorders. *Gastroenterol Int* 1995;8(2):47-90.

Drossman DA, Talley NJ, Olden KW, Leserman J, Barreiro MA. Sexual and physical abuse and gastrointestinal illness: review and recommendations. *Ann Intern Med* 1995; 123:782-94.

Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology* 1997;112(6);2120-37.

Gorard DA, Libby GW, Farthing MJG. Effect of a tricyclic antidepressant on small intestinal motility in health and diarrhea-predominant irritable bowel syndrome. *Dig Dis Sci* 1995;40:86-95.

Greene B, Blanchard EB. Cognitive therapy for irritable bowel syndrome. *J Consult Clin Psychol* 1994;62:576-82.

Hammer J, Phillips SF, Talley NJ, Camilleri M. Effect of a 6HT3-antagonist (ondansetron) on rectal sensitivity and compliance in health and the irritable bowel syndrome. *Ailment Pharmacol Ther* 1993;29184:2079-16640.

Jacobs EJ, White E, Weiss NS. Exogenous hormones, reproductive history, and colon cancer. Cancer Causes *Control* 1994;5(4):359-66.

Kampman E, Potter JD, Slattery ML, Caan BJ, Edwards S. Hormone replacement therapy, reproductive history, and colon cancer: a multicenter, case-control study in the United States. *Cancer Causes Control* 1997;8(2):146-58.

Kay L, Jorgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. *J Intern Med* 1994;236:23-30.

LeBoff MS. Is prolonged use of corticosteroids safe in patients with Crohn's disease? *Inflammatory Bowel Dis* 1997;3(2):169-73.

Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 1994;107:271-93.

McKenzie SJ, Baker MS, Buffinton GD, Doe WF. Evidence of oxidant-induced injury to epithelial cells during inflammatory bowel disease. *J Clin Invest* 1996;98:136-41.

Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterology* 1995; 109:40-52.

Division of Digestive Diseases and Nutrition Research Advances, 1992-1997. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst* 1995; 87(14):1067-71.

Norton N. Testimony presented at public hearing at Beyond Hunt Valley: Research on Women's Health for the 21st Century; 1997 Nov 17; Bethesda, Md. Sponsored by the Office of Research on Women's Health, National Institutes of Health.

Olans LB, Wolf JL. Gastroesophageal reflux in pregnancy. *Gastrointest Endosc Clin North Am* 1994;4(4):699-712.

Risch HA, Howe GR. Menopausal hormone use and colorectal cancer in Saskatchewan: a record linkage cohort study. *Cancer Epidemiol Biomarkers Prev* 1995;4(1):21-8.

Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology* 1990;99:409-15.

Scarinci IC, McDonald-Halle JM, Bradley LA, Richter JE. Altered pain perception and psychosocial features among women with gastrointestinal disorders and history of abuse: a preliminary model. *Am J Med* 1994;97:108-18.

Szurszewski J. Presentation to the Digestive Diseases Working Group on gut motility at: Beyond Hunt Valley: Research on Women's Health for the 21st Century; 1997 Nov 18; Bethesda, Md. Sponsored by the Office of Research on Women's Health, National Institutes of Health.

Talley NJ, Gabriel SE, Harmsen WS, Zinmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology* 1995;109(6):1736-41.

Toner BB. Cognitive-behavioral treatment of functional somatic syndromes: integrating gender issues. *Cognitive Behav Practice* 1994;1:157-78.

Toner BB, Garfinkel PE, Jeejeebhoy KN. Psychological factors in irritable bowel syndrome. *Can J Psychiatry* 1990;35:158-61.

Trimble E, Antman K. Cancer. In: Interim Proceedings of the workshop, Beyond Hunt Valley: Research on Women's Health for the 21st Century. Sponsored by the Office of Research on Women's Health, National Institutes of Health; 1996 Sep 26-27; Philadelphia, Pa; p. 85-91.

Wilson JAP. Testimony presented at public hearing at: Beyond Hunt Valley: Research on Women's Health for the 21st Century; 1997 Nov 17; Bethesda, Md. Sponsored by the Office of Research on Women's Health, National Institutes of Health.

IMMUNITY AND AUTOIMMUNE DISEASES

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BACKGROUND

Women'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. In addition to the traditional immune-mediated diseases, many diseases are now recognized to have an immune or inflammatory component. These include atherosclerosis, Alzheimer disease, and many neurologic diseases. 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.

Autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, scleroderma, Sjögren's syndrome, autoimmune thyroid disease, type 1 diabetes, idiopathic thrombocytopenia purpura, and inflammatory bowel disease, can affect every organ system. Many of these diseases are considered rare, that is, affecting less than 200,000 individuals. However, *in toto*, millions of women in the United States are afflicted by autoimmune diseases, leading to billions of dollars in health care costs per year. Because many of these diseases affect young women, there is significant impact on the health of families and lost productivity.

The Working Group on Immunity and Autoimmune Diseases consisted of researchers, clinicians, patients, and advocates who discussed advances in immunology since the first Hunt Valley meeting in September 1991. In addition, the group identified several gaps in our knowledge in this area. Many of these areas offer opportunities for increased emphasis in the coming years with significant likelihood for discoveries that will improve the health of women.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

In the years since the establishment of ORWH in 1990, the scientific community has made notable progress in several areas of immunological research.[1] Researchers have gained new understanding of many areas of basic immunology including: the degradation of antigens intracellularly and their presentation to the immune system; the identification of subtypes of T cells and their role in immune activation and regulation; the 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; the trafficking of immune cells to various areas of the body; inter- and intra-cellular signaling cascades; and the pathways leading to cell death. In addition, there have been significant new insights in our understanding of the interactions of the various components of the immune system. Furthermore, recognition that the immune system plays a critical role in many diseases that were not previously thought to be immunologically mediated has increased the need to understand immune function throughout the life span.

Tools and Methodological Advances

Much of the progress in the field of immunology has been possible because of the development of new research tools, which have had a significant impact on many areas of science. One of these tools, polymerase chain reaction, has allowed the measurement of very small amounts of material and facilitated the manipulation of DNA, which has been critical for the development of many other tools. The study of known molecules in the whole animal has been possible with genetically engineered animals — both transgenic and knock-out (or knock-in) mice. Analysis of large numbers of samples has been facilitated by synthetic and recombinant peptide libraries and will be further advanced with microchip technology. The screening of defined populations for genetic differences has been possible with the development of large patient and family repositories, as well as newer genetic screening and sequencing methods. New methods of analyzing data, including meta-analysis, have allowed new hypotheses to be developed by combining data from many studies. Thus, methodological, technical, and resource advances have permitted planning of experiments that previously were not possible. These developments have increased understanding of the immune response, but also disclosed its complexity, adding many new molecules and pathways.

Emerging Areas of Research

Recently, several previously unrecognized areas have emerged as important in the development of the immune response. Many of these have special importance for women's health. In particular, the following new areas of investigation are especially notable.

Neural-endocrine-immune interactions. There has been considerable progress in understanding the molecular and cellular mechanisms involved in interactions between the neural, endocrine, and immune systems. In particular, immune cells have been shown to synthesize and respond to neurotransmitters and hormones, neural cells synthesize and respond to cytokines, and endocrine cells respond to cytokines. Also, many hormones have been found to be members of neurotransmitter and cytokine families. The overlap and similarities in these systems have led to a recognition of molecular interactions, which could explain previously described clinical observations of the interactions of these systems.

Mucosal immunity. The mucosal immune system, composed of the gut, respiratory, reproductive, and urinary mucosa, is the first site of contact with pathogens as well as benign foreign antigens, including food and sperm. Understanding of the mechanisms leading to immunity or tolerance to these antigens may allow development of new methods to induce immunity to infectious agents or tolerance to self antigens, which could prevent or treat autoimmune diseases. Whether differences in the mucosal immune system exist between men and women has not been fully investigated. This could have implications for understanding sexually transmitted diseases (STDs), allergy, vaccine development, and tolerance induction (including both nasal and oral tolerance).

Microchimerism. The survival of cells of another individual (fetal, maternal, or transplant) in a normal host has only recently been appreciated within the scientific community. The implications of this exposure to foreign antigens for immune function and disease need further exploration.

Hormone receptors and their regulatory roles. The greater incidence and prevalence of autoimmune diseases in women has not been explained. Recently, the findings of sex hormone receptors in immune cells and the regulation of transcription of cytokine genes by sex hormones have suggested mechanisms by which hormones may influence the immune response. With the cloning of sex hormone receptors, including the recent identification of a second estrogen receptor, the molecular tools are emerging to examine the role of hormones in the immune response. It is likely that additional hormone receptors will be identified, as have many new molecules in the immune response. The identification of genes regulated by hormones may offer insight into novel influences on the immune system. The use of exogenous estrogens in oral contraceptives and hormonal replacement therapy, drugs that include modified hormones for therapeutic purposes, and the presence of phyto-estrogens from the environment should be examined for their interaction with the immune response. In addition, the cyclical changes in hormones in the female may have unique influences on the immune system.

Advances in Immune Physiology

In the years since 1991, there have been tremendous increases in our understanding of normal immune physiology and also its dysregulation in disease. These advances offer great promise for further understanding of disease etiology, prevention, and treatment. In particular, the increased understanding of the immune response offers encouragement that autoimmune and allergic diseases can be prevented with immune intervention. An understanding of genetic, environmental, and hormonal influences on the immune system should be possible. Areas of particular advances include:

Antigen processing and presentation. The pathways, enzymes, and proteins involved in degradation and binding of endogenous and exogenous antigens with the MHC molecules have been clarified. Recently, it has been appreciated that non-protein antigens can also be recognized by the immune system.

Inflammatory mediators. A host of molecules made by pathogens are capable of activating or amplifying an immune response. In addition, immune and other cells may secrete molecules that modulate the immune response. These include adjuvants, prostaglandins, complement proteins, and acute phase response molecules. Cytokines and chemokines are listed separately (see below).

Immune deviation. The response of immune cells is influenced by the cytokine environment, the cells that are present, and the manner of activation. Thus, the conditions during T cell activation can determine the immune response that is generated. The ability to shift the immune response may allow development of better vaccines or the prevention of autoimmune disease.

Costimulation. It is now recognized that interaction of the T cell receptor with the antigen-MHC complex or of the B cell with antigen is not sufficient to activate the T or B cell. Interaction of additional molecules, called co-stimulatory molecules, are needed. Blocking these interactions will prevent activation of the cells. The elucidation of the necessity of these interactions offers promise for manipulation of the immune response to prevent or treat disease.

Cell signaling. Increased understanding of the multiple pathways of intracellular signaling and their interactions has emerged. These complex cascades of molecules represent new targets for therapeutic interventions to modulate the immune response. It is likely further pathways will be discovered in the coming years.

Cytokines, chemokines, and their receptors. The number of soluble mediators of the immune response continues to grow. In addition, our understanding of their role in the immune response is being clarified. Administration of these molecules or antibodies to these molecules are now being utilized for treatment of various diseases, including autoimmune diseases.

Cell trafficking. Movement of immune cells to and from the vasculature, lymphatics, or tissues is a highly regulated process that is beginning to be understood. Modification of these movements may modulate the immune response.

Tolerance induction. Tolerance occurs when the immune system does not respond to an antigen. This process is part of the body's own mechanism to protect against autoimmunity. Increased understanding of this non-responsiveness of the immune system offers opportunities to prevent autoimmune or inflammatory diseases.

T cell receptor and antibody gene rearrangement. Through this process of gene rearrangement, cells dedicated to response to certain antigens are formed and available if needed. Understanding this process has increased our knowledge of the mechanism of response to antigen.

Advances in Understanding Cell Differentiation and Death

The isolation of stem cells and the ability to modulate their differentiation has been a significant advance. These studies have already been translated into clinical interventions improving bone marrow transplantation and immune reconstitution following chemotherapy or radiation therapy. In addition, they offer possibilities for treatment of autoimmune disease.

Turnover of cells, with some increasing and others dying, is a necessary part of the immune response. Considerable progress has been made in understanding the pathways leading to cell death (apoptosis) or survival. Investigators are now beginning to explore the molecular basis for cell death — learning which molecules cause cells to die, which ones prevent cells from dying, and which ones trigger shifts in the cell cycle. Most importantly, immunologists have now begun to appreciate the role of cell death in controlling autoimmunity and in regulating the normal inflammatory response.

GAPS IN KNOWLEDGE

Numerous areas offer opportunities for significant advances with promise to yield new insights and new strategies for clinical interventions.

Genetics and Genomics of Immune-mediated Diseases

Repositories for DNA from patients and families with immune-mediated diseases offer resources to identify susceptibility and resistance genes for these diseases, including those that are polygenic. Linkage of genetic information to careful analyses of clinical parameters — disease severity, disease subset, ethnic background, response to therapy, and response to environmental triggers, among others — offers the possibility to prevent disease or customize treatment. These resources also allow identification of genes that alter thresholds for immune activation or tolerance induction. However, very few large repositories or collections of families that are available to all investigators exist for numerous autoimmune diseases.

Environmental Influences

It is now clear that many external influences may alter immune function in an individual. An understanding of the interface between aspects of daily living and disease risk is of critical importance in preventive medicine. The principal factors related to immune function include:

- Diet, vitamins
- Previous or concurrent infections
- Stress
- Environmental estrogens — including estrogen replacement therapy, birth control pills
- Indoor and outdoor allergens
- Microchimerism (in pregnancy and transplantation)
- Lifestyle (physical activity and exercise, sexual orientation, etc.)
- Implanted devices

Sexual Dimorphism and Age

A significant amount is known about immune physiology in the adult, and there is some information about differences in immune function in children and neonates. However, no systematic information exists concerning differences in immune physiology based on gender and stage of life. In particular, are there differences in immune function in the fetal, neonatal, pubertal, mature woman, and postmenopausal woman? Are there differences in immune function during various parts of the menstrual cycle? This information may allow basic scientists and clinicians to develop more practical disease treatments. For example, some existing data suggest that tailoring asthma therapy to the menstrual cycle can significantly decrease both the cost and the side effects of asthma therapy.

Pregnancy

Previous investigations have looked at pregnancy outcome in women with autoimmune diseases, but few studies have examined the consequences of pregnancy for the disease process both during and after pregnancy. However, it has been observed that rheumatoid arthritis and multiple sclerosis improve during pregnancy, whereas systemic lupus erythematosus worsens. The underlying basis for this improvement or worsening of disease is not well understood. In addition, pregnancy as a risk factor for development of later disease is underexplored. Recent studies suggest microchimerism, induced by pregnancy, is increased in women with scleroderma. It is unclear if this is causal. The effect of fertility enhancement and prevention on the immune response has not been investigated.

Hormonal Effects

The tools now exist for a dramatic increase in knowledge regarding hormonal effects on all aspects of immune function, including in neonates when there is a transient increase in sex hormones, during puberty, during the menstrual cycle, and after menopause. Opportunities to increase the effectiveness of vaccines or to minimize the side effects of therapies will depend upon increased understanding of immune function during physiologic alterations in hormone levels. Some of the most significant research opportunities in this area include: identification of hormone receptors and their expression in immune cells and the influence of hormones on immune physiology. The thymus is known to be sensitive to hormone fluctuations. However, what is the effect of hormones on thymic selection, the process by which T lymphocytes are positively selected for survival or deleted. Hormonal fluctuations may serve to alter thresholds for death, survival, and activation of cells. It is known that cell trafficking is markedly affected by the expression of cell surface adhesion molecules. Research is needed on the effects of hormones on adhesion molecule expression and the movement of cells. The effects of hormones on cells and cellular signaling is just beginning to be understood. It is reasonable to postulate that hormones may have stimulatory or inhibitory influences on gene expression for most cytokines. It is also reasonable to speculate that hormones will influence the gene expression of cytokine receptors and their function. Hormones may also affect the composition and stability of the extracellular matrix. In addition to sex steroid hormones, the influence of other hormones, including hypothalamic, pituitary, and adrenal, should be examined.

Target Organs

Immune activation and response to immune mediators can be regulated locally with specific tissues differing in their ability to serve as sites of immune activation or immune destruction. For example, the brain has been shown to be a site for considerable apoptosis (programmed cell death) of lymphocytes. In addition, the eye has been described as an immune privileged site. Further exploration of the role of these target organs, as well as the thyroid, pancreas, and skin, in modulating the immune response is needed. Specifically, what are the differences in target organs with respect to activation of immune responses and response to autoimmune attack? Equally, certain tumors have mechanisms to evade immune destruction. What are the genetic, hormonal, cytokine, or other factors regulating the differences in these tissues?

How do these factors influence the response to implanted devices? What local factors influence the immune response in transplanted organs. Existing data suggest that the sex of a kidney transplant donor may be an important determinant of the success of engraftment.

Tolerance and Immunologic Unresponsiveness

Tolerance can be broadly defined as a selective block in the immune response to a particular antigen. Tolerance can be induced by the deletion or specific inactivation (anergy) of antigen reactive lymphocytes; alteration of the cytokine milieu to prevent inflammation; or induction of regulatory T cells or cytokines to down-regulate activation of antigen specific T cells. This is an area with great importance to clinical medicine, especially transplantation, and the prevention and treatment of allergy and autoimmune diseases.

Several areas offer particular promise. T cell ligands, which specifically activate (agonists) or inactivate (antagonists) cells, can differ by a single amino acid. Therefore, exposure of autoreactive T cells to an altered peptide ligand could potentially prevent activation of those cells. Activation of T cells requires co-stimulation in addition to binding of the T cell receptor and MHC-antigen complex; blocking this co-stimulation prevents T cell activation leading to tolerance. This approach is being utilized in pilot trials in autoimmune disease and to prevent transplantation rejection. Much has been learned about the active suppression and deletional mechanisms operative in mucosal (oral) tolerance. However, early trials have shown dosage of fed-antigen is critically important. More trials are needed to explore antigen dose and mechanism of mucosal tolerance in humans. Several different pathways, each involving different pairs of molecules, have been described for activation of apoptosis or programmed cell death. The regulation of these pathways in the development of tolerance or autoimmune diseases is needed. The thymus is actively involved in positive and negative selection in the infant and child, but becomes involuted in the adult. The role of the thymus in tolerance induction in the adult needs to be explored.

Innate Immunity

The nonadaptive, non-antigen-specific arm of the immune system has recently become a focus of immunologic study. Mast cells, neutrophils, and monocytes frequently contribute to the inflammation observed with protective or pathologic immune responses. Natural killer (NK) cells have become an area of active investigation. Investigators have only recently begun to appreciate the contributions of all of these cell types in the immune response to asthma, transplant rejection, and autoimmunity. Complement proteins that function by cooperating with the body's other defense mechanisms represent an indispensable part of the immune response. When activated, the complement proteins coat the surface of a foreign organism, flagging it for digestion by macrophages. Scientists have long recognized the impact of complement on immune response through the study of individuals with complement deficiencies. However, they have only recently begun conducting mechanistic studies to determine the basis for the observed immune dysregulation. More studies of innate immunity are required.

Clinical Investigation

More information is needed concerning the incidence, natural history, genetics, gender differences, and risk factors for immune mediated diseases, such as rheumatoid arthritis, multiple sclerosis, scleroderma, systemic lupus erythematosus, Sjögren's syndrome, and asthma. Easily available and reproducible assays that correlate with clinical risk, disease activity, or response to therapy are needed for these diseases to more accurately and more quickly test new therapies. Information about the response of men versus women in clinical trials may suggest gender specific therapies. An improved understanding of the appropriate assays to measure immune function in different diseases and at different stages of disease could lead to better management of these diseases.

RESEARCH RECOMMENDATIONS

The following recommendations are made for future research and to improve clinical care in areas of immunity and autoimmune disorders:

- Identify resistance/susceptibility genes for multigenic diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, scleroderma, Sjögren's syndrome, type 1 diabetes, and asthma.
- Identify the effects of environmental influences such as diet, stress, allergen exposure, and exogenous estrogens on immune function.
- Study the comparative effects of sex and age on normal and abnormal immune function in animals and humans; determination of 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 therapeutic interventions.

> *"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

- 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.

Overarching Issues

The working group agreed that the following broad recommendations should be generally applied to all aspects of immunological research in women's health.

- Researchers and clinicians should develop procedures for rational and wise selection of clinical trials, particularly in rare diseases. The limited number of patients with these diseases may limit the number of clinical trials that can be performed. Clinical trials must be designed to reflect a heightened sensitivity to the problems associated with retention of subjects from special populations (these populations include women of color and women of low socioeconomic status). Equal representation of subjects from all ethnic and socioeconomic groups should be assured and appropriate clinical studies on rare diseases undertaken. There is a vital need to maintain access to patients under managed care for clinical trials and to ensure that advances in clinical medicine and opportunities to participate in clinical studies are made available to patients in managed care programs.

- Achieving significant progress in these areas will require multidisciplinary approaches and, in studies of human populations, multicenter collaborations.[2] Access to data and tissue repositories should be simplified while protecting patient confidentiality. Expanded interactions between researchers, government, industry, and the private sector should be encouraged.

Communication and Information Access

Access to information that would be useful for management of patients with these diseases is not universally available. Access to archival information from clinical trials could enhance clinical care. Communication of information between clinical and basic investigators would facilitate translation of research findings into clinical practice. Increased communication between patients, basic scientists, and clinicians could lead to new areas of research.

Summary

In summary, the working group suggested implementation of the following recommendations for future research and strategies to improve clinical care in the areas of immunity and autoimmune disorders:

- Research designed to address the gaps in knowledge and to exploit the opportunities defined above.
- Design of information systems that allow easier access to archival material on clinical and genetic studies.
- Increased multidisciplinary research.
- Greater sharing of resources among researchers (this includes sharing of clinical samples, DNA banks, serum banks, animals, and reagents).
- Better communication between the lay public and the scientific community, making information readily accessible to researchers, health care providers, and consumers.
- Stratification of future and existing data from basic and clinical studies for sex and age of subjects.

Benefits that can be anticipated from increased knowledge of the unique aspects of the woman's immune response include a better understanding of autoimmune disease, asthma and allergic responses, transplant engraftment and rejection, tumor immunity, and protection from microbial infection. This information could lead to improved therapeutic protocols for vaccination, tolerance induction, and transplantation. Ultimately, new knowledge will permit us to predict how environmental factors and lifestyle will affect the immune response and how to identify those individuals who are genetically at risk for immune dysfunction. The rapid and reliable translation of such knowledge into the health care system, to inform the practice of both physicians and patients, is a goal that can be achieved with improvement in communication.

REFERENCES

1 Office of Research on Women's Health. Report of the National Institutes of Health: Opportunities for Research on Women's Health. Hunt Valley, Md: National Institutes of Health, 1992. p. 195-206.

2 Office of Research on Women's Health. Beyond Hunt Valley: Research on Women's Health for the 21st Century, Interim Proceedings of the Public Hearing and Scientific Workshop: September 25-27, 1996. Philadelphia, Pa: National Institutes of Health, 1997. p. 46-56.

INFECTIOUS DISEASES AND EMERGING INFECTIONS

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BACKGROUND

The startling advances since 1991 in the detection and treatment of infectious diseases in women indicate what still needs to be accomplished. The 1991 Hunt Valley report grouped together research recommendations in immunology and infectious diseases. The current report recognizes the growing importance of both these areas and treats their discussion and research recommendations in separate sections.

It was not possible for this working group to cover all infectious diseases of particular importance to women. Time was, of course, a consideration; however, the expertise of the working group as well as evidence of the increasing scope of the epidemics led to a focus on sexually transmitted diseases (STDs) and HIV/AIDS, with limited discussion of a significant number of other infectious diseases. The group did not discuss urologic diseases of women; this subject is covered in a separate report. The four sections that follow focus on STDs and HIV, with passing references to other infectious diseases from which women suffer disproportionately. Discussion within each section of this report is divided into basic science, epidemiology, clinical practice, and behavior and education.

Sexually transmitted diseases, 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.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Advances in Basic Science

Basic research progress in the fields of HIV and STDs during the past 5 years is evidenced in the many new studies being undertaken and in the significant increase over the past several years in research funding. The ambitious research and program agendas of NIH and CDC have included an increase in funding by the National Institute of Allergy and Infectious Diseases of STD centers that are focusing on an examination of the vaginal ecosystem. Other projects have begun to characterize the endogenous defense systems of the vagina and cervix. Grant-funded research is currently focusing on vaginal immunology and physiology, and is examining normal and abnormal vaginal ecosystem responses to preventive and therapeutic agents.

Examples of basic scientific progress include the development of single-dose azithromycin for treatment of chlamydia and research on mucosal factors in relation to STDs.

The medical literature has reported new advances in basic science research on HIV/AIDS. For example, the findings of the AIDS Clinical Trial Group 076 showed that in pregnant women with HIV, antepartum and intrapartum zidovudine (AZT) treatment of the mother followed by short-term treatment of the baby reduced the risk of vertical transmission of HIV infection from 25.5 percent to 8.3 percent. Recent data suggest that when used in conjunction with elective cesarean section, ZDV is associated with even lower vertical transmission rates. New antiviral drugs have been studied and approved for treatment of HIV-infected persons, including protease inhibitors, which are an entirely new class of antiviral drugs. People who elect antiviral therapy can now take a combination regimen that results in sustained suppression of virus production, increased CD4 cell counts, and improved quality of life. Specifically with regard to women's health, recent advances in basic research on HIV include, in addition to the focus on perinatal transmission of the virus, research on the natural history of the virus and its disease progression in women. The case definition for AIDS in women has been expanded to include new diagnostic criteria for HIV-positive persons (including invasive cervical cancer); this has resulted in improved identification of previously unsuspected HIV infection in women.

Epidemiologic Advances

Epidemiologic research has highlighted both the extent of the STD epidemic in the United States and its consequences. For example, a major finding in recent years is the demonstration of a causal relationship between human papilloma virus (HPV) and cervical cancer; so strong is that causal relationship that cervical cancer can now be considered an STD. With the advent of urine-based testing and regulations to obligate STD reporting, epidemiologists revised the estimates of the magnitude of chlamydia infections in the United States; whereas the estimate of American women infected annually had been around 4 million, that figure is now 8 to 10 million infections per year. The estimates for Americans infected with genital herpes and human papilloma virus are 43 million and 40 million, respectively. Hepatitis C, although seemingly less often transmitted sexually, can be transmitted heterosexually and from mother to child, and infects approximately 1.4 percent of Americans. In addition, scientists are beginning to identify individuals who are either nonprogressors or resistant to STDs despite exposure or infection.

One of the greatest advances in understanding the epidemiology of STDs and HIV is the finding that the diagnosis and the treatment of STDs decreases the risk of HIV transmission. One study has demonstrated that the treatment of persons with STDs resulted in a significant reduction in the incidence of HIV infection in the treated population. In addition, routine screening for asymptomatic chlamydia has proven efficacious in reducing the incidence of pelvic inflammatory disease.

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. More accurate and more timely diagnoses of HIV in women have resulted from the broadening of the case definition for AIDS, which includes increasing the range of symptoms that defines the presence of HIV in women, as well as the increasing recognition by clinicians that women are at risk for HIV infection. The risk factors for heterosexual transmission of HIV are now better defined.

Advances in Clinical Practice

Clinical and therapeutic triumphs of the past 5 years are evident in the availability of new diagnostic tests and new drugs, including antiretrovirals (especially protease inhibitors). The findings of the AIDS Clinical Trial Group 076 showed that when AZT was given to pregnant women during pregnancy and delivery, and to infants in the first six weeks of life, the risk of vertical transmission of HIV was reduced substantially (25.5 percent to 8.3 percent). Short course therapy (starting at 36 weeks of pregnancy) has also been shown to reduce rates of transmission. Single-dose therapies, such as azithromycin for treatment of chlamydia, show great promise in large part because ongoing patient compliance is not required. Better diagnostic methods have been developed, such as polymerase chain reaction (PCR) and liquid chain reaction techniques using urine-based (and therefore noninvasive) sampling for the diagnosis of chlamydia infection; multiplex PCR for congenital ulcer disease; and home-based tests for HIV. Other clinical progress includes earlier diagnosis of infections such as chlamydia and HIV that allows the prevention of complications of disease, and the development of the second-generation hepatitis B vaccine and the improved acellular pertussis vaccine.

Advances in Behavior and Education

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. For example, documentation of the increasing numbers of women diagnosed with HIV has led to growing awareness that the HIV epidemic is not limited to the homosexual male population. This awareness has prompted more diverse educational messages about HIV resulting in significantly increased awareness that women may be at risk for HIV infection. With counseling, voluntary testing for HIV infection has increased. In some settings, condom use has increased substantially; the Thailand prostitute study indicated that consistent condom use can substantially reduce STD transmission.

> *". . . 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

Advances in Scientific Perspective

What has begun to underlie the scientific progress described above is progress in the conceptual perspective about research on women's health. 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.

Change in Questions Since Hunt Valley

The working group observed that, in the years since the 1991 Hunt Valley Report, a conceptual paradigm shift has occurred regarding research on women's health. Because society and the health professions are now less likely to view women as mere reproductive beings, the concept of "women's health" has expanded beyond reproductive health issues; serious attention is being paid to the great variety of morbidity and mortality health issues affecting women.

The female genital tract is not simply a "receptacle" and conduit of infection or reproduction, but rather an ecological system not yet well understood. Complex and multiple events occur in the vaginal ecosystem, leading to questions such as "What does it mean to study the vagina?" and "How does what happens in the vagina affect the whole woman?"

GAPS IN KNOWLEDGE

Basic Science

The consensus about the importance of a research focus on the vagina as an ecosystem brings to light a myriad of gaps in basic science: general knowledge about the vaginal ecosystem, interactions of the vaginal ecology with multiple exogenous substances (topical microbicides, sperm, and douching), effective topical microbicides that are not necessarily spermicidal, and vaginal microbiology across the woman's life span. Gaps in prevention and diagnosis include the lack of an effective procedure for diagnosing syphilis at certain stages, understanding the role of STDs in adverse outcomes of pregnancy, the lack of an effective vaccine for most STDs, and the unavailability of rational advice to offer on the management of human papilloma virus infection. The need identified in the 1991 Hunt Valley report for useful animal models still exists. Other gaps include understanding what happens once an organism invades the host and how the host controls or eliminates the infection; adverse neonatal outcomes related to maternal STDs, including why herpes-infected newborns develop a wide range of different symptoms; and the pathogenesis of infertility and tubal scarring, including why some women recover reproductive ability after pelvic inflammatory disease whereas others do not.

Gaps in basic science knowledge of HIV infection range from understanding the precise mechanisms of transmission to delineating the pathogenesis of full-blown AIDS in women. Gaps in knowledge about transmission and initial infection include how to quantitate the infectious viral load in genital secretions, how infection is established (what is the first cell that gets infected?), the in vivo role of peptides that inactivate HIV and other organisms and viruses in test tubes, and the effectiveness of natural defense mechanisms such as pH level and the presence of lactobacilli. Gaps in knowledge about HIV, pregnancy, and hormones include the role of the placenta as a viral barrier (75 percent of infants born to an infected mother are not themselves infected); whether pregnancy increases susceptibility to HIV infection; the role of HIV in adverse outcomes of pregnancy; hormonal influences on viral expression; and the safety of antiretroviral drug treatment during pregnancy. Additional gaps include the biologic interaction of STDs and HIV, particularly regarding effects on the regulation of HIV expression, oral markers for HIV infection, vaginal yeast infections as early markers, and HIV strain differences regarding susceptibility to and progression of infection.

Epidemiology

Gaps in epidemiologic knowledge of STDs and HIV include the need to readdress the conditions that should be reportable as an STD and the legal and ethical barriers to reporting. Barriers exist to enrolling women in natural history studies, especially in the use of consent forms and conforming to study guidelines. Research is sorely lacking on women in medically underserved communities such as correctional facilities, where rates of STD and HIV infection are very high. There is a paucity of data on STDs in sexually abused children and adults. Long-term epidemiologic studies on STDs are needed; for example, research to evaluate the long-term outcome in babies who were given AZT for 6 weeks after birth to prevent HIV vertical transmission from the mothers.

Structural methods are needed to design community-based studies and to evaluate this data in a manner that leads to valid conclusions. These studies would focus on risk factors that occur on a community-wide level, including sociocultural factors.

Research should also be conducted to better define the transmission and epidemiology of herpes simplex virus; to determine the optimal timing for administration of the hepatitis B virus vaccine and the length of time its protective effect will persist; to understand chlamydial disease progression and the development of complications; to describe the natural history of Trichimonas vaginalis (T. vag.) infection in men as asymptomatic transmitters to women; to define, using population-based studies, the role of lacto-bacillus and other normal vaginal flora in preventing infection; and to understand better the findings of previous surveys that indicate that gonorrhea, syphilis, and HIV infection all overlap within the same population. Research is also needed to understand the natural history of human papilloma virus. A greater understanding of the contribution of heterosexual activity to the spread of hepatitis C is needed. Epidemiologic studies focusing on the serotypes of HIV and the relationship of these serotypes to mechanisms of HIV transmission and course of disease are needed. Finally, more powerful microbiologic tools are needed to facilitate epidemiologic research.

Clinical Practice

Despite progress since the 1991 Hunt Valley report, women are still not being sufficiently enrolled in clinical trials. This is true particularly for underserved women such as substance abusers or women who are incarcerated. In some prisons, women are screened for infectious diseases and are isolated if infected, while in other prisons this does not occur. For a variety of reasons, women who are incarcerated or who are drug abusers also do not have access to the latest treatments for infectious diseases. The failure to screen and treat incarcerated women not only presents a health concern inside prison walls but also creates a serious public health issue in the community, since most of the incarcerated women will return to the general population.

Clinical practice still does not have inexpensive, rapid, noninvasive, reliable diagnostic methods and vaccines for viral STDs, including HIV. Other clinical concerns include the increasing microbial resistance to therapies, the diagnosis and treatment of tertiary syphilis, methods for the complete elimination of chlamydia infection and subsequent prevention of tubal scarring, and the development of single-dose therapies for infections other than chlamydia. Significant gaps also exist in our understanding of the acceptance of, compliance with, and optimal immunologic timing and techniques for STD vaccination protocols; the immunologic consequences of such vaccines are also not currently understood.

Two additional factors may have contributed to the continued gaps in the laboratory diagnosis of STDs. First, the well-intentioned requirement of the CDC-issued Clinical Laboratory Improvement Act (CLIA) that mandates that clinics that routinely perform STD tests obtain special certification may have had the unexpected result of a decline in laboratory testing for STDs. Second, the emergence of managed care will almost certainly impact STD screening and may result in a decrease in prevention and screening. An emphasis on the cost effectiveness of prevention and screening over the treatment of established infection will be necessary to avoid a reduction in the availability and utilization of these services.

More information is needed about the effects of therapy for STDs and HIV on pregnancy. Finally, optimal methods for the prevention of perinatal infections remain an area for further investigation.

Behavior and Education

Fundamental knowledge and research are lacking on the conduct of patients and health care providers. For instance, given that messages from physicians have been shown to make a behavioral difference, we still do not understand how to successfully motivate providers to discuss behavior with their patients.

Knowledge about sexual behaviors is also inadequate, particularly with regard to adolescent behavior. The complex issues surrounding choices about reproductive health are not understood. For example, what are the behavioral outcomes related to the competing choices of birth control versus STD control? How can women effectively negotiate for safer sex and for risk-reducing behavior in their steady or casual consorts? Recent experience with multidrug therapy and the development of resistance has highlighted the need for greater understanding of the determinants of adherence.

RESEARCH RECOMMENDATIONS

Crosscutting Themes

To direct and develop the research questions and recommendations, the working group identified three crosscutting themes: emphasis on prevention; recognition of the changing parameters throughout the woman's life span; and understanding the continuum of health issues that ranges from the individual to the community. These themes are defined below and should be applied as a filter for all the recommendations for research on women's health.

1. *Emphasize prevention.* Research should focus on a continuum of prevention methods to avoid infections and their complications:
    - Primary: prevention of infection;
    - Secondary: prevention of disease; and
    - Tertiary: prevention of disease complications.
2. *Consider the changing context throughout women's life cycle.* Research on women's health should take 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 are childhood, puberty, age of reproduction, and menopause. For example, research should elucidate the impact of the given life stage of the individual on the progression of infectious disease from exposure to asymptomatic carriage to full-blown disease. In addition, there may be significant differences in the acceptance and efficacy of vaccines and therapy due to the effects of hormonal variations that occur throughout the menstrual cycle.
3. *Address the full continuum from the health of the individual to the health of the community.* Research studies should be undertaken that will affect not only an individual woman's health but also the health of her family and the communities within which the woman lives and works. Different infectious diseases impact certain communities to varying degrees; the reasons for this, and the influence of community on the diagnosis and treatment of the individual, must be better understood.

Basic Science

The Vagina. STD research should focus on the human vagina. Research is needed 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, both with single and with multiple partners, on disease; and changes in the vaginal ecosystem across the life span.

Primary Prevention Tools. Research should focus on the effectiveness of exogenous hormones, topical microbicides, barrier methods, and vaccines as primary prevention of STDs, including HIV. The development of nonspermicidal microbicides is necessary for women who want to prevent infectious disease but not necessarily pregnancy. An important public perception for researchers to consider is that, when the individual feels protected against pregnancy and/or against one STD because of the use of a barrier method, they also incorrectly feel protected against all STDs. For example, a condom does not protect the individual from contracting chlamydia or human papilloma virus; nevertheless, the public perceives condoms as protection against all STDs. This must be considered in STD primary prevention research.

Pathogenesis of STDs. Research on the pathogenesis of STDs should focus on the requirements for microbial growth, survival, and reproduction, and on environmental factors that enhance microbial growth; on determining whether genetic predispositions render certain hosts more or less susceptible to microbes; and on how the status of the host's immune system affects microbial growth and reproduction. Thus, research must address microbial, host-genetic, and host-immunologic factors. Research to investigate the interactions within the host between STDs and HIV is needed.

Basic Pathogenesis of HIV. Research to elucidate the pathogenesis of HIV/AIDS in women should be continued and include the study of the influences of hormonal and other natural defenses on viral expression, the local vaginal factors that affect susceptibility and disease progression, and mechanisms of vertical transmission.

Therapeutics for Adverse Outcomes of Pregnancy. 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.

Hormonal Birth Control Methods. A systematic research agenda is needed for the study of the potential effects of hormonal birth control methods on a woman's susceptibility to infection. Such research must include girls and women across a wide range of reproductive ages. A safe, female-controlled contraceptive method that would be effective in preventing pregnancy and the transmission of STDs, including HIV, should be developed. In this regard, studies are needed on the efficacy of the female condom for contraception and prevention of STDs.

Animal or Other Reproductive Models for Effective Study of STDs. While important, the development of animal models should not be undertaken at the expense of research devoted to women. Caveats for using animal models include the substantial differences between the mechanisms of action of hormones and microbes in humans versus other species, and the differences in frequency of sexual contact and number of sexual partners.

Epidemiology

Follow-up Studies. Follow-up studies should be conducted to determine the long-term sequelae of vaccines, treatments, and disease progression. For example, babies who were given AZT in utero and during their first 6 weeks of life to prevent vertical transmission of HIV are being followed, with particular emphasis on identifying potential late adverse effects of AZT. A few additional long-term epidemiologic studies exist for HIV, but very few exist for other STDs. Gonorrhea, syphilis, and HIV overlap significantly in some populations; followup studies should be done with these populations as well.

Community-based Studies. Risk behavior and risk factors for STDs, including HIV, that occur on a community-wide level need to be identified. Methods to design community interventions and evaluate the resulting data can then be developed.

Link Between Race and Disease. Conduct research to determine whether a relationship exists between race-based factors and specific infectious diseases. For example, gonorrhea is 60 times more prevalent in blacks than in whites; this could result from several different factors, such as genetic susceptibility or community behaviors. Understanding the reasons is essential to the development of effective prevention and treatment. Factors that may be implicated in disease progression and infection include genetic, environmental, socioeconomic, and sociocultural factors.

Access to Underserved Groups. Research should be conducted on populations with high rates of infectious diseases, which have typically been understudied or underaccessed. For example, STD/HIV rates in prisons are very high, and epidemiologic research on this population is sorely lacking.

Natural History of T. Vag. in Men. Conduct research to determine the role of men as reservoirs for T. vag. and as asymptomatic transmitters of the disease to women.

HIV Serotypes. Conduct epidemiologic studies to provide data on the effect of HIV serotypes on HIV transmission and development of disease. Delineate the factors that contribute to differences in virulence as well as differences in regional transmission of certain serotypes.

Microbiologic Tools. Develop microbiologic tools to facilitate epidemiologic research.

Clinical Practice

Product Development. The phrase "diagnose everything easily and cure everything simply" sums up the long-term recommendation for product development. New diagnostic methods and treatments should be inexpensive, rapid-acting, as noninvasive as possible, reliable, accurate, and easy to use; product research should make these characteristics a priority.

Clinical Trials. Enroll more women in efficacy and safety trials. This recommendation has 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. Specifically, clinical trials on microbicides and other barrier methods are needed to define the efficacy, the safety, and the long-term sequelae of STD and HIV therapy not only on the "typical" patient but also on pregnancy and neonatal outcome. Researchers will need access to clinical trials and treatment for women with HIV and women who are pregnant; both groups have often been excluded from studies in the past. In addition, studies should be conducted on patients with multiple infections.

Cures and Vaccines. 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. Train dental personnel to recognize oral lesions as a sign of HIV infection.

Public Health Policy Research. Evaluate ways to reduce the negative consequences of changes in public health policies. Begin to think about how to implement nationwide vaccine-delivery programs, patterned perhaps on the delivery of the measles vaccine, so that the medical establishment is prepared for the upcoming completion of the herpes simplex vaccine as the first in what will hopefully be a series of vaccines for STDs.

Prevention and Treatment for Underserved Women. Study the consequences of inadequate comprehensive prevention and therapy for STDs/HIV in prisons. Study the impact of needle exchange programs on the spread of HIV.

Behavior and Education

Behavioral Methodologies and Measurement. Conduct behavioral science research on both patients and health care providers. For behavioral theories that already exist, determine if they are being validated and used effectively to alter behavior. For new theories that may be formulated, provide access for utilization and validation in the field.

Sexual Behaviors, Especially of Adolescents. Develop a catalog of sexual behaviors as a base for any intervention strategy. This recommendation underpins many of the other research recommendations in this report. The development of effective vaccines, cures, and prevention messages relies on an understanding of sexual behavior across the life span and within and across communities.

Subject Participation and Compliance. Conduct research on how to increase recruitment and retention in clinical trials and how to enhance compliance with treatment regimens. If treatment compliance research results in only a 10 percent increase in compliance, this will indicate a substantial need for improvement in screening, prenatal care, vaccinations, condom use, microbicide use, and other prevention methods. There should be a focus on pregnant women and women who use illegal drugs, since compliance issues are often of particular concern within these groups.

Effects of Public Health Messages and Societal Norms on Behavior. Information is necessary, but not sufficient, for behavior change. Research is needed to determine not only what information should be disseminated but also how information is delivered. For example, most people know that HIV is fatal, but this information often does not change risk-taking behaviors. Public health messages must be evaluated with the understanding that societal beliefs and social norms are essential components of behavior change. Evaluation of public health campaigns should consider the behavioral outcomes of the competing choices women must make; for instance, a choice to prevent STDs but not necessarily to prevent pregnancy. Research on the impact of popular culture and societal norms on individual and group behavior change is crucial.

Other Research Recommendations

In addition to STDs and HIV, many other women's health issues related to infectious diseases should receive research attention in the next 5 years. The working group did not have the time or the expertise to deal with these issues in depth but believed they should be addressed in this report. These issues include the following:

Urinary Tract Infections. Morbidity associated with urinary tract infections encompasses such problems as "honeymoon cystitis" and incontinence.

Tuberculosis. After adolescence, a woman's risk of disease progression after exposure to tuberculosis is significantly higher than a man's risk. An understanding of the factors contributing to this increased susceptibility to disease, such as hormones, pregnancy, contraceptives, or lifestyle, is needed.

Chlamydia and Heart Disease. More women die from heart disease than from breast cancer. With recent findings that chlamydia may be involved in atherosclerotic lesions, this relationship in women must be evaluated.

Chronic Fatigue Syndrome. Investigators are currently searching for an infectious disease cause for chronic fatigue syndrome, a condition that affects women twice as often as men. Further research into the pathophysiology of this condition is warranted.

Malaria. Initial research indicates that pregnancy increases the death rate from malaria and that the disease has an affinity for certain placental cells. More research is needed on this reemerging infectious disease.

Group B Strep. This infection is the number one cause of neonatal septicemia. With additional research, particularly vaccine development, this disease could be diagnosed, treated, and eliminated.

Other Infectious Diseases. Other infectious disease issues for women's health research include 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.

Emerging Infections. Emerging infections are infections that either have newly appeared, appeared in species previously unaffected, or are rapidly increasing in incidence or geographic range. Recent examples include outbreaks of plague in Surat and India and the Ebola virus infection in Zaire. Most emerging infections are not caused by genuinely new pathogens. Shifting ecological, environmental, and demographic factors precipitate the emergence of disease either by placing nonimmune people in increased contact with a pathogen or its natural host in its native environment, or by promoting dissemination into new regions or new hosts. The current volume, speed, and reach of international travel make emerging infections a significant global problem. The working group made specific note of the importance of cooperative research and information sharing with other countries.

Recommendation for Developing a Full Agenda

The working group recommends that a 2-day retreat be arranged to delve more fully into the diseases listed. Infectious diseases are critical health issues for women, and a longer period of time is needed to develop a full agenda for women's health research in infectious diseases.

REFERENCES

Brown ZA, Berry S, Vontver LA. Genital herpes simplex virus infections complicating pregnancy. Natural history and peripartum management. *J Reprod Med* 1986;31(5 Suppl):420-425.

Eng TR, Butler WT, editors. The hidden epidemic: confronting sexually transmitted diseases. (Institute of Medicine) National Academy Press; 1997.

Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338(7):423-428.

Holmberg SD. The estimated prevalence and incidence of HIV in 96 large US metropolitan areas. *Am J Public Health* 1996 May;86(5):642-54.

Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell lifespan, and viral generation time. *Science* 1996;271:1582-1586.

Quinn TC. Global burden of the HIV pandemic. *Lancet* 1996; 348(9020):99-106.

Rosenberg PS. Scope of the AIDS epidemic in the United States. *Science* 1995;270(5240):1372-75.

MENTAL DISORDERS

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BACKGROUND

Although mental disorders were not a formal topic for discussion at the 1991 Hunt Valley conference, the mental health problems of women were noted. The integration of the National Institute of Mental Health into NIH has given mental disorders equal status with physical diseases, disorders, and conditions.

Gender-related biological and psychosocial factors are recognized as important factors in the etiology, cause, and treatment of mental disorders. With new awareness about the ways in which the differences between women and men affect both physical and mental health, it is critical to present, study, evaluate, and implement changes derived from gender-based research to positively influence the treatment of mental disorders in women. Concerns about mental disorders must be addressed through a multitiered approach with clinicians and researchers willing and able to work even more closely together to promote mental health for women in the 21st century.

The major mental disorders affect women and men to almost the same extent; certain disorders, however, are more likely to affect women than men. Major depression and dysthymia, for example, affect approximately twice as many women as men; thus an estimated 6 percent of U.S. women, in contrast to 3 percent of men, will experience a major depression during their lifetime. Another 6 percent of women have dysthymia, a less severe but often more chronic form of depression. Depression has been likened to an invisible plague spreading around the world — a disease that saps the productivity of people, distresses sufferers and their families, and adds greatly to a nation's health care costs. This description was strengthened by the worldwide Global Burden of Disease study conducted by the World Health Organization, the World Bank, and Harvard University, which found that unipolar depression ranked fourth in magnitude of disease burden (measured in disability-adjusted life years, or lost years of healthy life) in 1990. The study projected that this form of depression will continue to increase such that its burden will rank second only to that of ischemic heart disease by the year 2020.[1]

Another form of depression, manic-depressive illness (bipolar disorder) contributes an additional sizable disease burden. On an individual basis, depression ranges from severe, long-term, life-threatening forms to milder forms of shorter duration. An estimated 18.4 million people in the United States suffer from some form of depression each year and another 2.3 million from manic-depressive illness. More than 2.1 million people experience the most severe forms of depressive disorders. Severe depression may result in sustained productivity loss in the workplace and impairment in quality of life.[2] Research is showing that depression also may lead to other serious physical illnesses such as heart attacks and osteoporosis.

Anxiety disorders also predominate in women, affecting approximately two to three times as many women as men. The eating disorders anorexia nervosa and bulimia nervosa, conditions that may be related to obsessive compulsive behavior, occur 8 to 10 times more frequently in women than men. Anorexia and bulimia together affect 0.5 to 2 percent of adolescent girls and young women, and the prevalence of both is increasing. Like the affective disorders, these anxiety disorders can become life-threatening, even lethal; recovery is slow and relapse is common. Schizophrenia and manic depression also appear to be marked by gender differences in age of onset, pattern of symptoms, treatment response, and natural course; there is no gender difference in prevalence, however.

Mental disorders in women are inextricably linked to their own physical health and to the health and well being of their families. Because women are often care givers for their parents and children concurrently, mental disorders in women may affect two or three generations. Conversely, the burdens of women's multiple responsibilities often create stresses that can amplify mental disorders.

Simply studying a group termed “women” is not enough. Multiple variables, in addition to gender, affect research and treatment: age, physical health, ethnicity and race, marital status, parental status, education, income, occupation, sexual orientation, labor force participation, and geographic location. For example, women are affected by different illnesses depending on their age.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Recommendations from 1991 Hunt Valley Report

In the 1991 Hunt Valley Report, the working groups recommended attention to the following issues related to research on mental disorders in women:

- Comorbidity among mental illness, substance use, and physical illness; identification of certain subgroups of women at risk (genetically, by psychosocial history, chronic stress) for comorbid illness could prove useful for preventive treatment efforts.
- Genetic and environmental factors contributing to mental illness, which can guide development of promising prevention strategies.
- Significant gender differences in prevalence of mood, anxiety, and personality disorder.
- Biological and psychosocial gender-related variables important in the development, onset, course, treatment, and relapse of mental disorders, including early developmental history and role of sexual and physical abuse.
- Gender differences in cognitive and/or personality variables that may influence onset or recurrence of disorders.
- Psychological and biological factors linked to gender in suicidal behaviors across the life span.
- Gender differences in grief reactions and depression following bereavement.
- Gender differences in the development of phobic avoidance for social and specific phobias and agoraphobia.

Since the establishment of ORWH there has been considerable progress.

Mental Disorders in Women — Progress

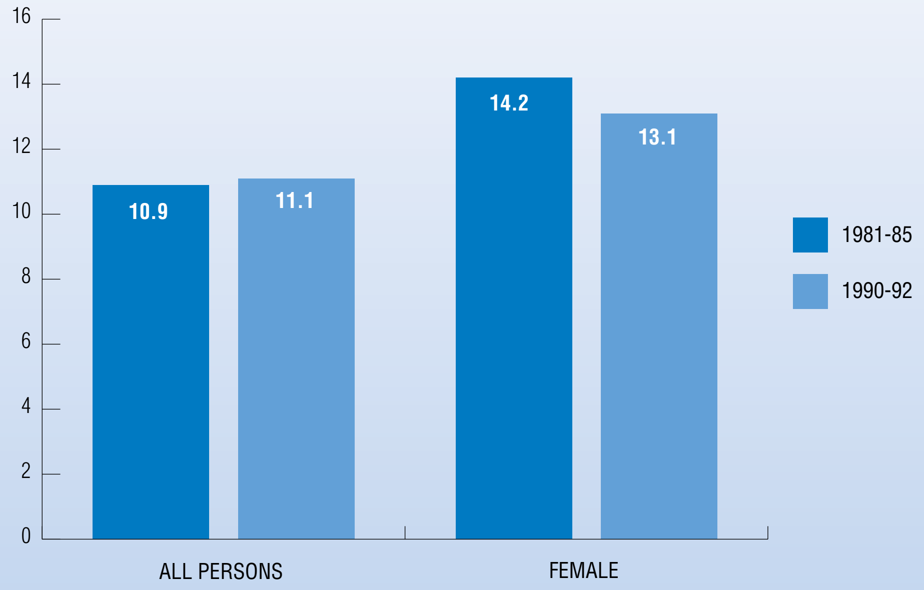
The latest data from epidemiological studies continue to show that depression, anxiety disorders, and eating disorders affect women more often than men. The recent National Comorbidity Study also showed that women are more likely to have more than two disorders. Some progress has been made in the search for causes of gender-based disparity, and investigators are generating novel hypotheses that are now propelling research forward. For example, preliminary data raise the possibility that estrogen's interactions with the circadian pacemaker may somehow be involved in seasonal affective disorder and rapid-cycling bipolar disorder, illnesses that affect women more than men.[3]

There is much to learn about mental disorders by studying gender differences in the biology, behavior, epidemiology, and treatment of these illnesses. The past decade has seen research flourish along these lines, and out of that effort has come a new understanding of the burden that mental disorders place on women. Research targeted specifically on women's mental health problems, including those resulting from violence, is necessary to help women reach their full potential — and society to reap the benefits of healthy women's full participation.

Research on gender differences in mental illnesses is shedding light on the roles and interactions of biological and environmental factors in the following disorders.

Depression and Related Disorders. Major depression, the most common affective disorder, is found twice as often among women as men, a ratio established at or before puberty (Figure 1). Women are more likely to have unipolar depression and depressive (rather than manic) episodes of bipolar (manic-depressive) illness. They also are more likely to have cyclical forms of mood disorders, including rapid-cycling bipolar illness and seasonal affective disorder. Furthermore, women are vulnerable to developing depressive episodes during times of natural or induced reproductive hormonal change (i.e., during puberty, while using oral contraceptives, premenstrually, postpartum, and during menopause). Comparative analysis of empirical studies of mental disorder worldwide reveals a consistency across societies and social contexts. Symptoms of depression and anxiety as well as unspecified psychiatric disorder

FIGURE 1. Proportion of adults with 1-year prevalence of depression: United States, 1981-85, and 1990-92.



Sources: Epidemiologic Catchment Area Study, 1981-85. Comorbidity Survey, 1990-92. National Institute of Mental Health, National Institutes of Health.

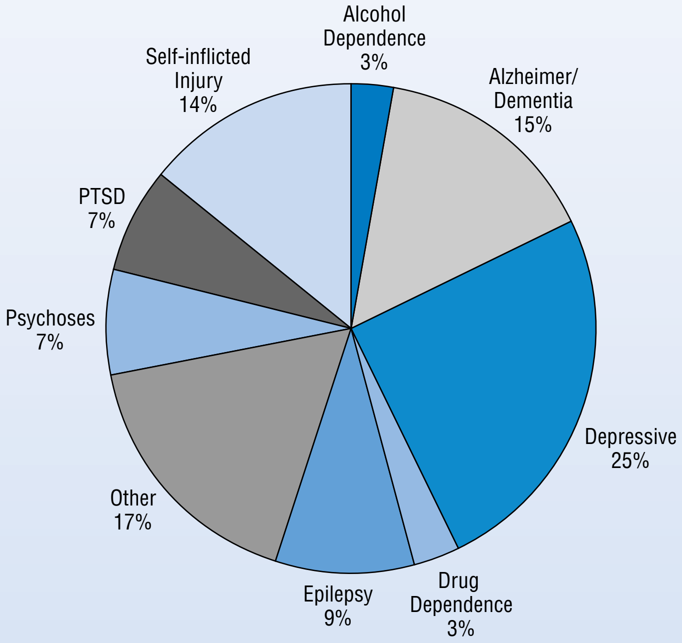
and psychological distress are more prevalent among women, whereas substance disorders are more prevalent among men. The Global Burden of Disease data reflect these differences (Figure 2). Depressive disorder accounts for close to 30 percent of the disability from neuropsychiatric disorders among women, but only 12.6 percent of that among men. Conversely, alcohol and drug dependence accounts for 31 percent of neuropsychiatric disability among men, but accounts for only 7 percent of the disability among women.[4] Weissman and Olfson[5] affirm the finding that epidemiologic data from around the world demonstrate that major depression is approximately twice as common in women as in men and is associated with substantial work and family impairment and high health care expenditures. Despite the robustness of this finding, little is known about specific etiologic factors that underlie this association. Clearly, gender is a proxy term for a system of psychosocial and biological variables. Further complexity stems from the reality that the mood disorders represent a broad spectrum ranging from those that arise primarily in reaction to environmental stressors to those related more strongly to endogenous factors. The role and relative weight of various gender-specific factors may differ across this spectrum and may also influence symptom patterns, comorbidity, course, treatment response, and outcome.

Many researchers assume that gender differences in the rates of depression have their root in adolescence primarily because that is when gender differences first appear. There is, however, some evidence from recent psychosocial studies suggesting that factors operating in childhood may set the stage for hormonal and neurobiological changes that occur in adolescence.[6] A longitudinal study of social development in young children found evidence supporting the idea that girls as young as age 4 have lower scores than boys on measures of perceived competence, self confidence, and self esteem and have more negative feelings following failure. These scores correlated with higher scores (more depressed feelings) on the Children's Depression Inventory. Scores on the depression inventory move toward normal as the girls proceed through the first 4 years of school, suggesting that girls are more vulnerable during periods of transition — entering school and entering puberty — than during times of stability. These observations of important developmental markers encourage consideration of interventions to help at-risk girls and women through transition periods and thus reduce their vulnerability for depression.[7]

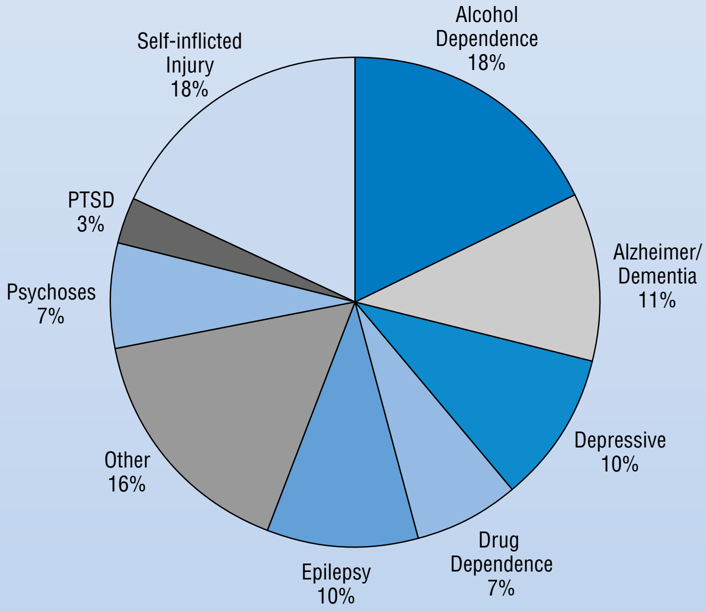
It is not widely appreciated that most affective disorders can be treated successfully. For example, under optimal treatment with the drug lithium, people with bipolar illness live an average of 7 years longer than those not receiving treatment, and they experience 9 to 10 years of more normal health and effective functioning, years that would otherwise have been lost to the illness. Nearly 85 percent of people with unipolar depression and dysthymia respond positively to treatment with antidepressant medication, modern electroconvulsive therapy (ECT), or psychotherapy, alone or in combination.

Approximately 10 percent of pregnant women become depressed during pregnancy. In addition to predicting postnatal depression, antepartum depression may place women at risk for anorexia and substance abuse (e.g., alcohol, drugs, and nicotine) and may inhibit their ability to obtain prenatal care. A woman's depression at this critical time also may have long-term effects on her newborn; infants of depressed mothers have been shown to exhibit behavioral changes and irritability. Despite the potential impact of antepartum depression, clinicians are hesitant to prescribe antidepressant medications for pregnant women because of concerns that the medications could harm the fetus. As an alternative to medications, an NIMH-supported researcher evaluated the efficacy of interpersonal psychotherapy (for up to 16 weeks) as treatment for a multicultural group of medically healthy pregnant women with depression. This group of black, Hispanic, and white women was significantly less depressed after psychotherapeutic treatment — and the effects lasted for at least 3 months after delivery — providing initial

FIGURE 2. Mental health problems of females and males: Worldwide percentage of DALYs* lost. (*DALY - Disability Adjusted Life Year)



FEMALES



MALES

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

evidence that depression during pregnancy may be successfully treated without medication.

Clinical depression can have a compounding deleterious effect on a person's general health. A study funded by NIMH prospectively examined whether a major depressive episode increases the risk of myocardial infarction. A large group of people (1,551) who had taken part in a study in the early 1980s documenting depression in the general population were contacted again in the mid-1990s. People who had been diagnosed with a major depressive episode in the 1980s were found to have a fourfold increased chance of having a heart attack in the intervening years. The data were statistically adjusted to account for factors such as age, sex, smoking, marital status, and history of high blood pressure, all of which can affect heart attack risk. This study is unique because, rather than examining depression in people who had already suffered a heart attack, the researchers determined the presence of depression years before the heart attacks occurred.[8]

Anxiety Disorders. In the term "anxiety disorders," anxiety refers to several conditions: a disabling feeling of panic, a constant sense of apprehension, a phobia, or unrelenting worry about normal life situations. Anxiety disorders rank as the most prevalent forms of mental illness in the United States, affecting more than 20 million Americans. NIMH-supported research has focused on four of the most serious anxiety disorders: panic disorder, posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and phobias. Fortunately, new, effective therapies can provide significant relief for most of them.

Phobias and Posttraumatic Stress Disorder. Panic disorder occurs about twice as often in women as in men, and there is evidence that panic disorder is affected by reproductive function, including premenstrual and postpartum exacerbation and possibly some decrease in symptoms during pregnancy. Phobias, a type of anxiety disorder, are extremely common in the general population. Two to three times as many women as men are affected by phobias, making research on these disorders a particularly important issue for women's mental health. Prevalence of agoraphobia is about four times greater in women than men. Data suggest that even simple phobias predispose to more serious anxiety and depressive disorder in late life.

PTSD is an anxiety disorder first characterized in male combat veterans but soon found to affect female victims of trauma as well. Core symptoms of PTSD include:

- Experiencing a distressing event that involved actual or threatened death or serious injury, or a threat to one's physical integrity, and that involved intense fear, helplessness, or horror;
- Re-experiencing the trauma in nightmares, intrusive thoughts, or flashbacks;
- Numbing of responsiveness or avoidance of thoughts or acts related to the trauma; and
- Symptoms of dysphoria and arousal.

Rape remains a significant problem for women, as does exposure to domestic violence. Overall, exposure-based interventions for rape-related PTSD, with single or multiple treatment components, have been found to produce a decrease or remission of post-trauma problems compared with no treatment. Exposure treatment, in which the victim mentally relives the trauma, permits full processing of the traumatic event and reduces PTSD symptoms. Few women receive such therapy, however; the most common professional intervention for rape victims is the limited crisis intervention counseling offered in rape crisis centers. Recent data show that such limited therapy is not enough to help many women overcome PTSD following sexual assault, suggesting that the nation's rape counseling network can be significantly enhanced. There has been little study of psychological sequelae and treatment of victims of domestic violence.

Studies of women victims of violent crimes have shown that cognitive-behavioral interventions can reduce post-trauma problems that plague these women and relieve anxiety and depression that can limit their daily activities. Unfortunately, few women receive such therapy. This points out the need to increase outreach and educational efforts aimed at women and women's health centers.[9]

Obsessive-Compulsive Disorder. Obsession is characterized by recurrent and unwanted thoughts, images, or ideas that are experienced as intrusive and senseless and compulsion by ritualized, repetitive, and purposeful actions perceived as unnecessary. The Epidemiologic Catchment Area (ECA) study revealed that during a 1-year period, 2.1 percent of the adult U.S. population, or nearly 4 million Americans, met diagnostic criteria for OCD.

Observations of OCD symptoms, combined with information about brain function from imaging and surgery, point to a specific area of the brain — the caudate nucleus — as the source of OCD. The caudate nucleus is a part of the basal ganglia, a section of the brain believed to be involved in a variety of functions, including memory, sensory activities, and motor control. The involvement of the caudate nucleus in OCD was revealed by positron emission tomography (PET) scanning, which showed that the metabolic activity of the caudate decreases after short-term behavior therapy. In most patients who receive the combination of exposure and response prevention, symptoms improve significantly, and this improvement persists over time. Research suggests that behavior therapy might modify or interrupt the pathological brain circuit driving the patient's OCD behavior.

A similar decrease in caudate activity occurs when patients are given medications that are selective serotonin reuptake inhibitors (SSRIs), such as Prozac, which are proving effective in alleviating the symptoms of OCD. Investigators are also using these drugs to probe the neurochemical and neuroanatomical origins of this disorder. Behavioral research is leading to treatments for anxiety disorders as well. For example, cognitive-behavioral therapies have proven effective in helping patients identify and change the feelings that lead to panic attacks and in correcting the adverse consequences such as agoraphobia. The benefits of at least one of these behavioral therapies appear to be long-lasting. Cognitive-behavioral therapies are also proving effective in alleviating the symptoms of generalized anxiety disorder.

Eating Disorders. The eating disorders anorexia nervosa and bulimia nervosa can be viewed as women's disorders because they occur 8 to 10 times more frequently in women than in men. People with anorexia starve themselves into extreme weight loss. They have a severely disturbed body image, frequently viewing themselves as fat despite being bone thin, and they irrationally fear gaining weight. Women with bulimia engage in frequent episodes of binge-eating followed by various purging behaviors such as self-induced vomiting, fasting, excessive use of laxatives and/or diuretics, and excessive exercise. About half of those with anorexia develop bulimia, and many bulimics display anorexia-like symptoms.

To better understand the course and outcomes of eating disorders, NIMH is supporting a longitudinal study of anorexia and bulimia nervosa that is now in its ninth year. A large group of women with these disorders are being interviewed at 6-month intervals. Most of the women have other mental disorders along with the eating disorders; the majority had a current major depression as well as at least one anxiety disorder when first seen by clinicians. The women participated in a variety of treatments, primarily individual therapy, but also group therapy, family therapy, pharmacotherapy, and nutritional counseling. At this point in the study, indications are that, with appropriate therapy, a majority of patients can recover partially or in full. This study is providing valuable knowledge of comorbidity and outcomes in anorexia and bulimia nervosa, knowledge that not only helps to unravel the largely unknown origins and nature of these disorders but also has practical clinical applications for treatment.[10]

This knowledge is also urgently needed as a base from which to develop appropriate educational efforts. A recent effort by independent educators to disseminate information about eating disorders demonstrated this need for knowledge. The educational effort had a reverse effect when the target audience of college girls viewed some of their colleagues describing their own experiences with eating disorders. At followup, the girls had slightly more symptoms of eating disorders than controls, suggesting that the educational program may have reduced the stigma associated with these disorders and may have inadvertently normalized them.[11]

Bulimia nervosa, a serious medical condition, affects women primarily, causing them to repeatedly binge-eat and then vomit or engage in other compensatory activities to avoid weight gain. Antidepressant medications and some forms of psychotherapy can be effective treatments, but they do not work for all patients. Research funded by NIMH examined both psychotherapy and medication treatments, demonstrating that both together are more effective than either alone, but only if the psychotherapy is directed specifically toward altering eating behavior. The researchers found that in patients who switched antidepressant medications partway through the trial when they either did not respond to the first or experienced severe side effects, the change yielded additional improvement. Studies that demonstrate the effectiveness of different types of therapies in combination with one another are particularly important, given the cost considerations of various treatment strategies, yet this type of research is not likely to be undertaken by pharmaceutical companies or other organizations outside the Federal Government.[12]

Mental Health and Other Illnesses

Mental Health and AIDS. In the progression of AIDS, issues of mental health and behavior arise at every point — from the risk-taking behavior that contributes to transmission of HIV; to the early signs of HIV entry into the central nervous system; to the psychological, social, and behavioral challenges faced by all HIV-infected individuals and their friends and families; to the devastating late-stage dementia that affects many AIDS patients; and ultimately to the profound loss and bereavement suffered by those left behind.

Recent accomplishments of basic and behavioral research related to mental health and HIV/AIDS include:

- 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 developed that permit closer investigation of different aspects of HIV infection of the central nervous system.

Research on the pathogenesis of HIV infection will ultimately lead to better ways to treat — and possibly prevent — the cognitive and motor impairments caused by HIV/AIDS.[13]

Mental Health and Physical Disorders. Mental disorders, in particular depression, coexisting with physical illness can increase levels of disability, increase use of health services, and reduce effectiveness of rehabilitation efforts. Mothers with mental and/or physical disorders, due to increased disability, have been found to have less effective parenting behaviors, which in turn, increases risk for behavior problems in their children. Women live longer than men, with more physical disabilities; women are therefore important to study with regard to the role of late-life depression, which in itself can create disability. Many physical disorders may confer risk for depressive or anxiety symptoms through the immune and cardiovascular systems (e.g., cortisol, cytokines, inflammation, pain), and conversely depressive and anxiety symptoms can exacerbate the course of a physical illness by poor treatment adherence and lack of self care. Treatment of mental disorders that are comorbid with physical disorders has been found to reduce hospitalization and rehabilitation services and to improve functioning. More research is needed on how to prevent and treat comorbid mental health problems that are common with physical illnesses (e.g., stroke, hip fractures, cancer and its treatments).

RESEARCH RECOMMENDATIONS

Research Across the Life Span

- Conduct both basic and applied research related to women's mental disorders across the life span to explain gender differences in age of onset, and in age-related differences in the course of mental disorders. Attention to differences in developmental trajectories within biological and psychosocial contexts is necessary in research that considers either gender differences in mental disorder or variation among females. There is a need to study postmenopausal women from their 70s through their 90s to find out why in this age group women often are more resilient than men.

Ethnic Minority Women

- Expand knowledge about mental disorders in ethnic minority women in terms of understanding the context and consequences of psychopathology, clinical course, intervention effectiveness, and service use related to these disorders. There is compelling empirical and theoretical evidence regarding important ways in which the varied cultural backgrounds of patients generally and ethnic minority patients in particular affect the content and form of behavior, psychiatric problems and the manifestations of psychiatric conditions, the context of evaluation, and the meaning of psychiatric disorder. Unlike other fields in medicine, where there are more objective measures and parameters of morbidity, diagnosis in psychiatry has relied almost entirely on signs, symptoms, and behavior that often have subtle differences not only from one mental disorder to another but also differences from one gender to another, one ethnic group to another, and one age group to another.[14] Because culture and ethnicity play such profound roles in shaping and defining the context and the content of both normal and abnormal experience, variables must be taken into account in studies on the nonbiological issues affecting mental disorders in ethnic minority women. With the emergence of research results pointing to a combination of medication and psychosocial treatment as the new standard for optimum treatment for mental disorders, attention to correct diagnosis takes on increased significance. The combination of misdiagnosis of disorders and inappropriate prescription of powerful medications has the potential of creating very serious problems for the patient and the clinician. Recent research in psychopharmacology reveal significant interethnic variation in response to an array of psychotropic medications. For example, research on lithium — one of the drugs used to treat manic depressive disorders — has consistently demonstrated ethnic variations among Asian, black, and white groups, but most of these studies have excluded females. Thus the research agenda to address the mental health concerns of ethnic minority women would encompass both biological and psychosocial factors.[15]

Impact of Violence

- Conduct long-term studies to determine the psychological and biological consequences of sexual assault and other abuses. Overwhelmingly, women are the more likely victims of violent abuse. A study of a representative national sample of women indicated almost 13 percent of women (about 12 million) have been raped and 11 percent more have been the target of aggravated assault at least once. Evidence indicates that mental disorders are more prevalent among women with a history of child abuse. Data are emerging that childhood sexual abuse is strongly associated with high-risk behaviors that can contribute to HIV/STD infection. PTSD is an anxiety disorder first characterized in male combat veterans, but soon found also to affect female victims of trauma. Although many forms of intervention exist for rape-related PTSD symptoms, only a few well-controlled studies have been conducted to systematically evaluate the treatment response of women who have been the victims of sexual assault. HIV-positive women tend to be victims of partner violence.

Gender Differences in Psychopharmacology

- Increase the knowledge base of gender differences in psychopharmacology. Epidemiologic surveys indicate that women are prescribed and use psychotropic medication at twice the rate of men. Historically, this knowledge gap is due, in part, to the exclusion of women of childbearing age from drug-development trials because of fear of unintended birth defects. This research strategy has not furthered the understanding of gender differences in pharmacokinetics and pharmacodynamics of psychotherapeutic drugs. Research should be undertaken to study the effects over time of psychotropic drugs and hormones, because millions of women take antidepressant drugs and hormone replacement medications concurrently and regularly.

Recommendations from Philadelphia Workshop

The following recommendations were reported from of the Philadelphia regional meeting in September 1996.

- Encourage research on the interactions among biological, psychological, and social factors related to mental disorders across the life span of women.

- Encourage research to identify the social, developmental, and biological factors that predispose adolescent girls and young women to a sharp increase in rates of mood, eating, and anxiety disorders.

- Stimulate research on gender differences in brain function, specifically the effect of gonadal hormones on the developing brain and their relationship to the formation of sexually dimorphic brain structures and processes and how these distinctions could be related to gender differences observed in persons affected by mental disorders.

- Further 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. Attempt to link these findings with studies showing that CCK interacts with serotonergic neurons, which have been implicated in the etiology of bulimia.

- Encourage and support research on 1) psychological and biological effects of sexual assault in childhood and 2) intervention research 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.

- Expand research examining the development and effectiveness of treatment models, which are 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.

- Address diversity in all research studies. Many measurement tools used today were normed on white male reference groups. These tools need to be re-examined and validated 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 racial, religious, socioeconomic status, and sexual orientation.

- Integrate cross-disciplinary research from molecular level through societal level. Mental disorders are complex problems that involve mutually interactive biological, behavioral, and societal factors. Research is needed that integrates across these levels of analysis to understand this complexity and provide comprehensive solutions. Given that researchers typically receive training in only one of these levels, cross-disciplinary collaborations are needed to develop more integrated programs of research. Prime topical areas for such cross-disciplinary collaborations in women's mental disorders include AIDS/HIV, abuse, post-traumatic stress disorder, and depression.

Recommendations from Bethesda Workshop

The following recommendations came from the Bethesda national meeting in November 1997.

- *Conduct interdisciplinary research.* Interdisciplinary research is important in all areas, especially in preventive and life span/longitudinal research.

- *Determine what is "normal."* Research is needed on the normal aging brain in women. Then based on what is normal, abnormality can be defined appropriately. The definition of "a normal person" as being someone who does not meet criteria for any diagnosis should include what we know about normal brain development. The effects of genetics and the hormones (e.g., estrogen, testosterone, thyroid hormones) on normal brain development should be studied.

- *Examine resiliency*. Investigate why some families develop female children who are resistant to mental disorders such as eating disorders. What helps most young girls not to develop this mental disorder? What makes them resilient against the overwhelming societal pressures to define themselves in terms of body image?

- *Examine comorbidity.* The traditional comorbidity definition looks at the relationship between drugs and alcohol and mental disorders and mental disorders with physical disorders, but research should broaden this concept to examine the relationship among mental disorders. For example, the work of Breslau and Kessler indicates that early anxiety disorders predispose to depression, for both men and women. Anxiety disorders are significantly more prevalent in girls than in boys, which leads to higher incidence of depression in women than in men.

- *Conduct mental disorders research outside of traditional clinical settings.* This is particularly important for women who may seek treatment more frequently than men so that clinic samples may therefore be biased. Examples of such studies are differing brain development in boys and girls, studies of mental disorders of poor women living in the community, or mental disorders studies in sites like jails, domestic violence centers, and primary health care settings. This includes basic research — population studies on basic brain development, intervention studies in populations that are difficult to reach and that generally do not participate in research studies (e.g., poor women, minority women). Intervention studies and community population studies should be conducted in service sites that are not mental health sites (e.g., jails, domestic violence shelters, homeless shelters, primary care settings, and schools). It is imperative that researchers change their venue from the clinical research setting and concentrate their investigations in the "real world" using probability (not convenience) samples.

- *Study reproductive hormones and their role in women's mental health, especially during the critical life transitions where they are particularly important — menarche, pregnancy, postpartum, and menopause.* Study the effects of drugs on the mental health of mother and baby both short- and long-term outcomes. Study the increased incidence of depression in women at menarche and during the perimenopausal period. Investigate the effect of reproductive hormones on mental functioning throughout the life span.

- *Study mood and menopause.* A recent increase in interest about cardiovascular diseases, mineral corticoid diseases, and reproductive diseases associated with menopause has not been matched by research related to mental illness associated with menopause. With the preliminary finding that there is new and increased onset of major depressive disorder in the perimenopausal years, the effect of hormone replacement on mood is an area that deserves particular attention. An offshoot of this finding that also needs investigation is how major mental illnesses — depression, anxiety, and schizophrenia — are affected by changing gonadal hormones.

- *Research the prevention of mental disorders in women.* Researchers should take a life span perspective, looking especially at the developmental precursors and the gender differences in early developmental trajectories and the likely precursors to mental illnesses.

- *Identify significant changes in the health care and social services systems that are beginning to give back enormous caregiving responsibilities to women.* This extra burden is expected to have enormous and important mental health implications for women. Research is needed to identify, prevent, and treat the serious mental illnesses resulting for women who are overburdened by these added responsibilities.

- *Study nutrition and eating disorders.* This area is of enormous importance to women themselves and because of women's general role as caregiver and provider of nutrition. Investigations of how women and men vary in addictive behaviors, ranging from drugs to food, are needed. For instance, men's addictions may center primarily on substances, whereas for women, the "drug" of choice may be food.

- *Research schizophrenia.* Schizophrenia is believed to be a disorder in which the genetic or environmental "insults" occur in the prenatal period; therefore, researchers need to study brain development and brain building in general and how that differs between girls and boys. The timing of these "insults" may have differential consequences for boys and girls. An early "insult" to the brain may occur, but because of the way the brain develops — prefrontal areas of the brain are not fully developed until 18 to 20 years of age — the areas involved in producing psychotic symptoms are not fully developed and the disorder is not expressed until those areas of the brain are developed. In high-risk children, for example, early cognitive deficits have been found in people who later become psychotic. Males have higher rates of "early" onset schizophrenia, while females are more frequently among late onset schizophrenia. Population-based studies to discover what constitutes normal brain development can illuminate the differences in aging of the brain by sex.

- *Study mental disorders in special populations of women with greater needs especially difficult-to-reach populations*, e.g., women who are poor or homeless, immigrants, women in jails, delinquent girls, women with physical disabilities, women who are developmentally disabled, lesbians (and subgroups like lesbians with physical disabilities), and rural women. These women have special treatment needs and are at much greater risk than women with greater economic resources and may have different etiologies needs and outcomes compared to middle-class women from easy-to-reach populations.

Priorities for subgroups to highlight should be garnered by ascertaining those that are fairly frequent and more likely to occur, then determining whether each of those groups has procedural risk factors for mental disorders. The most important subgroups of women to study will likely include:

- *Women living in poverty.* The majority of people living in poverty in the United States are women and their children. The women have a very different health profile than men. Because they lack access to treatment, these women have not been included in most studies. Researchers who are interested in studying people living at or below the poverty line have found success by reaching out to women.

- *Women in the justice system.* Overlap research studies with the criminal justice system, juxtapose the untreated mentally ill women in the criminal justice system. This emphasis will help fuel financial support for research on untreated mental illnesses in women in general.

- *Homeless women.*

- *Deliquent girls.* Rates of delinquency among girls is an emerging issue. Greater understanding of risk factors (e.g., attention deficit hyperactivity disorder) is needed to develop prevention efforts appropriate to girls.

Future Areas for Research on Mental Disorders

This research on mental health of women and gender differences is important to improve the mental health of U.S. women and to provide critical insights into the origins of mental disorders; such research will continue to be emphasized.

Research on the causes, prevention, and treatment of all forms of depression continues to be of the highest priority to NIMH. Research on manic-depressive illness, or bipolar disorder, will be particularly emphasized. Based on the accumulating knowledge of mental disorders, extremely promising research directions include the heritability of depressive disorders; the roles that interactions of inherited factors with a person's environment may play in inducing depression; the prevention of depression, especially through interventions during childhood; and the discovery of new and improved treatments — both behavioral and medical — for depressive disorders. The therapeutic effect of St. John's Wort (hypericum), an alternative natural treatment for depression, will be rigorously evaluated for benefit or risk in clinical depression.

While long suspected, research findings are now confirming that hormones play significant roles in many mental disorders. Certainly effects of steroidal hormones appear to be of primary importance in the pronounced gender differences found in the prevalence of certain mental disorders — for example, depression, which affects women two to three times as often as men; in the expression of a disorder, as in the gender-related differences in subtypes of schizophrenia; or in the pathogenesis of disorders affecting only women, such as postpartum psychosis, which may result from the sudden fall in estrogen and progesterone concentrations immediately after childbirth.

Steroid hormones also are involved in the effects of stress on brain development and aging, as well as on normal brain functions such as cognitive and emotional processing. Estrogen has begun to reveal some unsuspected talents, such as an apparent ability to preserve and even improve some of the brain's highest functions like learning and memory. At the same time, there is epidemiologic evidence that estrogen may exert protective effect in disorders like Alzheimer disease or schizophrenia.

Like estrogen, corticosteroids have been shown to have profound effects on the morphology of hippocampal neurons. It has long been known that various forms of stress cause changes in expression and release of CRF (corticotropin-releasing factor)-ACTH (adrenocorticotropic hormone), and cortisol that are accompanied by changes in behavior, cognition, and emotion. Similarly, recent work has shown that stressors occurring in the neonatal period may alter the set point of responsiveness for corticosterone release for life. NIMH expects to expand research on the study of hormones and their impacts on brain development, aging, behavior, and gender differences in mental disorders.

REFERENCES

1 Murray CJL, Lopez AD, eds. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, MA: Harvard University Press, 1996.

2 Kennedy C, Carlson D, Ustun TB, Regier DA, Norquist G, Sirovatka P. Mental health, disabilities, and women: A policy-oriented data review. *J Disability Policy Stud* 1997;8(1&2):128-56.

3 Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.

4 Desjarlais R, Eisenberg L, Good B, Kleinman A. *World mental health: Problems and priorities in low income countries*. New York: Oxford University Press; 1995.

5 Weissman MM, Olfson M. Depression in women: implications for health care research. *Science* 1995; 269:799-801.

6 Nolen-Hoeksema S, Girgus JS. The emergence of gender differences in depression during adolescence. *Psychol Bull* 1994;115(3):424-44.

7 Blehar MC, Oren DA. Women's increased vulnerability to mood disorders: Integrating psychobiology and epidemiology. *Depression* 1995;3:3-12.

8 Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA followup. *Circulation* 1996; 94(12):3123-9.

9 Foa EB, Hearst-Ikeda D, Perry KJ. Evaluation of a brief cognitive-behavioral program for the prevention of chronic PTSD in recent assault victims. *J Consult Clin Psychol* 1995;63:948-55.

10 Herzog DB, Nussbaum K, Marmor A. Comorbidity and outcome in disorders. *Psychiatr Clin North Am* 1996; 19(4):843-59.

11 Mann T, Nolen-Hoeksema S, Huang K, Burgard D, Wright A, Hanson K. Are two interventions worse than none? Joint primary and secondary prevention of eating disorders in college females. *Health Psychol* 1997;16(3):215-25.

12 Walsh BT, Wilson GT, Loeb KL, Devlin MJ, Pike KM, Roose SP, Fleiss J, Waternaux C. Medication and psychotherapy in the treatment of bulimia nervosa. *Am J Psychiatry* 1997;154(4):523-531.

13 Kelly JA, Murphy DA, Washington CD, Wilson TS, Koob JJ, Davis DR, Lepezma G, Davantes B. Effects of HIV/AIDS prevention groups for high-risk women in urban clinics. *Am J Public Health* 1994;84:1918-22.

14 Mezzich J, Kleinman A, Fabrega H, Parron D, eds. *Culture and psychiatric diagnosis: a DSM-IV Perspective*. Washington, D.C.: American Psychiatric Press, 1996.

15 Parron DL. Culture, gender, and diagnosis of psychiatric disorder. Presentation at Realizing a Gender-Sensitive Health Care. Amsterdam, The Netherlands: Dutch Foundation of Women and Health Research, 1997.

NEUROSCIENCE

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BACKGROUND

Shortly before establishing the Office on Research on Women's Health (ORWH), Congress declared the 1990s to be the Decade of the Brain.[1,2] Policymakers, scientists, and clinicians recognized that neuroscience research was rapidly expanding 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, opened up new avenues for study.

The interactions of neurotransmitters and hormones and the actions of drugs on these chemicals are major areas of research. Recently, the study of the differences between the sexes had added a new dimension to these investigations. Neurotransmitters relay tiny changes in electrical impulses from one neuron to another and bind to specific receptors. Neurotransmitters can be found throughout all body systems, performing different functions at receptors in different locations: initiating an action in one place and inhibiting a response in another. Hormones form the second great communication system in the body, overlapping with the neurotransmitters, as some chemical messengers affect nerves and travel in the bloodstream. In the last decade, basic and clinical research have revealed that varying gonadal hormone levels during the menstrual cycle and across the life span affect virtually all components of the nervous system.

Recent advances in basic and clinical neuroscience have enhanced the ability of researchers and clinicians to understand the neurobiology underlying diseases and conditions such as Alzheimer disease, anxiety disorders, chronic pain, depression, epilepsy, multiple sclerosis, Parkinson's disease, schizophrenia, and stroke. Such advances have occurred, in part, as a result of improvements in tools and technologies for studying and mapping the brain and its functioning in health and disease. New understandings of brain disorders have been achieved because of the focus on the roles of hormones and neurotransmitters such as estrogen, progesterone, dopamine, serotonin, and other naturally occurring chemical substances in cognition and emotion. Opportunities for direct simultaneous study of physiology and mental functioning have come from noninvasive imaging techniques. Using new and refined techniques, neuroscientists have begun to examine the physiology, neurochemistry, and anatomy of the human brain in living subjects. Supplementing older techniques such as electroencephalography (EEG), these new techniques include positron emission tomography (PET), computer tomography (CT), magnetic resonance imaging (MRI), and magnetic source imaging (MRS).

With the increased attention given to research on women's health and to gender differences, studies using combinations of these 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, such as epilepsy.[3-5] Research has expanded on the influence of hormonal states on important behavioral functions such as cognition and conscious emotion in health and disease.[6,7]

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

The broad recognition that scientifically and clinically significant sex differences exist in many aspects of brain development, organization, and functioning is a recent change and an important one for research. Building on the findings of the last decade, scientists are addressing questions of sex differences in study design. Increasingly, female animals are being used in research, particularly for investigating brain disorders that affect women more than men, such as multiple sclerosis (MS) and myasthenia gravis. With attention to hormonal levels and reproductive stage, questions can be posed more precisely and research findings interpreted more successfully. Research advances in which sex differences play an important role have been noted across the following areas: development of the brain and nervous system, cognition and the effects of hormones, manifestations of brain disorders, sensory perception and pain perception, responses to treatment of disease, and balance and the vestibular system, with the aid of methodological developments in research into sex differences.

Development of the Brain and Nervous System

Although there is much to be learned about normal brain development, explorations of genetic and environmental influences have shown some gains. The interaction between the environment and genetic makeup of the individual through critical periods in the development of the brain creates a pattern of connections unique to each person, but recognizable in general terms, as neurons migrate and connections are formed before and after birth. Scientists have identified the defective gene responsible for about two dozen neurological disorders and the chromosomal location of the defect in 50 to 100. A genetic component has been indicated in the muscular dystrophies, some forms of mental retardation, manic depression, and other neurological disorders. Still unknown are the factors that determine variations in genetic expression of a single gene abnormality, such as what contributes to the early or late start or the severity of a disorder. However, characterization of genes and gene studies have improved diagnosis and the potential for treatment.

New evidence for genetic imprinting (differences in gene expression according to the parent of origin of the gene) has been found in cognition and behavior. Personality effects have been noted in Turner's syndrome, depending on whether the X chromosome is inherited from the mother or father.[8] Mutations in mitochondrial genes have been found to cause rare neurological disorders. For example, a mitochondrial defect due to a gene inherited from the mother leads to hearing loss (triggered by an antibiotic).[9]

Communication between the endocrine system and the nervous system seems to cause anatomical differences in the developing brain and certainly helps the brain to adjust its performance and control of behavior in response to changes in the environment. Specific receptors uniquely responsive to specific hormones are found in selected classes of neurons in the brain. Under the control of the pituitary, which is itself controlled by the hypothalamus, these receptors process the signals, and the cells release neurotransmitters and other hormones into the blood. These hormones act on the pituitary, the brain itself, the adrenal gland, and other tissues. The brain contains receptors for thyroid hormones and steroid hormones (estrogens, androgens, progestins, glucocorticoids, mineralocorticoids and vitamin D).

Along the hypothalamic-pituitary-adrenal (HPA) axis, responses to stress and to changes in circadian and reproductive cycles stimulate hormone production. In the brain, these hormones alter synaptic transmission as well as the structure of brain cells, changing the circuitry of the brain and its capacity for neurotransmission over the course of hours and days. The complex interactions of hormones and bodily functions are only beginning to be explored (see below). For example, the presence of androgen receptors on the motor neurons and estrogen receptors on the sensory neurons may have implications for hormone treatment to enhance regenerative processes and recovery of function.

New developments in imaging techniques have enabled the examination of functional neuroanatomy and the effects of therapies on the brain. By means of imaging, differences in brain organization between men and women have been revealed, as well as new information about brain asymmetry.[10] These findings have led to hypotheses about the effects of laterality on function and on the differences in the male and female brain and how these arise. Sex differences are seen in brain organization for language, which can help explain sex differences in prevalence and symptoms of language and learning disorders.[11,12] The implications of sexual dimorphism for susceptibility to stress and injury and response to congenital abnormalities and injury remain to be explored.

Sex Differences in Cognition and Effects of Hormones

Scientific evidence on the effects of sex hormones on adult cognition has emerged since the 1991 meeting organized by ORWH in Hunt Valley, Maryland, to formulate a research agenda for women's health. Through basic science and clinical research, it is now known that varying estrogen and progesterone levels across the menstrual cycle and across the life span can influence an individual's performance on a number of cognitive tasks.

Estrogens have been shown to have many effects on the brain, beginning at gestation and continuing into adulthood. Investigators are exploring the relation between estrogen and attention and cognition across the life span. Many of the effects of estrogen implicate areas of the brain that are involved in memory processes and their alteration with age in healthy people, and this is important for understanding the pathophysiology and consequences of neurodegenerative disease.[13,14] Preliminary studies conducted in recent years have shown that the decline of estrogen and progesterone levels at menopause is associated with diminished cognition, but that estrogen replacement therapy (ERT) in postmenopausal women can enhance performance of cognitive functions.[7,15] In addition, there is now evidence that ERT can prevent or delay the onset of Alzheimer disease and stroke by affecting nerve-growth-factor systems, particularly cholinergic neurons (neurons that liberate or are activated by the neurotransmitter acetylcholine) in the basal forebrain.[16]

Recent research on animal and human subjects is challenging the long-held assumption that the adult brain does not undergo changes in its structure, particularly in relation to the actions of circulating hormones. It has been demonstrated that estradiol and progesterone have important effects on adult brain structure and function. Animal studies indicate that synaptic density of the hypothalamus is affected by estradiol and progesterone and influences the cyclicity of sexual behavior, as well as the cyclicity of performance on spatial reasoning and memory tasks.[14,15,17] Other research suggests that hormonal modification of the hippocampus may contribute to cognitive changes during menopause, as well as in temporal lobe epilepsy associated with polycystic ovaries or hypogonadotrophic hypogonadism.[18]

Other sex differences involve glucocorticoid hormones. In a study of the effects of gender and age on 24-hour cortisol levels, cortisol levels were seen to be lower in young adult women than in men, because the female response to circadian signals is slower and of lesser magnitude and the return to quiescence is more rapid. In older women compared with men of the same age, HPA reactivity was greater.[19] Older women also showed a significant correlation with cognitive decline of an increment in baseline urinary cortisol secretion over a 3-year period.[20] This is relevant to changes in the brain, because there is evidence from animal studies and some evidence in humans for a link between stress, glucocorticoid elevations, atrophy or damage to hippocampal neurons, and cognitive impairment.[21]

Sex Differences in Manifestations of Brain Disorders

Sex differences have long been recognized in the frequency and severity of a number of neurological and mental brain disorders (e.g., stroke, migraine headache, sleep disorders, movement disorders such as torticollis, immunological disorders such as multiple sclerosis, and mental disorders such as depression, schizophrenia). Recent work confirms the importance of gender considerations in neurology and psychiatry and indicates that reproductive hormones (gonadal steroids) may play an important role in pathophysiology and possibly treatment.

Several examples illustrate how such research can have both theoretical and clinical implications. Sex differences were noted in a prospective Finnish study that examined diabetes mellitus as a risk factor for death from stroke, with women being at a higher risk than men.[22] Similarly, women with myocardial infarction treated with thrombolytic therapy have a higher incidence of hemorrhagic stroke.[23] This may relate to higher rates of cerebral blood flow in healthy women compared with men.

Levels of ovarian hormones are linked to timing and incidence of migraine headache[24] and epileptic seizures,[25] as well as to sleep disorders, especially sleep apnea,[26] and torticollis.[27] Although premenopausal women have less cardiovascular disease than men and estrogen protects women from stroke, there appear to be complex interactions, e.g., ERT increases risk for stroke in women with a history of migraine.[28] Paradoxically, however, ERT may also be the best form of therapy for some women with migraine.[29] Progesterone treatment appears to reduce seizures,[30] but double-blind, placebo-controlled studies are needed to verify this finding. Self-injurious behavior in mentally retarded females is influenced by cyclic hormone levels.[31]

Meningiomas and neurofibromas have estrogen and progesterone receptors, and these neoplasms are sensitive to hormone levels.[32] Observation of the occurrence and size of such tumors will be needed in the context of increased use of estrogen and progesterone replacement (HRT).

Sex differences have also been documented in the manifestations of Alzheimer disease (AD). Women are at a higher risk for late-onset familial AD, and this might be related to gender differences in the apolipoprotein E epsilon 4 allele (EPOE) heterozygous genotype, which is more common in women.[33] Women with AD were found to perform worse than men with AD on measures of semantic memory and language, whereas healthy women performed better than healthy men on these tasks; however, this area of research is still open to study.[34,35] Neuropsychiatric manifestations in AD are also more severe in women, which is consistent with the greater frequency and severity of depression experienced by women.

In contrast, schizophrenia manifests itself less severely in women than in men. The symptoms occur later in life for women than for men, are less severe, have a milder course, and show a better outcome with treatment. It is noteworthy that this difference may be age related, as elderly women with schizophrenia have more severe symptoms than elderly men.

Estrogen and HRT affects the frequency and severity of symptoms of depression, anxiety, and eating disorders. Interactions of HRT with antidepressants and tranquilizers are recognized. In addition, clinical observations indicate that women with a history of head injury are more sensitive to benzodiazepines (Valium), sedatives, and hormone replacement than other women.

Sex Differences in Sensory Perception and Pain

Increasing numbers of studies have produced evidence for sex differences in response to noxious stimuli, trauma, and the experience of pain, although the data are inconsistent, with many confounding variables, and the differences are relatively minor.[36] Females often report higher pain levels than men for the same stimulus intensity.[36-38] Women who suffer pain during menstruation (dysmenorrhea) show increased sensitivity to pain in their muscles in response to pressure (the usual experimental pain inducer).[39-41]

Sex differences in mechanisms that modulate pain exist in animals; the mechanisms that produce these differences are not yet understood. Studies suggest that the effectiveness of treatment for chronic pain may be different for women and men. Estrogen is one modulator of the mechanisms of pain relief.[36,42] Basic research on pain has shown that estrogen appears to induce analgesia through a different pathway in female mice than in male mice. New discoveries of estrogen receptors throughout sensory/perceptual nervous pathways are changing views on estrogen's role. Another recent discovery is that sex-linked genes are associated with nonopioid analgesia in female mice.[43]

Sex differences are reported in coping strategies, internal responses to pain, and to endogenous pain modulation as well as reactions to pain medication. Studies using animal models and humans have demonstrated that pregnancy and parturition are associated with elevated pain thresholds in the mother.[44] During hormone-stimulated pregnancy, opioid-mediated maternal analgesia involving the spinal cord dynorphin/kappa-opioid system attenuates the pain associated with late pregnancy and labor.[45] In fact, kappa-opioids produce greater analgesia in women than in men.[45] Thus, drugs developed in studies with male research models and tested in males may be differentially effective in relieving pain in females.[36,46] Informed research could lead to the development of new interventions that are more effective in mitigating pain in both men and women.

> *". . . hormones effect epilepsy and epilepsy effects 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

Sex Differences in Response to Treatment of Disease

The increased recognition of sex differences in health and brain disease has implications for examining sex differences in response to treatment. The literature is limited, however, since most studies were conducted with men only or were not evaluated for sex differences. It is essential to integrate measurement and analysis of sex differences into research on treatment and on disease presentation.

Research in animals suggests that the development of drugs for the treatment of stroke, for example, should evaluate potential sex differences very carefully. In the rat, N-methyl-d-aspartate antagonists have been reported to induce greater age-associated neuronal necrosis in females than in males.[47]

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 them at greater risk for falls in old age. Also, some younger women experience episodes of falls that appear to be linked to hormone cycles. In the forebrain, ovarian hormones affect the nigrostriatal system, as well as the cerebellum, and affect motor coordination.

Methodological Developments

The number of studies in which sex and gender differences are included as study variables has increased since 1991. These range from studies focusing on the differences in the structure and functioning of the brain in males and females to research on the effects of hormones in the brain, the central and sympathetic nervous systems, and brain disease manifestations and treatment in women and men. The combination of basic and clinical neuroscience methodology has enabled examination of sexual dimorphism developmentally.

Animal studies provide the foundation for integrative research on neuroanatomy, neurochemistry, neuroendocrine function, and neurophysiology. The developmental perspective examines sex differences across these variables in relation to brain development and maturation. 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. Perhaps as important, investigators using these technologies can extend and test hypotheses that have implications for intervention.

Women subjects are needed for clinical studies; they volunteer less often than men. The fact that female hormone levels are variable should be viewed as an opportunity for investigation rather than a barrier. Consideration of hormone levels adds to methodological complexity but has potential for new theoretical insights.

GAPS IN KNOWLEDGE

The question that arises in many studies cited here is what difference do sex differences make for normal functioning? The baseline data on normal functioning are lacking for children, girls at puberty, pregnant and lactating women, and, in general, women throughout all stages in the reproductive cycle. Estrogen has been emphasized, and many studies of the effects of estrogen replacement are under way; however, distinctions must be made between different estrogen and combination hormone therapy preparations, some of which are delivered orally and others transdermally. Other gonadal hormones warrant study: progesterone and androgen levels in women and their effects. It is known, for example, that progesterone levels at the time of injury affect the experience of pain.

The use of female animals or of women in research must be justified and appropriate. Large enough samples must be included in study designs to allow for the heterogeneity of women. The study of sex and gender as factors in brain function requires that we reinvigorate the integrative approach to neuroscience and recognize that studies on whole animals are essential. Expertise and sophistication in these areas need to be appreciated by review panelists (both grant and journal peer reviewers) and also developed in young students through education and training.

Not enough data are available for evaluation and comparison. Many issues are ready for study: social and cultural impacts on brain function, stress, trauma, and injury; brain plasticity and rehabilitation;

strategies for coping with pain; and the effects of drug abuse on the nervous system, to name a few. 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 RECOMMENDATIONS

Virtually all components of the nervous system respond to gonadal hormones. Virtually all disorders involving the nervous system are affected by gonadal hormones. The recent interest in gonadal hormone effects on brain function and the nervous system have been galvanized by evidence about neuroprotective effects of estrogen replacement therapy on Alzheimer disease.

- Raise awareness in the neuroscience research community about the importance of sex differences and hormonal influences on all aspects of brain function.
  - training and retraining
  - research design
  - peer review
- Research basic mechanisms to develop better prevention and treatment strategies.
  - neural systems
  - plasticity and repair
  - mechanisms of hormonal action
- Focus on life-span issues, developmental stages, and hormonal states in females and males.
  - impact of early life events on later neural function
  - increased emphasis on neurobiology of childhood and adolescence
  - careful measures and analysis of hormonal states
  - neurobiology of pregnancy, postpartum, and lactation states
  - further study of the neurobiology of androgen in males and females
- Study neurobiology of interactions of gender and gonadal hormones with endocrine, immune, and other systems and disorders.
  - neurological disorders
  - mental disorders
  - autoimmune disease
  - sensory and motor disorders
  - pain disorders
- Explore impact of social and physical environment on neural development and function.
  - gene and environment interactions
  - life-span perspective
  - stress and trauma
  - nutrition

REFERENCES

1 Ackerman S. *Discovering the Brain*. Institute of Medicine, National Academy of Sciences. Washington, D.C.: National Academy Press, 1992.

2 Carey J, et al. *Brain Facts: A Primer on the Brain and Nervous System*, 2nd ed. Washington, D.C.: Society for Neuroscience, 1993.

3 Stouped E, Mirthful J, Rotenberg Z. Admissions of patients with epilepsy seizures (E) and dizziness (D) related to geomagnetic and solar activity levels: Differences in female and male patients. *Med Hypotheses* 1991;36:384–8.

4 Ahern GL, et al. Paraneoplastic temporal lobe epilepsy with testicular neoplasm and atypical amnesia. *Neurology* 1994;44:1270–4.

5 Herzog AG. Temporolimbic epilepsy and polycystic ovary syndrome. *Fertil Steril* 1996;65:210–1.

6 Kimura D, Hampson E. Cognitive pattern in men and women is influenced by fluctuations in sex hormones. *Curr Direct Psychol Sci* 1994;3:57–61.

7 Halbreich U, et al. Possible acceleration of age effects on cognition following menopause. *J Psychiatr Res* 1995;29:151–63.

8 Ogata T, et al. Turner syndrome and female sex chromosome aberrations: Deduction of the principal factors involved in the development of clinical features [review]. *Hum Genet* 1995;95:607–29.

9 Prezant TR, et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic induced and nonsyndromic deafness. *Nature Genet* 1993;4:289–94.

10 Gerendai I. Neuroendocrine asymmetry [review]. *Front Neuroendocrinol* 1997;18:354–81.

11 Shaywitz SE, et al. Prevalence of reading disabilities in boys and girls. The Connecticut Longitudinal Study. *JAMA* 1990;264:998–1002.

12 Shaywitz BA, et al. Sex differences in the functional organization of the brain for language. *Nature* 1995 (Feb. 16);373:607–9.

13 Rapp P, Amaral D. Individual differences in the cognitive and neurological consequences of normal aging. *Trends Neurosci* 1992;15:340–9.

14 McEwen BS, et al. Oestrogens and the structural and functional plasticity of neurons: Implications for memory, aging, and neurodegenerative processes [review]. *Ciba Found Symp* 1995;191:52–66; [discussion] 191:66–73.

15 Hampson E, Kimura D. Sex differences and hormonal influences on cognitive function in humans. In: Becker JB, Breedlove SM, and Crews D, eds., *Behavioral Endocrinology*. Boston: MIT Press, 1992.

16 Gibbs RB. Estrogen and nerve growth factor-related systems in the brain: Effects on basal forebrain cholinergic neurons and implications for learning and memory processes and aging [review]. *Ann NY Acad Sci* 1994;743:165–96.

17 McEwen BS, Wooley CS. Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adults as well as developing brain. *Exp Gerontol* 1994; 29(3,4):431–6.

18 Wooley CS, McEwen BS. Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle of the rat. *J Comp Neurol* 1993;336:293–306.

19 Van Cauter E, et al. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab* 1996;81:2468–73.

20 Seeman TE, McEwen BS, Singer BH, Albert MS, Rowe JW. Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *J Clin Endocrinol Metab* 1997;82:2458–65.

21 McEwen BS, et al. Possible mechanisms for atrophy of the human hippocampus. *Mol Psychiatr* 1997;2:255–62.

22 Tuomilehto J, et al. Diabetes mellitus as a risk factor for death from stroke: Prospective study of the middle-aged Finnish population. *Stroke* 1994;27:210–5.

23 White HD, et al. After correction for worse baseline characteristics, women treated with thrombolytic therapy for acute myocardial infarction have the same mortality and morbidity as men except for a higher incidence of hemorrhagic stroke. *Circulation* 1993;88:2097–103.

24 Herzog AG. Continuous bromocriptine therapy in menstrual migraine. *Neurology* 1997;48:101–2.

25 Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. *Epilepsia* 1997;38:1082–8.

26 Pickett CK, et al. Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women. *J Appl Physiol* 1989;4:1656–61.

27 Tarsy D, Thulin PC, Herzog AG. Spasmodic torticollis and reproductive function. *Movement Disord* 1997;12:847.

28 Tzurio C, et al. Case-control study of migraine and risk of ischaemic stroke in young women. *Br Med J* 1995;310:83.

29 Silberstein SD, and Merriam GR. Estrogens, progestins, and headache [views & reviews]. *Neurology* 1991;41:786–93.

30 Herzog AG. Progesterone therapy in women with complex partial and secondary generalized seizures. *Neurology* 1995;45:1660–2.

31 Taylor DV, et al. Self-injurious behavior within the menstrual cycle of women with mental retardation. *Am J Ment Retard* 1993;97:659-64.

32 Longstreth WT, Dennis LK, McGuire VM, Drangsholt MT, Koepsell TD. Epidemiology of intracranial meningioma. *Cancer* 1993;72:639–48.

33 Payami H, et al. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: A possible clue to higher incidence of Alzheimer disease in women. *Am J Hum Genet* 1996;58:803–11.

34 Henderson VW, Buckwalter JG. Cognitive deficits of men and women with Alzheimer's disease. *Neurology* 1994;44:90–6.

35 Henderson VW, Watt L, Buckwalter JG. Cognitive skills associated with estrogen replacement in women with Alzheimer's disease. *Psychoneuroendocrinology* 1996;21:421–30.

36 Berkley KJ. Sex differences in pain. *Behav Brain Sci* 1997;20:473–79.

37 Fillingham RB, Maixner W. Gender differences in the response to noxious stimuli. *Pain Forum* 1995;4:209–21.

38 Unruh AM. Gender variations in clinical pain experience. *Pain* 1996;65:123–67.

39 Giamberardino MA, Berkley KJ, Iezzi S, deBigontina P, Vecchiet L. Changes in skin and muscle sensitivity in dysmenorrheic vs normal women as a function of body site and monthly cycle. *Soc Neurosci Abstr* 1995;21:1638.

40 Hapidou EG, De Catanzaro D. Sensitivity to cold pressor pain in dysmenorrheic and non-dysmenorrheic women as a function of menstrual cycle phase. *Pain* 1988;34:277–83.

41 Procacci P. Chronobiological studies on pain threshold. *Pain* 1993;55:277.

42 Touchette N. Estrogen signals a novel route to pain relief. *J NIH Res* 1993;5:53–6.

43 Mojil JS. Identification of sex-specific quantitative trait locus mediating nonopioid stress-induced analgesia in female mice. *J Neurosci* 1997;17:7995–8002.

44 Medina VM, Dawson-Basoa ME, Gintzler AR. 17 Beta-estradiol and progesterone positively modulate spinal chord dynorphin: Relevance to the analgesia of pregnancy. *Neuroendocrinology* 1993;58 (3):310–15.

45 Gear RW, Miaskowski C, Gordon NG, Paul SM, Heller PH, and Levine JD. Kappa-opioids produce significantly greater analgesia in women than in men. *Nature Med* 1996;2:1248–50.

46 Dawson-Basoa MB, Gintzler AR. 17 Beta-estradiol and progesterone modulate an intrinsic opioid analgesic system. *Brain Res* 1993;601(1–2):241–5.

47 Fix AS, et al. Neuronal vacuolization and necrosis induced by the noncompetitive N-methyl-d-aspartate (NMDA) antagonist MK(+)901 (dizocilpine maleate): A light and electron microscopic evaluation of the rat retrosplenial cortex. *Exp Neurol* 1993;123:204–19.

ORAL HEALTH

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*"Most of us enter the world head first and throughout our lives our faces are a window to self-image and how the world sees us. Yet there is more to the craniofacial complex than is in the eye of the beholder. Although history has resulted in differences in training for dentists, physicians and researchers, the body's nerves, blood vessels, inflammatory mediators and the like don't recognize artificial demarcations."**

BACKGROUND

Analyses of recent oral epidemiologic data from the third National Health and Nutrition Examination Survey (NHANES III) indicate that women have shared in the positive oral health trends for the U.S. population. In fact, at face value most available oral health statistics are more favorable for women.[1] Thus, why highlight the need for additional research? Two reasons might be that the conditions under study are highly prevalent among both men and women and that a clustering of oral disease risk factor variables places significant numbers of women at high risk for development of oral diseases.

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 these can induce biological or behavioral changes that adversely affect oral health.[2]

The life situations of significant numbers of women, including their poverty, underinsurance, and status as single head of household or family caregiver, may make attending to oral health and dental treatment needs problematic. Social influences such as traditional gender-role expectations or low income may influence women to defer consideration of their own oral health status while ensuring the well being of others. Gender-role expectations may also bear on women's interactions with dental care providers, possibly affecting treatment recommendations. Similarly, behavioral patterns on the rise among women, including increases in smoking, unprotected sexual activity, and binging and purging, will likely lead to parallel increases in oral and pharyngeal cancers, AIDS-related oral pathologies, and tooth erosion and cavities.[2]

Another reason to consider oral health an important issue for women is its association with overall health and quality of life. The literature indicates that the progressive consequences of oral diseases are not only physical but economic, social, and psychological.[3-13] This point is underscored

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*Excerpt from the Oral Health Working Group Presentation: Putting It All Together: Research on Women's Health for the 21st Century.

by the frequency with which fiction and drama exemplify general pain, suffering, or demise with depictions of oral problems.[14]

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. Yet there are many opportunities throughout the life course to prevent oral problems and/or mitigate their sequelae.

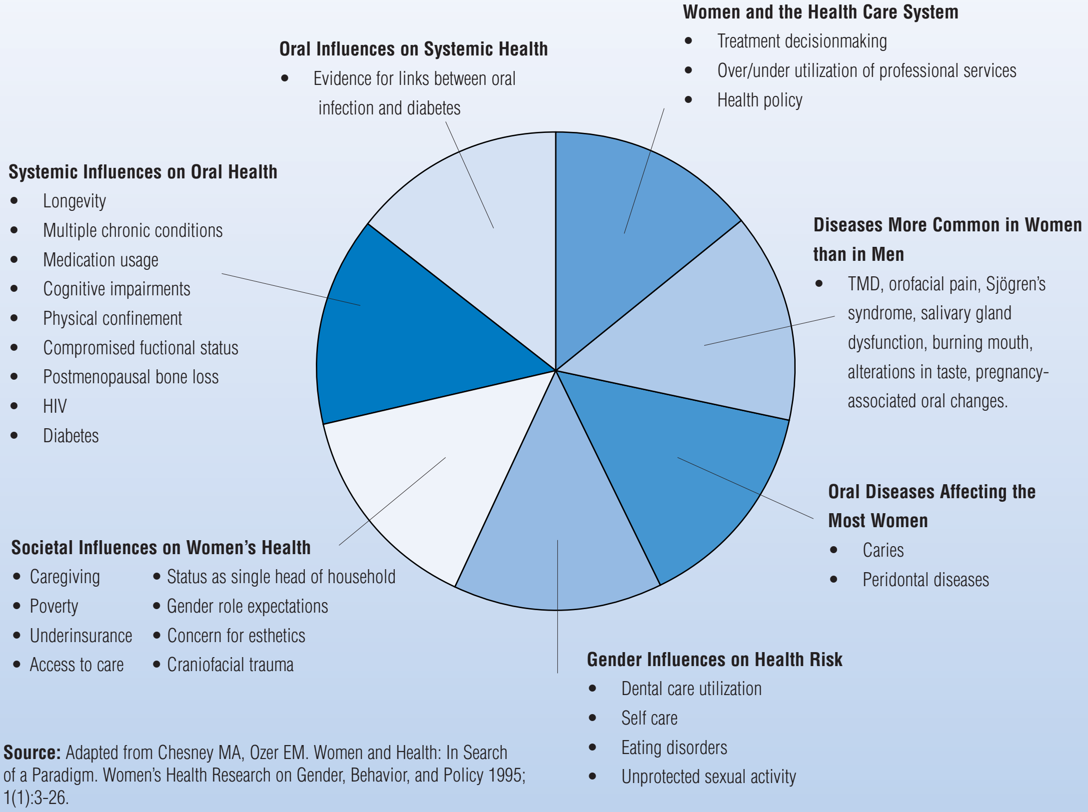
In incorporating orofacial issues into the study of women's health, the research community can gain a fuller understanding of women's health needs and help ensure that oral problems do not unnecessarily add to women's health and life burdens in the 21st century. (See Figures 1 and 2 for background information.)

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Since its inception in 1990, the Office of Research on Women's Health (ORWH) has worked with the National Institute of Dental Research (NIDR) to strengthen and enhance research related to oral diseases, disorders, and conditions that affect women. Collaboration has included the support of several major conferences, including the 1992 Osteoporosis and Oral Bone Loss Workshop, the 1995 Workshop on Selected Chronic Pain Conditions, and the 1997 Technology Assessment Conference on Management of Temporomandibular Disorders.

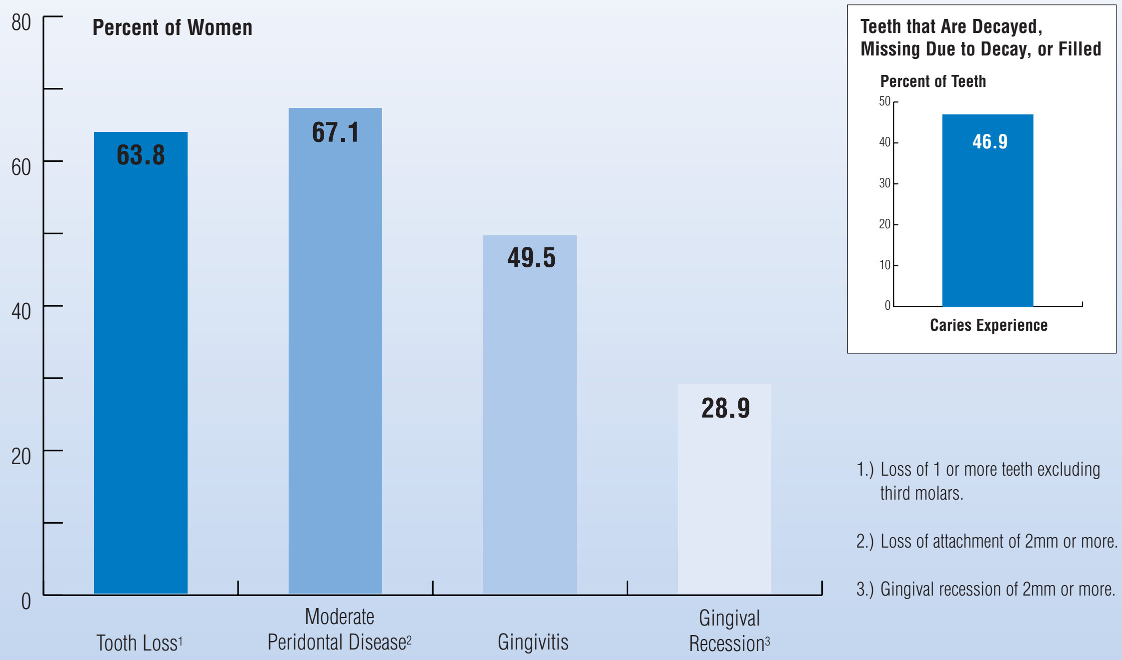
Similarly, the NIDR and ORWH have joined forces to support extramural grants and intramural research projects investigating a wide array of issues of special

FIGURE 1. Content Areas in the Study of Women's Oral Health



Source: Adapted from Chesney MA, Ozer EM. Women and Health: In Search of a Paradigm. Women's Health Research on Gender, Behavior, and Policy 1995; 1(1):3-26.

FIGURE 2. Prevalence of Select Oral Conditions Among Women 18 Years of Age and Older: United States 1988-94.



1.) Loss of 1 or more teeth excluding third molars.

2.) Loss of attachment of 2mm or more.

3.) Gingival recession of 2mm or more.

Sources: National Health and Nutrition Examination Survey III

relevance to women. Areas of focus include oral conditions that are unique to, more prevalent among, manifest differently in, have different risk factors for, or contribute significantly to morbidity among women.

By including an oral health working group in the “Beyond Hunt Valley” workshop, ORWH has afforded women’s health researchers, practitioners, and advocates an opportunity to integrate oral issues into the broader women’s health agenda. Such an integrated, multidisciplinary perspective is needed to fully capitalize on the scientific opportunities of the new millennium.

The timing of this opportunity to re-examine oral health issues within the context of gender could not be better. Fifty years of progress spurred on by federal investments in craniofacial research have paved the way for major advances in the 21st century. Recent advances in the fields of biomaterials, biomimetics, and tissue engineering are being applied to the development of new dental and facial implants, temporomandibular joint (TMJ) prostheses, bone matrix substitutes, and artificial replicas of calcified tissues, skin, and mucosa.[15] Clearly, the predictability of clinical success with these procedures may be influenced by gender.

Technological improvements have also sparked a renewed interest in using oral biochemical and structural markers to describe the risk for, presence, and outcome of oral and general health conditions. Taking advantage of the easy access to oral tissues, researchers are already using saliva as an investigational diagnostic aid and potential monitor of disease progression. Systemic disorders that affect salivary gland composition and gland function include Alzheimer disease, Sjögren’s syndrome, cystic fibrosis, diabetes, and diseases of the adrenal cortex.[16] Saliva is also proving to be an effective tool to monitor levels of hormones and therapeutic medications, as well as the presence of illicit drugs.[17] Despite these positive advances, the extent to which the oral cavity can be exploited in the study of women's health has yet to be fully realized.

Oral researchers have begun applying gene transfer technologies to the repair of diseased or damaged salivary glands and to exploring uses of the salivary gland to produce therapeutic drugs for delivery into the mouth or into the systemic circulation.[18-20] Research opportunities abound to apply these advances to a myriad of conditions affecting women.

A new series of experiments recently published indicate that female dental patients respond more favorably than their male counterparts to kappa opioid analgesics for control of postoperative pain.[21,22] Because most clinically prescribed analgesics are of the mu opioid type, including morphine, codeine, and percodan, these findings could be used to benefit the large numbers of women undergoing operative procedures. More research is needed to generalize these findings to other clinical situations and to translate them as appropriate to clinical practice.

This observed gender difference in postoperative analgesia has added fuel to longstanding conjectures about male and female nervous system differences in response to pain. Indeed, studies in mice have shown that some quantitative trait loci for genes associated with responses to pain and analgesia are gender-specific.[23-25] These findings may help explain why certain painful conditions, including temporomandibular joint disorders, trigeminal neuralgia, fibromyalgia, reflex sympathetic dystrophy, migraine headaches, and burning mouth, are more commonly reported in women.

Similarly, new research on gender differences in taste perception may shed light on women's greater propensity for some painful conditions.[26,27] Oral health scientists have demonstrated that women are more likely than men to be supertasters to a bitter compound known as 6-n-propylthiouracil (PROP).[28] Supertasters to PROP have more fungiform papillae than non or medium PROP tasters, and experience more intense tastes (especially for bitter and sweet), more intense oral burn (e.g., alcohol, capsaicin), and more intense touch sensations from fats in food (e.g., "creaminess," "oiliness").[29–31] These findings, coupled with the fact that fungiform papillae receive innervation from the trigeminal nerve, have led to speculation that taste perception and experiences with trigeminal neuralgia and burning mouth may be linked.

There is new appreciation for the ways in which host factors modulate the susceptibility to and pathogenesis of caries and periodontal diseases, long considered localized infections. For instance, preliminary data from an oral ancillary study of the Women's Health Initiative indicate significant positive correlations between oral and hip bone mineral densities.[32] These findings indicate that oral bone loss caused by periodontal pathogens may be exacerbated by postmenopausal estrogen deficiency. Recent evidence also indicates that persons with noninsulin-dependent diabetes mellitus are three times more likely to develop periodontal disease than nondiabetic individuals. As diabetes increases in severity, the rate at which vital tooth-anchoring bone is lost accelerates.[33,34] Both of these systemic health conditions account for significant morbidity among women; these recent oral findings suggest that there is more to this morbidity than previously considered.

Oral effects of systemic disease are by no means limited to the periodontium. From birth to death, the mouth's continued exposure to opportunistic infectious pathogens is in balance with host immunity. When the host's immune system is compromised, as with HIV infection, certain microbes' virulence and ability to adhere to and colonize oral tissues is enhanced. Such is the case with C. albicans, whose overgrowth in the oral cavity highly suggests immune suppression. In fact, oral candidiasis is the most common opportunistic infection seen in HIV and is often used to herald the presence of infection and/or to indicate disease progression.[35,36] NIDR-supported research to characterize the entire genome of C. albicans will accelerate progress in other areas of candida research including virulence factors, drug resistance, genomic evolution, and treatment. The information provided by this line of research will have considerable bearing on HIV-infected and uninfected women's experiences with oral and genital tract fungal infections. Similarly, saliva's known anti-HIV activity and the intense search to identify protective salivary constituents may ultimately be applied to the formulation of new topical microbicides. In fact, all of oral HIV research, particularly in the areas of opportunistic infections, mucosal immunity, synthetic drugs and vaccines, and innovative drug delivery systems have tremendous potential to benefit women in that they are the fastest growing population with AIDS.

In this new scientific era, there are many reasons to consider oral and general health interactions as bi-directional. In the case of diabetes, new evidence points to chronic periodontal disease as a disrupter of glucose control, possibly due to induction of insulin resistance.[37] Perhaps even more surprising is preliminary evidence implicating periodontal disease as an independent risk factor for myocardial infarction and stroke. Epidemiologic findings indicate a nearly two-fold risk for fatal myocardial infarction and stroke for persons with established periodontal disease.[38] More research is needed, including of a mechanistic nature, to further substantiate these findings. Future research in both the diabetes and heart disease/stroke arena should include greater numbers of women and examine potential gender differences in systemic responses to treating oral infections.

Furthermore, the impact of oral infections on the lives of women may relate not only to their own health but also to that of their offspring. Recent studies of microbial colonization between spouses and between parents and children have demonstrated that oral pathogens are transmitted among members of extended families.[39,40] Perhaps even more surprising is emerging evidence that poor maternal periodontal health increases an infant's potential for low birthweight and for preterm or premature birth. Recent findings indicate that severe periodontal disease in pregnant women is linked to a sevenfold increase in the risk of delivering preterm low-birthweight babies. It is estimated that as many as 18 percent of the 250,000 premature low-birthweight deliveries in the United States each year may be attributed to infectious oral disease.[41,42] Scientists working in this area theorize that oral pathogens release toxins that reach the human placenta via the mother's blood circulation, as shown by results from animal studies. Additional research is needed to substantiate this hypothesis and to confirm this intriguing link.

> *"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

With remarkable advances in science and technology have come increased responsibilities to ensure an adequate supply of competent investigators in the years to come. Education of dental care providers is an increasingly expensive endeavor for the school and for the individual. In 1996, the average accumulated debt of a graduating dental student was more than $81,000. This debt is a significant deterrent to continuing studies by the dental school graduate, including research training. Furthermore, research training is not part of the undergraduate dental school curriculum nor is it included in dental residency programs. As a consequence, dental graduates are not generally exposed to research and are not oriented to pursuing advanced research training. In the case of female dental students, the situation is further compounded by a lack of role models. Women are underrepresented at all levels of academic dentistry; only 15 percent of associate professors and 5 percent of full professors are women. These figures are significantly lower than those in the academic medical environment, where twice as many women are at the full professor level. The result of these circumstances is a dearth of women in academics and research. Continued support and enhancement of oral research training and career development programs are needed to help ensure that women can assume leadership roles in academic and health professional institutions, government agencies, and the private sector.

GAPS IN KNOWLEDGE

Large gaps in knowledge limit the ability to interpret oral health within the context of gender. For instance, there are areas in which oral health information for either gender, even at the descriptive level, is partial or nonexistent. Data gaps in the areas of craniofacial trauma, soft tissue pathologies, and salivary gland dysfunctions are notable illustrations.

Even in the presence of descriptive data, the lack of knowledge about etiologic factors, mechanisms, and clinical course of oral diseases limits the utility of available oral health statistics. For example, women are reported to be more inclined to self care, more likely to visit a dentist, and more likely to report symptoms such as pain. The degree to which these behaviors influence oral disease patterns is unknown. Similarly, there is a dearth of information on the influence of gender on dental treatment decision-making and care delivery. Is women's oral health status a reflection of primary disease experience or gender-specific treatment patterns?[2]

In addition, large gaps in knowledge limit the ability to translate scientific advances to improvements in health. As previously mentioned, breakthrough discoveries in the areas of biomimetics, biomarkers, gene transfer technologies, and pain research have paved the way for a myriad of clinical applications. More research is needed to clarify the influence of gender on the predictability of clinical success for new procedures and pharmacologic regimens.

Although progress has been made in recognizing some oral and general health interactions, considerable research is needed to confirm putative associations for both genders and uncover biologic bases for these links. Additional research is also needed to determine whether there are gender differences in responses to therapies for the oral and general health conditions involved in these links.

RESEARCH RECOMMENDATIONS

Although the oral health research community can exult in its many recent successes, new-found knowledge challenges all of us to do more. It is within this context that oral health working group members encourage additional research in all the areas of oral health study discussed in this report.

The bulleted list below highlights research areas that are particularly ripe for study and that have the greatest capacity to control oral diseases and improve the general health and quality of life of women.

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.

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.

> *". . . Sjögren's syndrome affects women primarily, and women's health problems, especially problems occurring in middle-aged women, have been notoriously understudied."*
>
> Evelyn J. Bromet, Ph.D.
> Sjögren's Syndrome
> Foundation, Inc.

- 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 response 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.
- 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.

Dental Education, Research, and Training

- Establish mentoring programs for girls to encourage them to pursue science courses and careers, including programs linking high schools to universities.
- Expand short-term research opportunities for female undergraduate dental students to stimulate interest in research careers.
- Develop research training programs targeted for women with the capacity to accommodate the increasing pool of women dental graduates.

- Develop clinical research training programs targeted for women as part of advanced primary care dental education programs.

- Continue to provide supplemental research training and funding opportunities to women who must often interrupt their careers because of family care responsibilities.

REFERENCES

1 Redford M, Drury TF. Gender differences in oral disease patterns among U.S. adults. *J Dent Res* 1997;76:Abstract No. 2879.

2 Redford M. Beyond pregnancy gingivitis: Bringing a new focus to women's oral health. *J Dent Ed* 1993;57:742-8.

3 Sheiham A, Cushing A, Maizels J. The social impacts of dental disease. In: Slade GD, ed., *Measuring Oral Health and the Quality of Life*. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 47-56.

4 Reisine S. Oral health and the sickness impact profile. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 57-64.

5 Dolan TA, Gooch B. Dental health questions from the Rand health insurance study. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 65-70.

6 Atchison KA. The general oral health assessment index. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 71-80.

7 Strauss RP. The dental impact profile. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 81-92.

8 Slade GD. The oral health impact profile. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 93-104.

9 Locker D. Subjective oral health status indicators. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 105-12.

10 Kressin NR. The oral health-related quality of life measure (OHQOL). In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 113-20.

11 Leao AT, Sheiham A. The dental impact on daily living. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 121-34.

12 Cornell JE, Saunders MJ, Paunovich ED, Frisch MB. Oral health quality of life inventory (OH-QoL). In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 135-50.

13 Adulyanon S, Sheiham A. Oral impacts on daily performances. In: Slade GD, ed., Measuring Oral Health and the Quality of Life. Chapel Hill: University of North Carolina Dental Ecology, 1997, pp. 151-6.

14 Gift HC, Redford M. Oral health and quality of life. *Clin Geriatr Med* 1992;8:673-84.

15 Slavkin HC. Biomimetics: Replacing body parts is no longer science fiction. *J Am Dental Assoc* 1996;127(8):1254-7.

16 Atkinson JC, Fox PC. Salivary gland dysfunction. *Clin Geriatr Med* 1992;8:499-511.

17 Malamud D, Tabak L, eds. Saliva as a diagnostic fluid. *Ann NY Acad Sci* 1993;694.

18 Mastrangeli A, O'Connell B, Aladib W, Fox PC, Baum BJ, Crystal RG. Direct in vivo adenovirus-mediated gene transfer to salivary glands. *Am J Physiol* 1994;29:G1146-55.

19 Delporte C, O'Connell BC, He X, Lancaster HE, O'Connell AC, Agre P, Baum BJ. Increased fluid secretion after adenoviral-mediated transfer of the aquaporin-1 cDNA to irradiated rat salivary glands. *Med Sci* 1997;94:3268-73.

20 Adesanya MR, Redman RS, Baum BJ, O'Connell BC. Immediate inflammatory responses to adenovirus-mediated gene transfer in rat salivary glands. *Hum Gene Ther* 1996;7(9):1085-93.

21 Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. Kappa-opioids produce significantly greater analgesia in women than in men. *Nat Med* 1996;2:1248-50.

22 Gear WG, Gordon NC, Heller PH, Paul S, Miaskowski C, Levine JD. Gender difference in analgesia response to the kappa-opioid pentazocine. *Neurosci Lett* 1996;205:207-9.

23 Mogil JS, Kest B, Sadowski B, Belknap JK. Differential genetic mediation of sensitivity to morphine in genetic models of opiate antinociception: Influence of nociceptive assay. *J Pharmacol Exp Ther* 1996;276:532-44.

24 Mogil JS, Marek P, Flodman P, Spencer MA, Sternberg WF, Kest B, Sadowski B, Liebeskind JC. One or two genetic loci mediate high opiate analgesia in selectively bred mice. *Pain* 1995;60:125-35.

25 Mogil JS, Richards SP, O'Toole LA, Helms ML, Mitchell SR, Belknap JK. Genetic sensitivity to hot-plate nociception in DBA/2J and C57BL/6J inbred mouse strains: possible sex-specific mediation by 2-opioid receptors. *Pain* 1997;70:267-77.

26 Bartoshuk LM, Duffy VB, Fast K, Garvin V, Lucchina L, Rodlin J, Snyder D, Streigel-Moore R. Variability in taste, oral pain, and taste anatomy: Evidence for menstrual control over oral perception. *Appetite*, in press.

27 Bartoshuk LM, et al. Do taste-trigeminal interactions play a role in oral pain? *Chem Senses* 1996;21:578.

28 Bartoshuk LM, Duffy VB Miller IJ. PTC/PROP tasting: Anatomy, psychophysics, and sex effects. *Physiol Behav* 1994;56:1165-71.

29 Bartoshuk LM, Fast K, Karrer TA, Marino S, Price RA, Reed DA. PROP supertasters and the perception of sweetness and bitterness. *Chem Senses* 1992;17:594.

30 Duffy VB, Bartoshuk LM, Lucchina LA, Snyder DJ, Tym A. Supertasters of PROP (6-n-propylthiouracil) rate the highest creaminess to high-fat milk products. *Chem Senses* 1996;21:598.

31 Tepper BJ, Nurse RJ. Fat perception is related to PROP taster status. *Physiol Behav* 1997;61:949-54.

32 Jeffcoat MK, Lewis CE, Reddy MS, Wang CY, Redford M. Post-menopausal bone loss and its relationship to oral bone loss. *Periodontology 2000.* In press.

33 Genco RJ, Löe H. The role of systemic conditions and disorders in periodontal diseases. *Periodontology 2000* 1993;2:98-116.

34 Gossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ. Response to periodontal therapy in diabetes and smokers. *J Periodontol* 1996;57:1094-102.

35 Shiboski CH, Hilton JF, Greenspan D, Westenhouse JL, Derish P, Vranizank K, Lifson A, Canchola AJ, Katz MH, Cohen JB, Moss AR, Greenspan JS. HIV-related oral manifestations in two cohorts of women in San Francisco. *AIDS* 1994;7:964-71.

36 Shiboski CH, Hilton JF, Neuhaus JM, Canchola AJ, Greenspan D, UCSF Oral AIDS Epidemiology Collaborative Group (Cohen JB, Moss AR, Padian NS, Greenspan JS). HIV-related oral manifestations and gender: A longitudinal analysis. *Arch Intern Med* 1996;156:2249-54.

37 Taylor GW, Burt BA, Becker MP, Genco RJ, Glossman M, Knowler WC, Pettitt DJ. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontal* 1996 (Suppl);67:1085-93.

38 Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol* 1996;67(Suppl):1123-37.

39 Tuite-McDonnell M, et al. Concordance of Porphyromonas gingivalis colonization in families. *J Clin Microbiol* 1997;35(2):455-61.

40 Li Y, Caufield PW. The fidelity of initial acquisition of Mutans streptococci by infants from their mothers. *J Dent Res* 1995;74(2):681-5.

41 Offenbach S, et al. Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol* 1996;67(10)(Suppl):1103-13.

42 Dasanayake AP. Pregnant women's poor health and low birth weight. Presented at Sunstar-Chapel Hill Symposium, Periodontal Disease and Human Health; March 24-25, 1997; Chapel Hill, NC: University of North Carolina, Chapel Hill.

ADDITIONAL REFERENCES

Tissue Engineering

Alper J, Gibbs WW. Boning up: Newly isolated proteins heal bad breaks [news]. Published erratum appears in *Science* 1994 Mar 11;263(5152):1359.

Bruder SP, Fink DJ, et al. Mesenchymal stem cells in bone development, bone repair, and skeletal regeneration therapy. *J Cell Biochem* 1994;56(3):283-94.

Goldberg VM, Caplan AL. Biological resurfacing: An alternative to total joint arthroplasty. *Orthopaedics* 1994;7(9):819-21.

Saliva Diagnostics

Marder MZ, Joshi U, Mandel LD. Estrogen concentration in human parotid and submaxillary saliva. *J Dent Res* 1979;58(12):2370.

Mounib N, Sultan C, Bringer C, Hedon B, Nicolas JP, Cristol P, Bressot N, Descomps B. Correlations between free plasma estradiol and estrogens determined by bioluminescence in saliva, plasma, and urine during spontaneous and FSH stimulated cycles in women. *J Steroid Biochem* 1988;31(5):861-5.

Pain and Analgesia

Berkley KJ. Female vulnerability to pain and the strength to deal with it. *Behav Brain Sci*. In press.

Bodnar RJ, Romero M, Kramer E. Organismic variables and pain inhibition: Roles of gender and aging. *Brain Res Bull* 1988;21:947-9.

Carlsson G, LeResche L. Epidemiology of temporomandibular disorders. In: Sessle B, Bryant P, Dionne R, eds. Progress in pain research and management. Seattle: IASP Press, 1995, pp. 211-26.

Cicero TJ, Nock B, Meyer ER. Gender-related differences in the antinociceptive properties of morphine. *J Pharmacol Exp Ther* 1996;279:767-73.

Cogan R, Spinnato JA. Pain and discomfort thresholds in late pregnancy. *Pain* 1986;27:63-8.

Dawson-Basoa ME, Gintzler AR. Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms. *Pain* 1996;64:607-15.

Dao TTT, Knight K, Tenenbaum HC, Lue F, Ton-That V. Influence of oral contraceptives on the fluctuations of myofascial pain over three consecutive menstrual cycles: A preliminary report. Abstracts, 8th World Congress on Pain. Seattle: IASP Press, 1996, p. 278.40.

Dworkin SF, Huggins KH, LeResche L, Von Korff M, Howard J, Truelove E, Sommers E. Epidemiology of signs and symptoms in temporomandibular disorders: Clinical signs in cases and controls. *J Am Dent Assoc* 1990;120:273-81.

Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. *Pain Forum* 1995;4:209-21.

Gintzler AR. Endorphin-mediated increases in pain threshold during pregnancy. *Science* 1980;210:193-5.

Goulet JP, Lavigne GJ, Lund JP. Jaw pain prevalence among French-speaking Canadians in Quebec and related symptoms of temporomandibular disorders. *J Dent Res* 1995;74:1738-44.

LeResche L, Saunders K, Von Korff M, Barlow W, Dworkin SF. Use of exogenous hormones and risk of temporomandibular disorder pain. *Pain* 1997;69:153-60.

LeResche L. Epidemiology of temporomandibular disorders: Implications for the investigation of etiologic factors. *Crit Rev Oral Biol Med* 1997;8:291-305.

Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. *J Am Dent Assoc* 1993;124:115-21.

Locker D, Slade G. Prevalence of symptoms associated with temporomandibular disorders in a Canadian population. *Community Dent Oral Epidemiol* 1988;16:310-3.

Marcus DA. Clinical review: Interrelationships of neurochemicals, estrogen, and recurring headache. *Pain* 1995;62:129-39.

Sander HW, Kream RM, Gintzler AR. Spinal dynorphin involvement in the analgesia of pregnancy: Effects of intrathecal dynorphin antisera. *Eur J Pharmacol* 1989;159:205-9.

Silberstein SD, Merriam GR. Estrogens, progestins, and headache. *Neurology* 1991;41:786-93.

Spagnoli D, Kent JN. Multicenter evaluation of temporomandibular joint proplast-teflon disk implant. *Oral Surg Oral Med Oral Pathol* 1992;411-21.

Von Korff M, Dworkin S, LeResche L. Graded chronic pain status: An epidemiologic evaluation. *Pain* 1990;40:279-91.

Unruh AM. Gender variations in clinical pain experience. *Pain* 1996;65:123-67. *Science* 1980;210:193-5.

Oral Bone

AAP. Glossary of periodontic terms. *J Periodontal* 1986; Supplement:1-31.

Jeffcoat MK, Chesnut C. Systemic osteoporosis and oral bone loss. *J Am Dent Assoc* 1993;124:49-56.

Nakagawa S, Fujii H, Machida Y, Okuda K. A longitudinal study from prepuberty to puberty of gingivitis. Correlation between the occurrence of Prevotella intermedia and sex hormones. *J Clin Periodontol* 1994 Nov;21(10):658-65.

Sooriyamoorthy M, Gower DB. Hormonal influences on gingival tissue: Relationship to periodontal disease. *J Clin Periodontal* 1989;16(4):201-8.

Zachariasen R. Oral manifestations of metabolic bone disease: vitamin D and osteoporosis. *Compendium* 1990;11(10):614-8.

Zachariasen RD. The effect of elevated ovarian hormones on periodontal health: Oral contraceptives and pregnancy. *Women's Health* 1993;20(2):21-30.

PHARMACOLOGIC ISSUES

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BACKGROUND

This meeting marked the first time that pharmacology has been addressed in a formal working group of the "Beyond Hunt Valley" series of meetings held between September 1996 and November 1997. The recognition of pharmacology as a separate topic is a result of discussions held during three regional meetings (Philadelphia, New Orleans, and Santa Fe), where there was repeated emphasis on the importance of research to (a) elucidate how pharmacologic agents are handled in women throughout the life span and in different racial and ethnic groups (possible pharmacokinetic and pharmacogenetic variations) and (b) determine how the female body is affected by specific agents, alone or in combination (pharmacokinetic and pharmacodynamic variations). The importance of preclinical information to elucidate mechanisms of diseases important to women was extended to elaborating on pharmacologic mechanisms as well.

In approaching discussions about pharmacologic issues, the working group incorporated an interdisciplinary approach to the gender framework for health research.[1-3] This approach encompasses knowledge from varied disciplines such as medicine, nursing, pharmacy, and the basic sciences of molecular biology, genetics, public health, epidemiology, anthropology, agriculture, health education, and sociology. This framework takes into account economic, social, personal, as well as biologic characteristics of individuals.

This report deals with pharmacologic agents, gender-based differences in response and possible variations during a woman's life span. For the purposes of this report and for research agenda planning, pharmacologic agents are defined as traditional therapeutic drugs and biologics, dietary supplements (vitamins and minerals), and alternative medicines. However, the majority of this chapter reflects information regarding traditional therapeutic drugs.

Two terms used frequently throughout this report are pharmacokinetics (PK) and pharmacodynamics (PD). They bear definition at this point.

- *Pharmacokinetics.* PK encompasses the study of the rate and extent of drug absorption, distribution, metabolism, and excretion. It is used to relate the dose of a drug to the concentration of the drug in the blood as a function of time. Thus any physiological process that influences the PK of a drug and is functionally different between the genders will contribute to gender-related differences in drug response.

- *Pharmacodynamics.* PD encompasses the study of the rate and extent of drug response and is used to relate the concentration of drug in the blood to the extent of pharmacological response. Thus for any given concentration of drug in the blood, if a drug receptor has gender-related differences in sensitivity, the drug may elicit gender-related differences in drug response including differential efficacy or safety of the drug.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Since the Hunt Valley meeting in 1991, extensive progress has been made in advancing the understanding of issues and in describing gaps in our knowledge that need to be examined. First and foremost is the progress made in promoting participation of women, including women of childbearing potential, in all phases of clinical trials to acquire more scientific information on how drugs work in women. In 1993, the Food and Drug Administration (FDA) published the "Guideline for Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," which lifted the ban on including these women in early phases of drug studies and called for analysis of data for gender effects in all new drug applications submitted to FDA. In 1994, the National Institutes of Health (NIH) published its *NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research.*

We are much more aware today than we were in 1991 of the clinically significant PD differences in drug-induced responses between men and women. For example, women have a heightened sensitivity to developing cardiac rhythm disorder upon exposure to a number of agents, including common antiarrhythmics and antihistamines.[4-9] This potential hypersusceptibility of women underscores the need to perform additional research on the mechanisms of gender-specific adverse drug events.

Advances in Understanding Mechanisms of Drug Action

Progress has been made in identifying and understanding factors related to mechanisms of drug action such as the role of various metabolic enzymes. There has been elaboration of the cytochrome P450 (CYP 450) isoenzymes and the role of hormonal variation in drug effects. For example, the participants of a 1995 conference sponsored by the FDA recommended that in cases where metabolism of a drug occurs primarily through CYP 450 1A2 or 3A4, PK differences due to hormonal effects are more likely, and this influence should be examined in early drug testing.

At that same conference it was suggested that PD differences between men and women, as well as PK differences, were important to study, because PD predicts clinically important safety and efficacy effects more accurately than PK. It was also recognized that PK differences do not always translate into clinically significant PD differences. Similarly, PD differences may occur without noted PK differences. Figure 1 provides a drug development approach that emerged at that conference for uncovering clinically important gender differences.[10] Few drugs have undergone gender analysis.[11] Progress has also been made in identifying mechanisms of drug action, such as enzyme activity (for an overview of current understanding of factors influencing gender-based PK and PD, see Harris et al., 1995).[12]

Understanding Hormonal Impacts

NIH has embarked upon extensive study of the changing hormonal milieu in postmenopausal women in relation to their overall health and the occurrence of certain diseases. The results of the Postmenopausal Estrogen/Progesterone Intervention (PEPI) trial provide surrogate endpoint information (e.g., lipid levels) regarding cardioprotective effects of current hormonal preparations. The Women's Health Initiative (WHI), when complete, is expected to yield vital information about cardiac events, bone integrity, incidence of certain cancers, and Alzheimer disease. Major research efforts have been undertaken to identify and assess impacts on various estrogen receptors such as those in the heart, brain, blood vessels, genito-urinary system, and skin and the influence of such receptors on PD variation. Much more research progress is expected as newer forms of hormone-analog molecules such as the selective estrogen receptor modulators enter clinical investigation and the marketplace.

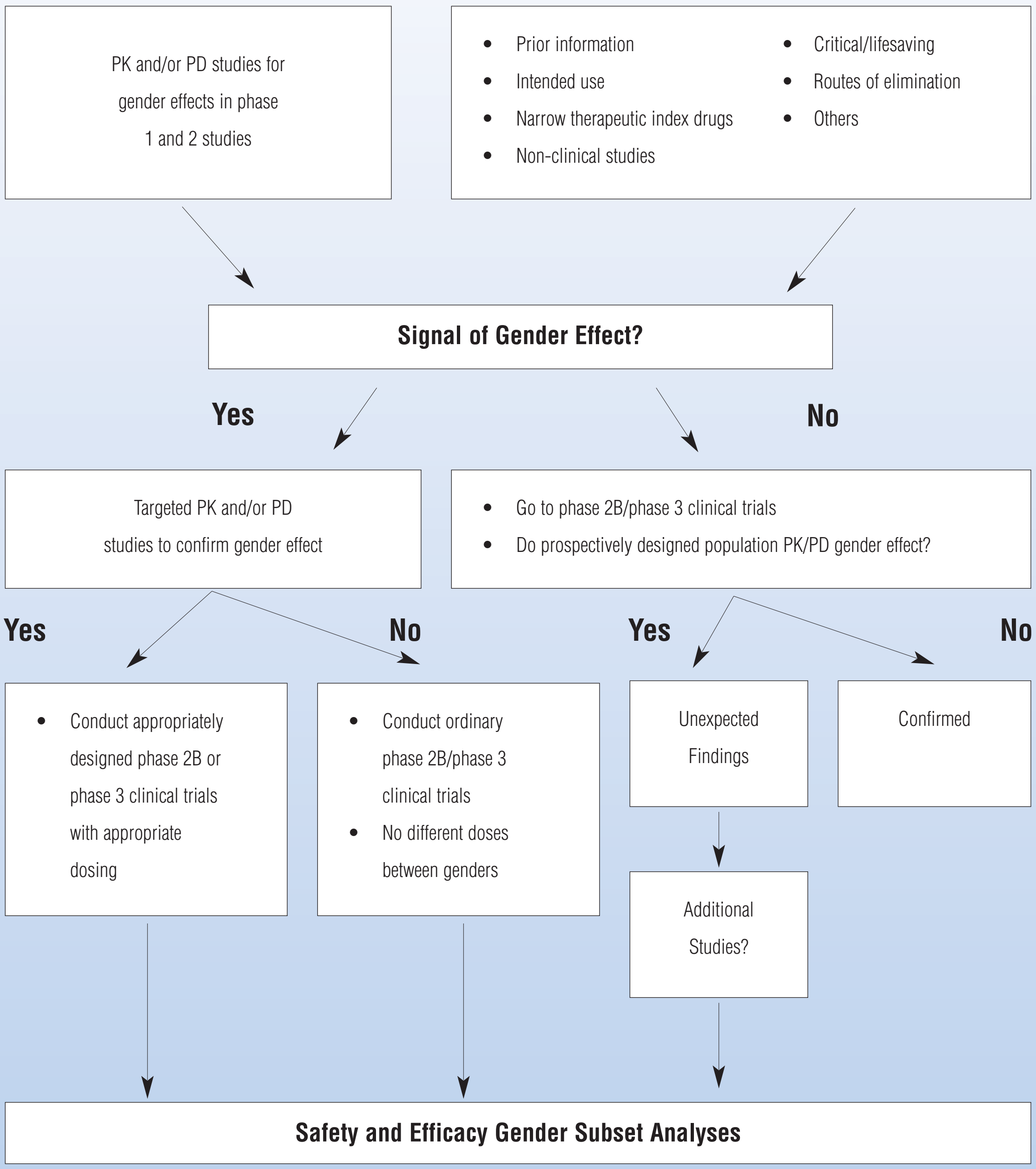


FIGURE 1. Gender Studies

Clinical Practice

Studies advancing the understanding of PK/PD gender issues have begun to generate an understanding of the differences in clinical effects. For example, a study published in 1996 showed that a class of opiate drugs were more effective in women than men following dental surgery.[13] It has been shown that the menstrual cycle changes the PK of only a few commonly prescribed medications.[13] Treatment of women with HIV has sparked research interest in the relationship between new antiviral agents and effects on menstrual cycles. Similarly, principal investigators have begun to address questions about menstrual cycle effects while conducting clinical trials to evaluate specific drug effects on women. Significant advances have also been made in recognizing the importance of adverse effects occurring during drug therapy and/or following ingestion of dietary supplements.

GAPS IN KNOWLEDGE

Despite the impressive advances in policies regarding the participation of women as subjects in research and analysis of data for gender effects, gaps in our knowledge remain regarding the behavior of drugs in women. Areas where much additional research is needed include mechanisms of drug action, which include PK, PD, pharmacogenetics; biological/molecular basis 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. Similarly, progress is also needed for analysis of data by sex.

Research is also needed in identification and quantification of risks associated with use of pharmacologic agents at different points in the life span. For example, there are major gaps in our knowledge of basic mechanisms of action for drugs taken by pregnant women. Long-term safety data of therapeutic agents in regard to fetal outcome are also lacking. Studies are needed to explore the interaction of drugs that have parallel metabolic pathways with exogenous hormones (hormonal contraceptives and hormone replacement therapy).

Components of Pharmacologic Effects

Recent reviews describe the status of gender-based PK and PD research.[11,12] Although significant research advances have been made, the gaps in our knowledge base in this area represent a serious impediment to understanding and assessing the benefits and risks of both current and proposed clinical interventions during a woman's life cycle. Research is needed to evaluate the altered susceptibility to pharmacological agents throughout the life span with special issues pertinent to:

- Children
- Adolescents
- Women with childbearing potential
- Pregnant women
- Lactating women
- Perimenopausal women
- Postmenopausal women
- Senior women

Although gender differences have long been observed in many areas of biology, until relatively recently it has not been appreciated that these differences may contribute to the variability of drug response in humans. However, it is becoming increasingly clear that males and females have differences in drug response (traditionally thought to be related to changes in body mass, body fat, and muscle mass), for both PK and PD reasons. For example, fluvoxamine plasma concentrations are 40 to 50 percent lower in men than women, but the mechanism underlying this difference is unknown and gender-based PD data are not available.[14] In a drug interaction study, isradipine was shown to significantly decrease the area under the curve (AUC) of lovastatin in male but not female subjects.[15] A systematic study of the mechanisms for such gender-related variability in drug response has yet to be undertaken. Nor is there presently any systematic requirement to carry out PD studies whenever gender-related PK variability is observed.

Pharmacogenetics. Pharmacogenetics is defined as hereditary variations in response to drugs,[16] where the majority of variability is caused by alteration in the functional activity of metabolic enzymes. The study of polymorphism (i.e., capacity to exist in many forms) of genes and their proteins (including enzymes involved in drug metabolism) is a rapidly expanding field. Families of enzymes including cytochrome P450s, UDP glycosyltransferases, sulfotransferases, and N-acetyltransferases catalyze a large number of metabolic reactions. Gender differences in the metabolism of certain drugs metabolized by specific isozymes of P450 have been found.[17] However, for the most part gender differences in the amount of the enzymes are not well defined in vitro.[18,19]

Genetic differences in the activity of enzymes have been demonstrated for N-acetyltransferases and the cytochrome P450 isozymes, CYP 2D6 and CYP 2C19.[20-22] There are definite ethnic and racial differences in the genetic polymorphism found. For example, although 5 to 10 percent of whites lack CYP 2D6, less than 2 percent of Asians and blacks are deficient. Similarly, CYP 2C19 deficiency occurs in 15 to 25 percent of Asians, but in only 2 to 5 percent of whites and blacks. However, there are few data available regarding the interaction between gender and genetic polymorphism. Only a few of the studies that have both (a) measured the incidence of genetic polymorphism and (b) also specifically mentioned the inclu-sion women in the study population have analyzed the data based on gender. For example, a review of the literature on the polymorphism of CYP 2C19 is given in Table 1. Of the 38 studies evaluated, only nine studies performed any type of gender analysis and only six studies provided these data. In two of the studies, the incidence of the poor metabolizer phenotype/genotype was numerically smaller in women than in men; in a single study, the incidence was higher in women than in men, and in two studies no difference was noted. However, as demonstrated by Evans et al.,[23] the gender effect may be race dependent. In Saudi Arabian women, the incidence of CYP 2C19 deficiency tended to be greater, and in Filipino women the incidence tended to be lower. Based on these studies, it appears that CYP 2C19 genetic polymorphism may not be strongly influenced by gender. This conclusion must be tempered, however, with the possibility that all the studies cited may have lacked the necessary statistical power to determine gender differences.

> *"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, M.Ed., Ph.D.
> Catherine A. White, Ph.D.
> University of Georgia
> College of Pharmacy

If most drugs had been developed in mixed-gender populations then the extent to which these issues contribute to gender-related variability in drug response would be clearer. However, women were systematically excluded from many clinical trials until relatively recently, and gender-related differences in drug response have only been sporadically reported.

On the other hand, there is some evidence that the biological mechanisms that contribute to PK and PD of drugs have gender-related differences. For example, among the P450 drug-metabolizing enzymes, women have been reported to express higher levels of CYP3A[24,25] and lower levels of the several other P450 isozymes than do men,[24] although with sparteine as a marker, there was reported to be no effect of gender on CYP 2D6 activity.[26] In another study in which 300 mg of oral caffeine were administered, female subjects exhibited significant toxic effects. These women had markedly lower N-demethylation indices as

TABLE 1. Inclusion of Women in Population Studies of CYP2C19 Incidence of Poor Metabolizers

Reference	Race	# of Subjects (Female/Total)	Gender Analysis of Polymorphism	Results: Incidence of Poor Metabolizers in Females vs. Males	Results: CYP2C19 Activity in Females vs. Males
Wedlund 1984[65]	Caucasian	7/156	NO		
Kupfer 1984[66]	Swiss	127/221	YES	Females less than Males 5/127 (3.9%) vs. 7/94 (7.5%) N.S.	
Nakamura 1985[67]	Japanese Caucasian	14/100 14/83	NO		
Jurima 1985[68]	Caucasian Japanese Chinese	127/221 12/31 16/39	YES but did not separate by race	Females greater than Males 9/87 (10%) females vs. 5/101 (5%) males	
Jacqz 1989[69]	French Caucasian	74/132	NO		
Sanz 1989[70]	Swedish	139/253	NO		
Drohse 1989[71]	Danish	136/358	YES	No difference; 3% in females, 2.2% in males	
Horai 1989[72]	Chinese Japanese	26/98 114/200	NO		
Guttendorf 1990[73]	Caucasian	NG/519	NO		
Sohn 1992[74]	Korean	50/206	YES	Incidence of PM was lower in females 4/50 (8%) vs. 4/177 (2.226%) but N.S.	
Bertilsson 1992[76]	Swedish Chinese	NG/137 NG/488	NO		
Llerena 1993[76]	Spanish patients Spanish 'normas'	13/72 26/54	NO		
Kiivet 1993[77]	Estonians	101/156	NO		
Revirigo[78]	Spanish Chinese	196/373 NG/488	YES	Incidence of PM is lower in females 1/196 (0.51%) vs. 4/177 (2.226%) but N.S.	
Weerasuriya 1994[79]	Sinhalese	NG/111	NO		
Setiabudya 1994[80]	Indonesian	25/104	NO		
Basci 1994[81]	Turkish	1/109	NO		
Hadidi 1995[82]	Jordanian	36/194	NO		
Chang 1995[83]	Swedish	88/160	NO		
de Moralis 1995[84]	Chinese	NG/244	NO		Lower S/R ratio in women indicating higher CYP2C19

TABLE 1. Inclusion of Women in Population Studies of CYP2C19 Incidence of Poor Metabolizers

Reference	Race	# of Subjects (Female/Total)	Gender Analysis of Polymorphism	Results: Incidence of Poor Metabolizers in Females vs. Males	Results: CYP2C19 Activity in Females vs. Males
Brockmoller 1995[85]	German	62/174	YES	No gender effect, No data given	
Masimirembwa 1995[86]	Black Shona	NG/103	NO		
Balian 1995[87]	Mixed	64/142	NO		
Evans 1995[23]	Saudi Arabian Filipino	10/102 17/55	YES	1/10 (10%) vs. 1/92 (1%) 2/17 (12%) vs. 11/38 (29%) Female vs. male	No gender difference in either group
Marinac 1996[88]	Black	71/99	YES	No gender effect	
Kubota 1996[89]	Japanese	85/186	NO		
Edeki 1996[90]	Black	97/191	NO		Higher S/R ratio indicating lower CYP2C19 in women
Jurima-Romet 1996[91]	Canadian Inuit	57/152	NO		
Takakubo 1996[92]	Japanese	NG/217	NO		
Roh 1996[93]	Korean	48/103	NO		
Persson 1996[94]	Black Ethiopian	54/114	NO		
Roh 1996[95]	Korean	9/152	NO		
Basci 1996[96]	Turkish	1/89	NO		
Marandi 1996[97]	Estonian	144/210	NO		
Goldstein 1997[98]	Japanese Caucasian Chinese African American	NG/53 NG/105 NG/118 NG/108	NO		
Xie 1997[99]	Chinese	116/245	YES	No gender difference 11.2% vs. 10.9% F to M	
Xiao 1997[100]	Chinese Han	53/101	NO		
Ruasi 1997[101]	Portugese	NG/153	NO		

NG: Number of women in study not given.

well as lower levels of CYP1A2.[27] Women also apparently express lower levels of glucuronyltransferases.[24,26] However, among the other families of drug-metabolizing enzymes, including the sulfotransferases and the glutathione-S-transferases, less is known.

Biologic/Molecular Basis of Pharmacological Factors

Membrane Transporters. Besides differences in drug-metabolizing enzymes, other gender-specific processes may contribute to differences in absorption, distribution, and excretion of drugs. These include the many membrane transporters, for which therapeutic agents may be substrates, such as the drug efflux pumps p-glycoprotein and multidrug resistance protein (MRP). These transporters pump substrates out of the cell, and the overexpression of MRP has been shown to be linked with resistance to anticancer therapies. The metabolite of the female hormone estradiol, estradiol-17-beta-glucuronide, is pumped into the bile by MRP and is also pumped out of tumor cells that express MRP.[28,29] In addition, female mice express a higher basal mdr2 p-glycoprotein than do male mice and thus are able to secrete phospholipids with greater activity.[30] Although gender differences in the expressions of the efflux pumps could contribute to differences in drug pharmacokinetics and response, little work has been done in this area.

Ion Channels. In recent years, sex hormones have been shown to have effects on tissues other than those involved in reproduction. The heart has sex hormone receptors, and exposure to these hormones can alter the expression of ion channels responsible for the electrical activity of the heart. These relationships may help us understand clinical observations such as the relationship between the menstrual cycle and the occurrence of cardiac arrhythmias. Importantly, it may also explain gender differences in cardiac response to drugs. A large number of diverse drugs such as antiarrhythmic drugs, terfenadine, astemizole, cisapride, halofantrine, and erythromycin have the potential to induce a possibly lethal cardiac arrhythmia, torsades de pointes. The mechanism of this not uncommon adverse drug reaction is blockage of potassium channels. One remarkable feature of this adverse event is that the risk of developing this type of arrhythmia is far greater in women than in men who take these drugs.[4-8] Most likely, this is because potassium channel expression and sensitivity to drugs are regulated by sex hormones.[7] Further research in this area is urgently needed.

Increased sensitivity of cardiac sodium channels to bupivacaine has been demonstrated after treatment with progesterone.[8] Such sensitivity is the most likely explanation for reported deaths among pregnant women given this drug for local anesthesia during delivery.

In an example of gender differences in receptors, the density of 5-HT2 receptors was found to be significantly up-regulated in platelets from depressed women.[31] Therefore, a measure of the 5-HT2 density may, in the future, be used as a marker for depression in women, although not in men. However, further research is needed to verify this finding. When monitoring for changes in physiological levels of prolactin as a function of drug therapy, both buspirone and dl-fenfluramine were associated with greater prolactin responses in women than in men.[32,33] Buspirone and dl-fenfluramine may cause greater changes in normal physiological functions in women than in men.

Modulators: Sex Hormones. The sex hormones are obviously expressed differently between the genders. Exogenously administered steroidal hormones, such as oral contraceptives, have been shown to have effects on drug metabolism.[24] Rat data have shown that ethenyl steroids bind irreversibly to rat hepatic cytochrome P450, thereby blocking this pathway of metabolic activity.[34] In vitro evidence suggests that progesterone affects CYP3A4 by either inhibition or activation.[35] Such impairment of metabolic capability has significant implications for drug-drug interactions when another drug is also metabolized by the same P450 enzyme. Whether endogenous sex hormones are responsible for gender-related differences in drug response is unknown, but existing evidence is intriguing. There is evidence, for instance, that changes in hormonal levels during the menstrual cycle may influence the disposition of drugs. For example, among debrisoquine (a marker for CYP2D6) extensive metabolizers, the debrisoquine metabolic ratio (MR) was significantly lower in the luteal phase of the menstrual cycle than in the ovulatory phase or pre-ovulation.[36] The metabolism of alfentanil and prednisolone, both metabolized by CYP3A4, are decreased after menopause during a time when estrogen and progesterone are greatly reduced.[37,38]

Pregnancy and its dramatic effect on sex hormones are known to alter drug metabolism. An example is the increased elimination of antiepileptic drugs in pregnant women.[24] Interestingly, women who have never given birth were reported to have decreased CYP1A2 levels, but those who had given birth had the same level of CYP1A2 as men.[39] We are currently unable to predict whether these changes are generalizable. Until this is studied systematically, variability in drug response will continue to be a problem in therapeutic dosing.

Chronopharmacology. Chronopharmacology is the study of the time-dependent dosing of pharmacologic agents. Chronopharmacology is dependent upon inherited factors such as gender-related differences and genetic variations,[40,41] age-related differences,[42,43] inter-individual differences in chronoeffectiveness of drugs related to diseases such as cancer,[44,45] as well as drug-dependent alteration due to biological rhythms. Chronopharmacology also takes into consideration specified chronobiotics, agents that can influence biologic rhythms.

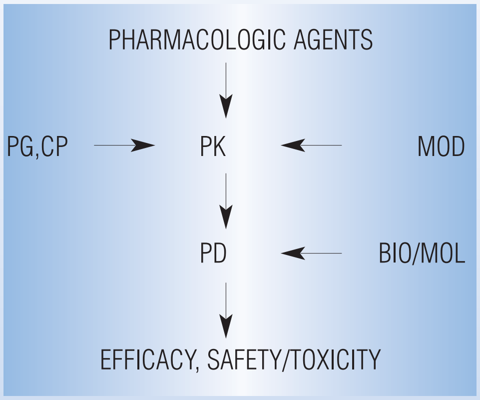
The area of chronopharmacology is relatively new, with the establishment of a journal in that area in the 1980s. Therefore, chronopharmacology must take into consideration basic principles of medicine and individual patient characteristics. Minimal work has been done to examine the chronopharmacologic differences or similarities between women and men.

A chronopharmacokinetic gender-related difference in men and women was demonstrated for the cephalosporin antibiotic, cefodizine. When this drug was administered at four separate times over a 24-hour period, the AUCs for women were significantly higher ($p<0.001$) than those for men. The largest AUC occurred at midnight for both women and men, and the smallest occurred at 6:00 p.m.[46] Even when chronopharmacokinetic effects are observed, other factors may need to be considered. For example, in the case of indomethacin, a nonsteroidal anti-inflammatory drug, chronopharmacokinetic variation has been noted in young, healthy subjects and in patients with arthritis,[42] but not in elderly patients.[43]

Summary Statement

Importance of Combining Pharmacokinetic and Pharmacodynamic Data: Consideration of the Interactive Nature of Factors Yielding Pharmacological Effects. Although it has become apparent that there are many gender differences in the PK of drugs, the existence or magnitude of PD differences cannot always be predicted accurately. This phenomenon is well illustrated in the case of the drug propranolol. In the NIH-sponsored "Beta Blocker Heart Attack Trial," women seemed to have higher plasma concentrations of propranolol than men given equivalent dosages. A natural response to this information would have been to recommend that women be given lower dosages of propranolol to correct for their lower clearance of the drug. However, Flockhart et al. compared the actual degree of beta adrenoceptor blockade with propranolol in men and women using an isoproterenol challenge infusion and found that women had a lower sensitivity to propranolol that compensated for their higher plasma concentrations.[9] This difference negated the need for lower doses, which could have reduced the overall efficacy of the drug. Examples such as these clearly demonstrate the need to examine

FIGURE 2. Interrelationship of Pharmacological Parameters



Legend:
PK = pharmacokinetics
PD = pharmacodynamics
PG = pharmacogenetics
CP = chromopharmacology
MOD = modulators of pharmacologic effects
BIO/MOL = biologic/molecular basis of pharmacologic effects

PD research in conjunction with PK research in order to avoid erroneous conclusions. In addition, emerging information on other components of pharmacological effects should be considered in terms of their interactive effects. Figure 2 provides a new model for considering these interactive effects on overall drug safety/toxicity and efficacy.

Preclinical Studies

In keeping with newer approaches to the study of pharmacological effects, there is an urgent need to develop reliable preclinical (animal and in vitro) models that will provide information about mechanisms of action of drugs, pharmacokinetics and pharmacodynamics, and aid in assessing the role of hormones in drug metabolism. More detailed preclinical information is also needed to guide the planning and implementation of clinical development programs and to improve the efficiency of human testing.

Drug Use in Pregnancy

Pregnant women, like all other groups of individuals, may benefit from pharmacological agents. However, concern for potential fetal harm caused by drugs taken during pregnancy has resulted in exclusion of pregnant women from clinical research. This exclusion was also extended to women of childbearing potential to prevent fetal exposure to unknown effects of a new drug. In 1993, FDA issued a guideline that removed previous policies that had recommended that women of childbearing potential be excluded from phase I and II studies of non-life-threatening diseases.[47] Protocols for drug testing have included criteria to minimize the risk of pregnancy in women of childbearing potential enrolled in clinical trials and taking the experimental agent. Thus, the number of pregnancies where there is exposure to experimental agents is limited. To further compound this problem, no systematic program exists to monitor new drugs for untoward effects on pregnant women once they are approved despite the widespread use of pharmaceutical agents by pregnant women. Although there may be unexpected adverse consequences when pregnant women take therapeutic agents necessary for treatment of a medical problem, the precise etiology of an adverse event is often difficult to determine. Background rates of 3 to 4 percent fetal anomalies, and even higher rates of spontaneous and therapeutic abortions, confound the clinical picture and may mask a drug-related outcome.

In addition to the lack of information on safety of therapeutics with regard to fetal outcome, data are not available to address safety or dosing considerations for the pregnant woman herself. The physiology of pregnancy may provide an environment in which some toxic effects (such as those involving hormone-sensitive organs) of particular drugs may be more likely to be manifest. Also, changes in renal and hepatic function, plasma protein binding, and volume of distribution may substantially alter the pharmacokinetics of drugs in pregnancy so that some drugs may need to be dosed very differently in pregnant women and nonpregnant women.

Pregnant women have great potential for exposure to medications,[48,49] for pre-existing medical conditions (such as epilepsy), for conditions occurring during pregnancy (such as hypertension), and also through inadvertent exposure before becoming pregnant or during early-phase pregnancy (before a woman is aware she is pregnant; in the United States, 50 percent of pregnancies are unplanned).[50] Because most medications have little or no information on use during pregnancy or on the risk for the developing human fetus, scientifically valid and rigorous preclinical methods for evaluating potential risks in pregnant women must be developed. Current methods for collecting information on pregnancy exposure to drugs are limited. Some pharmaceutical companies may have a registry to receive reports on birth outcomes from women who have taken a particular drug while pregnant. However, the value of these registries is limited: these registries are not widely known, reporting is voluntary, the numbers of reports may be small, followup may be incomplete, and other factors related to pregnancy outcome may not be well described.

The FDA may receive an individual report when a baby is born with a major malformation and the mother remembers having taken a drug during her pregnancy. If the birth defect is very rare, cluster reports may be helpful. However, this technique is “numerator” oriented and is unable to determine the frequency of adverse event occurrence within the exposed population. This approach can be used for generating hypotheses, but not for providing definitive information. Additional studies are usually needed to determine the nature and strength of any association between an adverse event and exposure to a drug. The problem of establishing whether a true association exists is compounded by the bias introduced in any retrospective study. Whenever there is an adverse outcome, recall of preceding events is greater than after a normal outcome. Such recall bias can be eliminated in prospective studies. Attention should be devoted to devising systems for prospective monitoring of fetal outcomes and of performing longer followup studies monitoring therapeutic exposure of pregnant women. The benefits of conducting clinical trials with AZT in pregnant women was demonstrated in the 1990s. There have also been limited clinical trials of pharmacological agents in halting preterm labor or treating pre-eclampsia.

Another potential problem during pregnancy is use of dietary supplements. Even though many of these substances are not currently tested for safety and efficacy, they are being taken in increasing amounts by women, including pregnant women, who believe they are safe when in fact their safety is not known.

Breast Feeding and Maternal Drug Use. Although the benefits of breast feeding on newborn and infant health and for the maternal-infant relationship are well established, it is important to understand the potential for drug-related infant morbidity, via breast feeding, following maternal drug intake. Because pharmacologic agents are rarely tested for use in lactating women, there are many uncertainties regarding their safety for breast-fed infants. Research is also needed to ensure the safety of breast-feeding women and their nursing infants following drug administration during delivery and puerperium. Potential risks to such infants are increased following multidose, high-dose, or long-standing therapy, particularly in highly vulnerable premature neonates. For example, the limited data regarding the safety of agents with CNS activity raise concerns about toxicity and abnormal neurological development in the breast-feeding infant.[51] Similarly, there are safety concerns for antithyroid drugs, such as the thioureylenes, which are known to be secreted in breast milk.[52]

Factors that facilitate the transfer into milk, as well as the PK and PD properties of the drug in the mother and infant, must be evaluated. Drug properties that promote low milk concentrations include large volume of distribution in the serum, high protein binding, low lipid solubility, ionization at physiologic pH, and large molecular weight. Following transfer into breast milk, drugs with low bioavailability and short elimination half-lives in neonates provide increased safety margins.[53]

For drugs that may pose a potential concern to the newborn, steps can be taken to minimize risk. These include such interventions as selection of alternative effective drug regimens with safer profiles in breast feeding, timing of drug dosing to minimize accumulation in the breast milk, surveillance for newborn or infant symptomatology that may be a sign of toxicity, or even the determination of drug levels in the infant's circulation.[54]

RESEARCH RECOMMENDATIONS

Recommendations are grouped into the following areas: Components of Pharmacologic Effects, Preclinical Studies, and Drug Use in Pregnancy.

Components of Pharmacologic Effects

Recommendations. Examine the underlying mechanisms that contribute to gender differences in drug effects and disposition encompassing topics including, but not limited to, 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.

Research Goals. Carry out basic and applied research on the following:

1. *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 childbearing potential, pregnant women, lactating women, perimenopausal women, menopausal women, and senior women. The examples cited earlier in this report clearly demonstrate that gender-specific biology, reflected by such modulators as the sex hormones, can have a dramatic influence on the physiological response to drugs. Further research into the mechanism of these differences will be essential before it will be possible to predict in advance, or even identify, gender differences that result in increased drug toxicity or lack of responsiveness in either sex. Adequate research support will be required when PD studies are warranted.

   - 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. With regard to women of childbearing years, the pharmacology working group strongly supported continued emphasis on including these women in all phases of clinical trials as part of drug development. To maximize safety and effectiveness of drugs used by these women, interaction of drugs with hormonal contraceptives must be studied routinely as should pharmacological agents for diseases that are common for this age group (e.g., autoimmune disorders, depression, HIV, migraine). Other specific topics for research include:

- Conventional hormone therapy vs. SERM
- Long-term effects of lifetime estrogen exposure (e.g., cancer)
- Gender differences in response to chemotherapy
- PK/PD of specific drugs or drug classes such as chemotherapeutic agents (e.g., tamoxifen), and potassium channel blocking antiarrhythmic drugs
- Examine drug interactions, an area that includes two components: drug-drug and drug-nutrient interactions; women are underrepresented in studies for both. Drug-nutrient (food, vitamin supplements) interactions have not been well studied. Examination of the broad spectrum of possible drug-drug and drug-nutrient interactions is warranted both for available pharmacologic agents and for those currently in clinical trials.

2. *Pharmacogenetics*

- Research studies are needed that have sufficient statistical power to determine the nature of the interaction between gender and genetic polymorphism. CYP 450 isoenzymes, such as CYP 3A4 and CYP 1A2, which are responsible for estrogen metabolism, may also differentially affect other substrates. Isoenzyme 1A2 is thought to influence the production of 16a-OH and 4-OH, whereas 3A4 is predominantly responsible for the less active 2-OH estrogen metabolite.[55] There may be other examples of drug-metabolizing enzymes currently unknown that may be differentially expressed in women as a whole or in specific racial groups.
- Drug action and disposition may be altered by endogenous and exogenous sex hormones. Estrogen has been shown to inhibit the metabolism of CYP 1A2 model compounds, but its effect on the action and disposition of other therapeutic agents is not well studied. 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.
- The importance of the cytochrome P450 isoenzymes has long been established. CYP 3A4 is quantitatively the most important isoenzyme, making up at least 60 percent of the total P450 hepatic content and is responsible for metabolizing the majority of medications.[56] P450 metabolism is affected by steroid, dietary, and medication inhibition and induction.[57] There is evidence that CYP 3A4 activity is greater in younger women compared with men and postmenopausal women.[58] Demonstrated decreased metabolism in postmenopausal women[59,60] may make them more liable to adverse effects of certain medications. Careful study of this possibility is needed.
- CYP 1A2 is also thought to have gender-related differences in expression. Higher plasma levels of 1A2 drug substrates have

been reported in women.[61,62] In addition, the activity of this isoenzyme has been found to be reduced in women receiving contraceptive medications and during pregnancy.[63] The potential inhibition of CYP 1A2 by estrogen is demonstrated by decreased caffeine metabolism in women receiving estrogen replacement therapy.[64]

3. *Membrane Transporters*

   - Multidrug resistance may be caused by overexpression of either p-glycoprotein or the multidrug-resistance protein (MRP); such resistance is characterized by a decreased cellular drug accumulation due to an enhanced drug efflux. There may be gender-specific expression of p-glycoprotein and MRP related drug efflux pumps and other membrane transporters. Such gender-related differences have important value in the clinical setting, where decisions must be made regarding selection of drug type and dosage (e.g., in cancer chemotherapy).

4. *Ion Channels*

   - Differences in sodium and potassium channel sensitivities between men and women may explain differential adverse effects observed following intake of certain medications. Further preclinical and clinical research is needed to better define these differences.

5. *Modulators*

   - Sex Hormones as Possible Causes of Receptor Sensitivity. Differences in receptor sensitivity need to be studied. For example, women are known to have a longer QT interval, which may differentially predispose them to cardiac arrhythmias. In addition, women have been shown to have lower sensitivity to the beta-blocker, propranolol, which would not have been predicted by PK studies alone; therefore, this lower sensitivity is a PD issue.

6. *Chronopharmacology*

   - When examining treatment of diseases specific to women, the gender differences related to biologic rhythms and their application to efficacy of drugs needs to be studied. The chronopharmacology of disease needs to be studied because biologic rhythms may change during the disease process and affect the dosing requirements for a specific drug.

Preclinical Studies

Recommendation. 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. With these models in hand, progress may be made in understanding safety and efficacy profiles of drugs and predicting PK and PD with greater accuracy.

Research Goals

1. Evaluate therapeutic efficacy and potential side effects through whole animal studies. Thus, the effects of estrogens on the cardiovascular system must include information on the heart itself as well as the peripheral vasculature.

2. 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

Recommendation. 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 infant.

Research Goals

1. Women have a great potential for exposure to medications not only for conditions occurring during pregnancy but also inadvertent exposure prior to knowledge of the pregnancy. Since most medications have little or no information on risk for the developing human fetus, we must begin to 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. Some anomalies may not manifest themselves until later in neonatal development; thus it is necessary to conduct followup of birth outcomes at different times during early child development.

2. Critical research should be performed 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.

3. For those drugs commonly used by pregnant women, clinical trials in pregnant women, particularly in the second and third trimester, should be performed to 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.

4. Most reported birth anomalies are major and visible; research is needed on anomalies that are more difficult to detect, such as those that are neurodevelopmental or immunologic. Because of the large number of pharmacologic agents that may used and the potential for adverse effects, this could be a very large project. Thus, it is important to establish priorities based on the therapeutics taken most often by women. For example, what effect will antidepressants, especially the selective serotonin reuptake inhibitors taken by pregnant women, have on the cognitive function and development of the child? Because currently used classic animal teratology models do not examine immunologic markers, research, both animal and human, is needed to determine appropriate endpoints for assessment of immunologic function.

5. Research is needed on 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. Based on an understanding of mechanisms and principles of drug excretion into milk, methods should be developed to predict infant exposure levels.

Summary of Recommendations

Recommendations for Research

1. Examine underlying mechanisms that contribute to gender differences in drug action and disposition. Define the pharmacokinetics, pharmacogenetics, chronobiology, modulators, biologic/molecular factors, and pharmacodynamics of pharmacologic agents across the life span (prenatal, infants, children, adolescents, women of childbearing potential, pregnant women, lactating women, perimenopausal women, postmenopausal women, seniors) taking into consideration various racial and ethnic groups. Specifically, assess:

    - CYP 450s and other drug-metabolizing enzymes

    - p-glycoprotein and MRP-related drug efflux pumps and other membrane transporters

- Effects of endogenous and exogenous sex hormones
- Differences in receptor sensitivity

In addition, examine drug-drug interactions and drug-nutrient effects.

2. Perform preclinical research in the development and validation of in vitro and whole animal models to test and predict gender specific pharmacologic differences:
    - Animal models (e.g., rabbit) to test cardiac QT interval differences
    - Gender-based whole animal studies of pharmacological effects
    - Therapeutic agents in pregnancy in prediction of teratologic effects for pharmacological agents apt to be used during pregnancy.
3. Incorporate research on potential adverse effects on the pregnant woman, the fetus, and the newborn in evaluating PK and PD of new drugs. Develop methods of assessing subtle effects, such as possible neurodevelopmental and immunologic impairment in the child.
4. Include pregnant women in clinical trials.

Recommendations for Promoting Implementation. Interagency and public-private collaboration is required in order to carry out the full range of research recommended for studying pharmacologic issues in women, including pregnant women. It is essential that NIH prioritize studies needed to fill the serious data gaps described in this report. NIH should increase funding allocation for research on this topic and encourage interdisciplinary collaboration across all health professions and the basic sciences, and development of longitudinal studies to cover both basic and translational research. Finally, attention to studying mechanisms of pharmacologic effects should become an integral component of the review process across institutes and offices whenever a pharmacologic agent is part of a study protocol for prevention or treatment of a disease or condition.

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REFERENCES

1 Rathegeber EM, Vlassoff C. Gender and tropical diseases: a new approach. *Soc Sci Med* 1993;37:513-20.

2 Levy G. Patient-oriented pharmaceutical research: focus on the individual (editorial). *Pharmaceut Res* 1995;12:943-4.

3 Vlassoff C, Bonilla E. Gender-related differences in the impact of tropical diseases on women: what do we know? *J Biosci Sci* 1994;26:37-53.

4 Benton RE, Sale M, Flockhart DA, Woosley R. Greater quinidine induced QTc interval prolongation in women (submitted for publication). 1998.

5 Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for Torsades de Pointes associated with cardiovascular drugs. *JAMA* 1993;270:2590-7.

6 Wesche D, Schuster B, Chen Y, Wang WX, Woosley, RL. Mechanism of cardiotoxicity of Halofantrine (submitted for publication). 1998.

7 Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. *Circulation* 1996;94(6):1471-4.

8 Baum VC, Miletich DJ, Curran MA. Progesterone potentiation of bupivacaine arrhythmogenicity in pentobarbital-anesthetized rats and beating rat heart cell cultures. *J Cardio Pharmacol* 1992;20(533):537.

9 Flockhart, DA, Drici, MD, Samuel, C, Abernethy, DA, Woosley, RL. Effects of gender on propranolol pharmacokinetics and pharmacodynamics. *FASEB J* 1996;10(3):2476.

10 FDA Executive Summary. Gender studies in product development. Executive Summary. November 6-7, 1995.

11 Berg MJ, Franke GN, Rollings MR, editors. Status of research on gender differences. In: Proceedings: Gender Related Health Issues, An International Perspective. Washington, D.C.: American Pharmaceutical Association; 1996. p. 37-68.

12 Harris RZ, Benet LZ, Schwartz JB. Gender effects in pharmacokinetics and pharmacodynamics. *Drugs* 1995;50(2):222-39.

13 Gear RW, Miaskowsi C, Gordon NC, Paul SM, Heller PH, Levine JD. Kappa-opiods produce significantly greater analgesia in women than in men. *Nat Med* 1996;2;1248-50.

14 Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997;32 Suppl 1:1-21.

15 Zhou LX, Finley DK, Hassell AE, Holtzman JL. Pharmacokinetic interaction between isradipine and lovastatin in normal, female and male volunteers. *J Pharmacol Exp Therap* 1995;273(1):121-7.

16 Lennard M, Tucker G, Woods H. Inborn “errors” of drug metabolism: pharmacokinetics and clinical implications. *Clin Pharmacokinet* 1990;19:257-63.

17 Bonate P. Gender-related differences in xenobiotic metabolism. *J Clin Pharmacol* 1991;31:684-90.

18 Wrighton S, Stevens J. The human hepatic cytochrome P450 involved in drug metabolism. *Crit Rev Toxicol* 1992;22:1-21.

19 Harris R, Benet L, Schwart J. Gender effects in pharmacokinetics and pharmacodynamics. *Drugs* 1995;50(2):222-39.

20 Guttendorf R, Wedlund P. Genetic aspects of drug disposition and therapeutics. *J Clin Pharmacol* 1992;32:107-17.

21 Kalow W. Pharmacogenetics: past and future. *Life Sci* 1990;47:1385-97.

22 Wood A, Zhou H. Ethnic differences in drug disposition and responsiveness. *Clin Pharmacokinet* 1991;20(5):350-73.

23 Evans D, Krahn P, Narayanan N. The mephenytoin (cytochrome P450 2C 19) and dextromethorphan (cytochrome P450 2D6) polymorphisms in Saudi Arabians and Filipinos. *Pharmacogenetics* 1995;5:64-71.

24 Gleiter CH, Gundert-Remy U. Gender differences in pharmacokinetics. *Eur J Drug Metabol Pharmacokinet* 1996;21(2):123-8.

25 Hunt CM, Westerkam WR, Stave GM. Effect of age and gender on the activity of human hepatic CYP3A. *Biochem Pharmacol* 1992;44(2):275-83.

26 Bock KW, Schrenk D, Forster A, Griese EU, Morike K, Brockmeier D, Eichelbaum M. The influence of environmental and genetic factors on CYP2D6, CYP1A2 and UDP-glucuronosyltransferases in man using sparteine, caffeine, and paracetamol as probes. *Pharmacogenetics* 1994;4(4):209-18.

27 Carrillo JA, Benitez J. CYP1A2 activity, gender and smoking, as variables influencing the toxicity of caffeine. *Br J Clin Pharmacol* 1996;41(6):605-8.

28 Loe DW, Almquist KC, Cole SP, Deeley RG. ATP-dependent 17 beta-estradiol 17-(beta-D-glucuronide) transport by multidrug resistance protein (MRP). Inhibition by cholestatic steroids. *J Biol Chem* 1996;271(16):9683-9.

29 Jedlitschky G, Leier I, Buchholz U, Barnouin K, Kurz G, Keppler D. Transport of glutathione, glucuronate, and sulfate conjugates by the MRP gene-encoded conjugate export pump. *Cancer Res* 1996;56(5):988-94.

30 Frijters CM, Ottenhoff R, van Wijland MJ, van Nieuwkerk CM, Groen AK, Oude Elferink RP. Regulation of mdr2 P-glycoprotein expression by bile salts. *Biochem J* 1997;321(Pt 2):389-95.

31 Hrdina PD, Bakish D, Chudzik J, Ravindran A, Lapierre YD. Serotonergic markers in platelets of patients with major depression: upregulation of 5-HT2 receptors. *J Psychiatry Neurosci* 1995;20(1):11-9.

32 Meltzer HY, Maes M. Effects of buspirone on plasma prolactin and cortisol levels in major depressed and normal subjects. *Biol Psychiatry* 1994;35(5):316-23.

33 McBride PA, Tierney H, DeMeo M, Chen JS, Mann JJ. Effects of age and gender on CNS serotonergic responsivity in normal adults. *Biol Psychiatry* 1990;27(10):1143-55.

34 Gustarson LE, Legler UF, Benet LZ. Impairment of predisolone disposition in women taking oral contraceptives or conjugated estrogens. *J Clin Endocrinol Metab* 1986:62;234-7.

35 Kerlan V, Dreano Y, Bercovici JP, Beaune PH, Floch HH, Berthou F. Nature of cytochrome P450 involved in the 2-/4-hydroxylations of estradiol in human liver microsomes. *Biochem Pharmacol* 1992;44:1745-56.

36 Llerena A, Cobaleda J, Martinez C, Benitez J. Interethnic differences in drug metabolism: influence of genetic and environmental factors on debrisoquine hydroxylation phenotype. *Eur J Drug Metabol Pharmacokinet* 1996; 21(2):129-38.

37 Rubio A, Cox C. Sex, age and alfentanil pharmacokinetics. *Clin Pharmacokinet* 1991;21:81-2.

38 Harris RZ, Tsunoda SM, Mroczkowski P, Wong H, Benet LZ. The effects of menopause and hormone replacement therapies on prednisolone and erythromycin pharmacokinetics. *Clin Pharmacol Ther* 1996;59:429-35.

39 Horn EP, Tucker MA, Lambert G, Silverman D, Zametkin D, Sinha R, Hartge T, Landi MT, Caporaso NE. A study of gender-based cytochrome P450 1A2 variability: a possible mechanism for the male excess of bladder cancer. *Cancer Epi Biomark Prev* 1995; 4(5):529-33.

40 Minors D, Waterhouse J. Aspects of chronopharmacokinetics and chronergy of ethanol in healthy men. *Chronobiologia* 1980;7:465-80.

41 Bruguerolle B, Bouvenot G, Bartolin R. Temporal and sex-related variations in lorazepam kinetics. *Annu Rev Chronopharmacol* 1984;1:21-4.

42 Clench J, Reinberg A, Zziewanowska Z, Ghata J, Smolensky MH. Circadian changes in the bioavailability and effects of indometracin in healthy subjects. *Eur J Clin Pharmacol* 1981;20:359-69.

43 Bruguerolle B, Barbeau G, Belanger P. Chronolinetics of indometracin in elderly subjects. *Annu Rev Chronopharmacol* 1986;3:425-8.

44 Bruguerolle B, Levi T, Touitou Y, et al. Alteration of the physiologic circadian time structure of six plasma proteins in patients with advanced cancer. *Annu Rev Chronopharmacol* 1986;3:207-10.

45 Touitou Y, Levi T, Bogdan A. Bruguerolle B. Abnormal patterns of plasma cortisol in breast cancer patients. *Ann Rev Chronopharmacol* 1990;7:245-8.

46 Jonkman JHG, Reinberg A, Oosterhuis B, et al. Dosing time and sex-related differences in the pharmacokinetics of cetodizime. *Chronobiologia* 1988;15:89-102.

47 Food and Drug Administration. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs; Notice. Part VI, in DHHS (ed): *Federal Register*, Thursday, July 22, 1993.

48 Piper JM, Baum C, Kennedy DL. Prescription drug use before and during pregnancy in a Medicaid population. *Am J Obstet Gynecol* 1987;157:148-56.

49 Weiss S, McFarland B, Corelle C, McCloskey C, Vega A. Patterns of drug use in pregnancy. (Abstract) *Pharmacoepi Drug Safety* 1997;6(Suppl 2):S69.

50 Abma JC, Chandra A, Mosher WD, Peterson L, Piccinino L. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. National Center for Health Statistics. *Vital Health Stat* 1997;23(19).

51 Chisholm CA, Kuller JA. A guide to the safety of CNS-active agents during breastfeeding. *Drug Saf* 1997 Aug;17(2):127-42.

52 Bishnoi A, Sachmechi I. Thyroid disease during pregnancy. *Am Fam Physician* 1996 Jan;53(1):215-20.

53 Breitzka RL, Sandritter TL, Hatzopoulos FK. Principles of drug transfer into breast milk and drug disposition in the nursing infant. *J Hum Lact* 1997 Jun;13(2):155-8.

54 Dillon AE, Wagner CL, Wiest D, Newman RB. Drug therapy in the nursing mother. *Obstet Gynecol Clin North Am* 1997 Sep;24(3):675-96.

55 Aoyama T, Korzekwa K, et al. Estradiol metabolism by complementary deoxyribonucleic acid-expressed human cytochrome P-450s. *Endocrinology* 1990;126:3101-6.

56 Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 1996;153:311-20.

57 Pollock BG. Recent developments in drug metabolism of relevance to psychiatrists. *Harvard Rev Psychiatry* 1994;2:204-13.

58 Pollock BG. II. The endocrine-treatment interface: Gender differences in psychotropic drug metabolism. *Psychopharmacol Bull* 1997:33:235-41.

59 Barbbalya RH, Buch AB, Greene DS. A study of the effect of age and gender on the pharmacokinetics of nefazodone after single and multiple doses. *J Clin Psychopharmacol* 1996;16:19-25.

60 Schwartz J, Capili H, Daugherty J. Aging of women alters S-verapamil pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1994;55:509-17.

61 Ford JM, Truman CA Wilcock GK, Roberts CJC. Serum concentrations of tacrine hydrochloride predict its adverse effects in Alzheimer's disease. *Clin Pharmacol Ther* 1993; 53:691-5.

62 Hartter S, Wetzel H, Hammes E, Hiemke C. Inhibition of antidepressant demethylation and hydroxylation by fluvoxamine in depressed patients. *Psychopharmacology* 1993;110:302-8.

63 Lambert GH, Kotake AN, Schoeller D. The CO_2 breath test as monitors of the cytochrome P450 dependent mixed function oxygenase system. In: McLeod SM, Okey AB, Spielberg, SP, eds. *Developmental pharmacology.* New York: Alan R Liss, Inc., 1983, p. 119-45.

64 Pollock B, et al. Personal communication.

65 Wedlund P, Asianian W, McAllister C, Wilkinson G, Branch R. Mephenytoin hydroxylation deficiency in Caucasians: Frequency of a new oxidative drug metabolism polymorphism. *Clin Pharmacol Therap* 1984;36:773-80.

66 Kupfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. *Eur J Clin Pharmacol* 1984;26:753-9.

67 Nakamura K, Goto F, Ray W, et al. Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian population. *Clin Pharmacol Therap* 1985;38:402-8.

68 Jurima M, Inaba T, Kadar D, Kalow W. Genetic polymorphism of mephenytoin p(4´)-hydroxylation difference between Orientals and Caucasians. *Br J Clin Pharmacol* 1985;19:483-7.

69 Jacqz E, Dulac H, Mathieu H. Phenotyping polymorphic drug metabolism in the French Caucasian Population. *Eur J Clin Pharmacol* 1988;35:167-71.

70 Sanz E, Villen T, Alm C, Bertilsson L. S-mephenytoin hydroxylation phenotypes in a Swedish population determined after coadministration with debrisoquin. *Clin Pharmacol Therap* 1989;45:495-9.

71 Drohse A, Bathum L, Brosen K, Gram L. Mephenytoin and sparteine oxidation: genetic polymorphisms in Denmark. *Br J Clin Pharmacol* 1989;27:620-5.

72 Horai Y, Nakano M, Ishizaki T, et al. Metoprolol and mephenytoin oxidation in polymorphisms in Far Eastern Oriental subjects: Japanese vs. mainland China. *Clin Pharmacol Therap* 1989;46:198-207.

73 Guttendorf R, Britto M, Blouin R, et al. Rapid screening for polymorphisms in dextromethorphan and mephenytoin metabolism. *Br J Clin Pharmacol* 1990;29:373-80.

74 Sohn D-R, Kusaka M, Ishizaki T, et al. Incidence of S-Mephenytoin hydroxylation deficiency in a Korean population and the interphenotypic differences in diazepam pharmacogenetics. *Clin Pharmacol Therap* 1992;52:160-9.

75 Bertilsson L, Lou Y-Q, Du Y-L, et al. Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquin and S-mephenytoin. *Clin Pharmacol Therap* 1992;51:388-97.

76 Llerena A, Herraiz A, Cobaldea J, Johansson I, Dahl M-L. Debrisoquine and mephenytoin hydroxylation phenotypes and CYP2D6 genotypes in patients treated with neuroleptic and antidepressant agents. *Clin Pharmacol Therap* 1993;54:606-11.

77 Kiivet R, Svensson J, Bertilsson L, Sjoqvist F. Polymorphism of debrisoquine and mephenytoin hydroxylation among Estronians. *Pharmacol Toxicol* 1993;72:113-5.

78 Reviriego J, Bertilsson L, Carrillo J, Llerena A, Valdivielso M, Benitez J. Frequency of S-mephenytoin hydroxylation deficiency in 373 Spanish subjects compared to other Caucasian populations. *Eur J Clin Pharmacol* 1993;44:593-5.

79 Weerasuriya K, Jayakody R, Smith C, Wolf C, Tucker G, Lennard M. Debrisoquine and mephenytoin oxidation in Sinhalese: a population study. *Br J Clin Pharmacol* 1994;38:460-70.

80 Setiabudy R, Kusaka M, Chiba K, Darmansjah K, Ishizaki T. Dapsone N-acetylation, metoprolol α-hydroxylation, and S-mephenytoin 4-hydroxylation polymorphisms in an Indonesian population: a cocktail and extended phenotyping assessment trial. *Clin Pharmacol Therap* 1994;56:142-53.

81 Basci N, Brosen K, Bozkurt A, Isimer A, Sayal A, Kayaalp S. S-mephenytoin, sparteine and debrisoquine oxidation: genetic polymorphisms in a Turkish population. *Br J Clin Pharmacol* 1994;38:463-5.

82 Hadidi H, Irshaid Y, Woosley R, Idle J, Flockhard D. S-mephenytoin hydroxylation phenotypes in a Jordanian population. *Clin Pharmacol Therap* 1995;58:542-7.

83 Chang M, Dahl M, Tybring G, Gotharson E, Bertilsson L. Use of omeprazole as a probe drug for CYP2C19 phenotype in Swedish Caucasians: comparison with S-mephenytoin hydroxylation phenotype and CYP2C19 genotype. *Pharmacogenetics* 1995;5:358-63.

84 de Morais S, Goldstein J, Xie H-G, et al. Genetic analysis of S-mephenytoin polymorphism in a Chinese population. *Clin Pharmacol Therap* 1995;58:404-11.

85 Brockmoller J, Rost K, Gross D, Schenkel A, Roots I. Phenotyping of CYP2C19 with enantiospecific HPLC-quantification of R- and S-mephenytoin and comparison with the intron4/exon5 G->A splice mutation. *Pharmacogenetics* 1995;5:80-8.

86 Masimirembwa C, Bertilsson L, Johansson I, Hasler J, Ingelman-Sundberg M. Phenotyping and genotyping of S-mephenytoin hydroxlase (cytochrome P450 2C19) in a Shona population of Zimbabwe. *Clin Pharmacol Therap* 1995;57:656-61.

87 Balian J, Sukhova N, Harris J, et al. The hydroxylation of omeprazole correlates with S-mephenytoin metabolism: a population study. *Clin Pharmacol Therap* 1995;57:662-9.

88 Marinac J, Balian J, Foxsworth J, et al. Determination of CYP2C19 phenotype in black Americans with omeprazole: correlation with genotype. *Clin Pharmacol Therap* 1996;60:138-44.

89 Kubota T, Chiba K, Ishizaki T. Genotyping of S-Mephenytoin 4´hydroxylation in an extended Japanese population. *Clin Pharmacol Therap* 1996;60:661-6.

90 Edeki T, Goldstein J, de Morais S, et al. Genetic polymorphism of S-mephenytoin 4´-hydroxylation in African-Americans. *Pharmacogenetics* 1996;6:357-60.

91 Jurima-Romet M, Goldstein J, LeBelle M, et al. CYP2C19 genotyping and associated mephenytoin hydroxylation polymorphism in a Canadian Inuit population. *Pharmacogenetics* 1996;6:329-39.

92 Takakubo F, Kuwano A, Kondo I. Evidence that poor metabolizers of (S)-mephenytoin could be identified by haplotypes of CYP2C19 in Japanese. *Pharmacogenetics* 1996;6:265-7.

93 Roh H, Dahl M, Johansson I, Ingelman-Sundberg M, Cha Y, Bertilsson L. Debrisoquine and S-mephenytoin hydroxylation phenotypes. *Pharmacogenetics* 1996; 6:441-7.

94 Persson I, Aklillu E, Rodrigues F, Bertilsson L, Ingelman-Sundberg M. S-mephenytoin hydroxylation phenotype and CYP2C19 genotype among Ethiopians. *Pharmacogenetics* 1996;6:521-6.

95 Roh H, Dahl M, Tybring G, Yamada H, Cha Y, Bertilsson L. CYP2C19 genotype and phenotype determined by omeprazole in a Korean population. *Pharmacogenetics* 1996;6:547-51.

96 Basci N, Bozkurt A, Kortunay S, Isimer A, Sayal A, Kayaalp S. Proguanil metabolism in relation to S-mephenytoin. *Br J Clin Pharmacol* 1996;42(6):771-3.

97 Marandi T, Dahl M, Kiivet R, Rago L, Sjoqvist F. Debrisoquin and S-mephenytoin hydroxylation phenotypes and CYP2D6 genotypes in an Estonian population. *Pharmacol Toxicol* 1996;78:303-7.

98 Goldstein J, Ishizaki T, Chiba K, et al. Frequencies of the defective CYP2C19 alleles responsible for the mephenytoin poor metabolizer phenotype in various Oriental, Caucasian, Saudi Arabian and American Black populations. *Pharmacogenetics* 1997;7:59-64.

99 Xie H-G, Huang S-L, Xu Z-H, Xiao Z-S, He N, Zhou H-H. Evidence for the effect of gender on activity of (S)-mephenytoin 4´hydroxylase (CYP2C19) in a Chinese population. *Pharmacogenetics* 1997;7:115-9.

100 Xiao Z, Goldstein J, Xie H, et al. Differences in the incidence of the CYP2C19 polymorphism affecting the S-mephenytoin phenotype in Chinese Han and Bai populations and identification of a new rare CYP2C19 mutant allele. *J Pharmacol Exp Therap* 1997;281(1):604-9.

101 Ruas J, Lechner M. Allele frequency of CYP2C19 in a Portuguese population. *Pharmacogenetics* 1997;7:333-5.

REPRODUCTIVE HEALTH

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BACKGROUND

Three issues dominated the discussions of the Working Group on Reproductive Health: (1) progress of reproductive health in women's health research, (2) gaps in knowledge about reproductive health in women, and (3) the current status of women's health based on updated information from the past three regional meetings in Philadelphia, Santa Fe, and New Orleans.

Historically, "women's health research" was generally limited to the study of obstetrics and gynecology. In the late 1970s, however, 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.

From the late 1980s through the early 1990s, the government began to increase funding for women's health research. The Hunt Valley report, *Report of the National Institutes of Health: Opportunities for Research on Women's Health, 1991,* reflected this new interest. The report took two approaches to women's health: (1) a developmental perspective, looking at women's health throughout the life span, and (2) a basic science perspective, looking at women's health in terms of the state of current biological knowledge. These two perspectives still permeate discussions on research in women's health.

The Hunt Valley report posed a series of questions intended to guide the women's health research agenda. The questions about female reproductive health encompassed basic biology and clinical practice. In addition, the report emphasized the need for interdisciplinary work to study the effect of social context on women's health.[1]

The framework outlined in the 1991 Hunt Valley report and in the 1996 Philadelphia report governed the current working group's discussions. This framework delineated content areas (e.g., reproductive health, reproductive disorders, special populations) and research strategies (e.g., basic biology, clinical research, and social and behavioral approaches) within the context of research progress, gaps in knowledge, and development of research recommendations. In particular, emphasis on priorities appropriate to NIH biomedical and biobehavioral research were addressed. In this context, this report is an updated compilation of research recommendations and other agenda issues for NIH's Office of Research on Women's Health (ORWH).

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Pregnancy

Progress has occurred in knowledge relating to the biology and management of pregnancy. Advances have been made in research on infectious diseases of pregnancy and preterm labor and on other pathophysiologic aspects of abnormal pregnancy. Research suggests that pregnancy can be viewed as a screen for detecting diseases or disorders that may develop later in life. Knowledge is emerging on the effects of somatic disease on pregnancy. Advances such as genetic testing and other diagnostic tests have provided information on prevention of malformations. An active area is the relationship of implantation (normal vs. abnormal) and fetal development.

Recent research has identified external factors with potential effects on pregnancy. These include environmental factors, diet and nutrition, exercise, smoking, and violence. Other external factors include the effects of hormones and medications (including over-the-counter drugs). Diagnostic systems are under development that are better focused than more traditional diagnostic systems and that address the needs of specific populations.

Contraception

Some progress has been made in the knowledge of contraceptive use behavior and in generating new contraceptive technologies. An increased awareness has made the long-term effects of contraceptive use an important issue, with more research still needed. Availability of Norplant (levonorgestrel subdermal implants), Depo-Provera (medroxy-progesterone acetate injection), and the female condom are promising advances for pregnancy prevention.

There have also been advances in microbicides and spermicides and in their use among women. This has led to progress in understanding the need for women to have more options for the prevention of STDs. Recognition of the need for development of new contraceptive technologies has important implications, especially in specific populations. These groups need to be provided with several options for different circumstances.

Infertility

An important advance in the area of infertility is 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. Advances were realized in genetic causes of male infertility with the potential for heritable infertility. Advances occurred in the area of ovulation induction based on developing knowledge of ovarian physiology.

A better selection of treatments for infertility has emerged from scientific data. Trial and error treatment is obsolete. The best fertility treatment would be individualized, based on the couple’s characteristics. Pressure for progress in this area is being exerted at two points. First, managed care and monetary constraints tend to limit choices to the most cost-effective treatments. Second, choosing effective therapy quickly is imperative for couples who have delayed childbearing and who face a natural decline in fecundity with time.

Progress has been recognized in ectopic gestation, but more knowledge is needed about its etiology, risk factors, and the effects of therapies on fertility in the future. 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

Progress has been made in promoting greater awareness of reproductive tract diseases and disorders and their prevalence and morbidity. These diseases and disorders include myoma, abnormal uterine bleeding, premenstrual syndrome, endometriosis, pelvic pain, and pelvic floor relaxation. New information is emerging on abnormal biology in these conditions and in medical and conservative surgical therapies. Recently identified steroid receptor subtypes may hold clues to development of diseases and approaches for treatment. Information is still needed, however, regarding the prevalence, etiology (including potential environmental factors), and pathophysiology of these diseases and how they become symptomatic.

GAPS IN KNOWLEDGE

General Considerations

Two major themes encompass all the recommendations on reproductive health issues. First is the need for education. Educating the public and health professionals will 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.

The second theme focuses on specific populations of women who may have particular health care needs or concerns. The interplay of physical, biological, psychological, cultural, and socioeconomic factors that affect their access to health care services should not be ignored. Neither should there be barriers to participation by these groups in clinical trials. It is important to 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 women living in poverty and in rural areas)
- Women of color (having cultural, ethnic, and biological differences)
- Women with disabilities
- Adolescents
- Postmenopausal and elderly
- Lesbians
- Women with somatic and/or developmental illnesses.

Pregnancy

Overall, knowledge is needed on the impact of pregnancy and its outcome on women's physical and psychological health throughout life. A number of gaps exist in all areas of pregnancy. Rigorous scientific research is warranted in the physiology, management, and sequelae of pregnancy, from preconception to the postpartum period. The following conditions should be given priority: preterm labor, intrauterine growth retardation (IUGR), preeclampsia, ectopic pregnancy, spontaneous abortion, labor and delivery, and lactation.

Sound maternal physical and mental well-being is essential in bearing a healthy baby; therefore, technology is needed for better monitoring the entire pregnancy including screening for fetal genetic abnormalities and maternal diseases, specialized prenatal care followup strategies, pregnancy-related medical and surgical interventions (cesarean section, labor pain management), and use of alternative treatments. Better data are required on the external factors affecting the health of the pregnant woman such as: environment, diet, exercise, alcohol intake, smoking, violence, and nutritional supplements.

More research is needed on the pharmacodynamics and pharmacokinetics of prescription and over-the-counter drugs.

Sex and Contraception

Three major concerns are related to sex and contraception. First, although knowledge about contraceptive use is emerging, more research is needed on how to use this knowledge to increase responsible contraceptive and sexual behavior. Research is needed on human oocyte physiology including the use of advanced immunologic technology (e.g., targeting the egg and not the whole menstrual cycle). A continuing need exists to improve and develop new microbicides, spermicides, barriers, and reversible methods of sterilization. The goal is not only to suit the individual couples' contraceptive needs but also to prevent sexually transmitted diseases. Finally, study is needed on the long-term effects of existing and emerging contraceptives and on their interactions with other drugs in relation to women's health.

Fertility and Infertility

Gaps occur in all areas of knowledge about fertility and infertility. Research is needed to develop measures to prevent infertility and discover cost-effective, safer, and less invasive diagnostic and therapeutic options through the study of its etiology and pathogenesis (e.g., increase safety while decreasing the cost of ovulation induction). There is speculation, but few solid data, on the etiology of infertility, such as the impact of extreme exercise and activity, smoking, alcohol, eating disorders, obesity, and over-the-counter medications. More should be done on the behavioral aspects of infertility: effects on the couple, effects of the diseases that can cause infertility, negative effects of assisted reproductive technology and other infertility treatments, effects on gamete donors and surrogate mothers, and social concerns about reproductive ethics and socioeconomic effects of multiple births.

Benign Reproductive Diseases and Disorders

More knowledge is needed about ovarian diseases and disorders — polycystic ovarian syndrome, premature ovarian failure, and ovarian dysfunction — and reproductive tract diseases and disorders — endometriosis, myoma, abnormal uterine bleeding, pelvic floor relaxation, premenstrual syndrome, and pelvic pain. The working group identified four recurring areas for additional research, as follows:

1. Application of basic biology leading to the evolution of safer, cost-effective, and more acceptable treatments (e.g., improve current management, develop new diagnostic strategies and therapeutic techniques). This includes the use of molecular and genetic studies in identifying new disease activity markers, and the utility of these markers to probe the diseases' pathogenesis. More study is needed on the relationship between etiology and epidemiology of the above-mentioned diseases and disorders to determine the prevalence and risk factors. This information could then be a basis for prevention. The impact of environmental factors should also be emphasized (e.g., the role of smoking in ovarian failure, the role of exogenous estrogen).

2. Long-term biological and psychological effects of these diseases and disorders on reproductive health, for example, long-term effects of current medical and surgical treatments and complementary therapies, such as endometrial ablation in abnormal uterine bleeding; combination or low-dose hormonal treatments in ovarian failure, myoma, and endometriosis; physical therapy and exercises in pelvic floor relaxation; and behavioral and psychological therapy in pelvic pain and PMS.

3. Individualization of management.

4. Changes in the reproductive axis and its hormones over time as contributing factors to disease pathogenesis.

Maturation and Aging

Much is to be learned regarding menopause. Menopause is part of the life of the aging woman. Considerable variation exists among individuals in manifestation and severity of a variety of symptoms accompanying the transition from pre- to postmenopause. These symptoms are poorly defined and less understood. Studies should be undertaken to fully explore and define the physiological stages during this transition and its accompanying behavioral and psychological effects. The etiology of reduced or defective ovarian function may differ in menopause versus other ovarian diseases. More research should be conducted on the endocrine and metabolic changes in normal menopause and accelerated ovarian aging. Endogenous and exogenous hormones affect the physiological processes of multiple target organs in somatic and behavioral health, during the peri- to postmenopausal period. More studies on HRT are needed to develop novel treatments based on steroid receptor subtypes, steroid actions, and interactions. Specific areas that need to be explored include:

- The safety and efficacy of hormones and nonhormonal treatments for menopausal symptoms, methods of reducing their side effects and of optimizing and individualizing regimens for patients.

- The role of estrogen in the initiation and growth of hormone-dependent neoplasms and other benign diseases and disorders.

- The role of androgens and dehydroepiandrosterone (DHEA) in quality of life, including sexual function of maturing women.

RESEARCH RECOMMENDATIONS

The working group agreed that two vital themes must be emphasized in conceptualizing the recommendations on reproductive health issues. These are (1) education of the public and health professionals and (2) access of specific female populations to health care services as well as their participation in clinical trials.

Pregnancy

- Conduct more research to better understand the whole 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 (decision-making and compliance), especially among adolescents and women with gynecological infectious diseases. More research is needed regarding the role of contraceptives in 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

The working group's recommendations aim to provide more options that suit individual couples' needs and problems, and pinpoint external factors that may contribute to infertility.

- Learn from biology of the reproductive system and focus research 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

Benign ovarian diseases and disorders include polycystic ovarian syndrome, premature ovarian failure, and ovarian dysfunction. Benign reproductive tract diseases and disorders include endometriosis, myoma, abnormal uterine bleeding, pelvic floor relaxation, premenstrual syndrome, and pelvic pain. The recommendations reflect the working group's concerns regarding the need to learn about the etiology, pathophysiology, and effects of gynecological diseases and their treatments. The group also emphasized the identification of disease markers to estimate prevalence and risk.

- 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

The working group decided to include this topic under reproductive health issues. There have been major surprises in how the reproductive system changes normally with time; therefore, the working group suggested the need for rigorous scientific studies.

- Study consequences of maturational changes of the hormonal axes and their effect on fertility, menopause, and hormone-dependent diseases and behavior.
- Study HRT, both existing (estrogen and/or progesterone) and potential (androgens, DHEA, etc.) — its role in 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 impact on the quality of life over time.

The group wished to remind readers that all of these recommendations are meant to be viewed from the perspective of the general considerations introduced earlier: (1) the need for public and professional education and (2) the need for attention to the individualized needs of specific populations.

REFERENCE

1 Kirschstein RL. Introduction. Report of the National Institutes of Health: Opportunities for Research on Women's Health. Bethesda, Md: National Institutes of Health, 1992.

UROLOGIC AND KIDNEY CONDITIONS

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BACKGROUND

Diseases 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.[1] 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. Death rates are, of course, very age dependent, and the average dialysis age of a new dialysis patient is close to 60, but even a 50-year-old who develops end-stage renal disease has only about a 20 percent chance of being alive 10 years later.[1] 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.[1] While the increase in incidence has affected women and men alike, the frequency with which specific diseases cause renal failure differs between the two genders. 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. They are often chronic, frequently misdiagnosed, and inappropriately or inadequately treated. These conditions can result in social embarrassment and isolation of the afflicted individual. The chronicity of these disorders may result in excessive self-treatment to mask symptoms but not cure the underlying disorder. The pathogenesis of many of these disorders remains poorly understood, and current preventive and therapeutic strategies are inadequate.

Renal and urological issues were addressed for the first time at the conference "Beyond Hunt Valley: Research for Women's Health in the 21st Century," held in Bethesda, Maryland, in November 1997. The Working Group on Kidney and Urologic Conditions developed an agenda identifying specific diseases of high priority for their impact on women's health. For each of these conditions, working group participants summarized ongoing research and research advances and gaps in knowledge and developed a set of research recommendations. The working group identified five aspects of renal health that impact heavily on women and need research emphasis: (1) end-stage renal disease, (2) kidney disease of diabetes mellitus,

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particularly Type II diabetes, (3) analgesic nephropathy, (4) nephritis due to systemic lupus erythematosus, and (5) renal complications during pregnancy. The working group also identified four clinical areas in urology that are particularly deserving of research emphasis: (1) urinary incontinence, (2) pelvic floor disorders, (3) urinary tract infections, and (4) interstitial cystitis and related disorders of bladder function.

End-stage Renal Disease

When the filtering units of the kidney, the glomeruli, are damaged, the remaining units must act to compensate for the loss of the damaged tissue. With progressive disease, this compensation eventually fails, and the kidney filters less and less. When chronic kidney disease results in a reduction in kidney filtration rate to 10 percent or less of normal capacity, a person is considered to have renal failure. Irreversible renal failure is called end-stage renal disease. Individuals with end-stage renal disease require regular dialysis or a kidney transplant to survive. Renal failure is largely gender-blind, affecting women and men almost equally. Approximately 250,000 people in the United States, approximately 48 percent women, are currently receiving renal replacement therapy, with about 70,000 new patients a year.[1]

Therapy for End-stage Renal Disease. Survival with end-stage renal disease requires some form of renal replacement therapy. The commonest therapy is some form of dialysis, either hemodialysis, a procedure that cleans and filters the blood through an extra-corporeal filter, or peritoneal dialysis, which uses the lining of the abdomen as the filtering membrane. In the United States, of the more than 120,000 women with end-stage renal disease, 64 percent are treated with hemodialysis and 11 percent are treated with peritoneal dialysis.[1] Cardiovascular disease, both heart disease and stroke, accounts for the greatest proportion of deaths on dialysis.[1] Despite the large impact of vascular disease on the mortality of this population, the risk factors for cardiovascular disease are poorly defined, and there are currently no randomized clinical trials that address potential strategies for reducing this risk.

The other form of therapy for end-stage renal disease is kidney transplantation. Kidney transplantation rates are severely limited by the number of available organs, and waiting times to receive kidney transplants often exceed 2 years, almost tripling in length over the last 10 years.[1] Although life expectancy of transplant recipients is not fully restored to normal, it is substantially better than with other forms of renal replacement therapy. Transplant recipients need continued immunosuppression, but they have a life quality that is substantially closer to normal than dialysis patients. Women and members of certain racial minority groups seem less likely to receive a kidney transplant than are white men and are more likely to serve as donors for living-related transplantation.[2,3] The problems that may limit access of both women and racial minority groups to transplantation need continued analysis.

Pregnancy in Dialysis Patients and After Renal Transplantation. Dialysis patients have reduced fertility, and pregnancies are unusual. The estimated success rate of carrying to gestation a viable child vary from 30 to 50 percent, but these values may be skewed by the greater tendency to report successful outcome.[4] Women with kidney transplants, however, quite commonly have successful pregnancies,[5,6] but they are considered high-risk obstetric patients. Specific concerns include an increased risk of hypertension and infection as well as deterioration in kidney function. Pregnancy is not infrequently associated with deterioration in function of the transplanted kidney, and careful monitoring of blood pressure and renal function throughout gestation is critical. Statistics suggest that about 12 percent of pregnancies end in spontaneous abortion, the majority within the first trimester. Two to 3 percent of pregnancies end in second-trimester abortions or stillbirth, a rate somewhat increased over that of the general population. Pre-term delivery (prior to 37 weeks of gestation) is required in as many as a third of births.

The Kidney Disease of Diabetes Mellitus

Diabetes mellitus is the most common cause of end-stage renal disease, and currently approximately 40 percent of new cases are due to diabetes.[1] Both Type I or insulin-dependent diabetes mellitus and Type II or non-insulin dependent diabetes produce renal failure, but much of the growth in diabetic renal disease is due to the increase in numbers of patients with Type II diabetes. According to NHIS data, 58 percent of people with Type II diabetes are women.[7] Certain minority populations, notably blacks, Hispanic populations, and American Indians, are disproportionately afflicted by Type II diabetes. The enhanced susceptibility of these minority populations, especially blacks and American Indians, results in substantial disease burdens for these populations. The factors that account for the increased susceptibility of certain populations to both diabetes mellitus and progressive renal disease are not well understood. While environmental factors and poorer access to optimum health care may play a role, uncharacterized genetic factors appear to play a large role.

Analgesic Nephropathy

A number of studies suggest that daily ingestion of high doses of analgesics over a period of years, particularly of mixtures containing at least two such drugs, may lead to adverse effects on the kidney. European studies document a rather high prevalence of radiographic abnormalities of the renal pelvis in long time users of analgesics and suggest that analgesic nephropathy makes a significant contribution to end-stage renal disease, causing as much as 5 to 15 percent of new cases of renal failure.[8] In European populations, most patients diagnosed with this disorder are women. In the United States, analgesic nephropathy is an infrequent diagnosis among the end-stage renal disease population, accounting for less than 1 percent of new cases. However, use of over-the-counter analgesics, such as acetaminophen, aspirin, and ibuprofen, is quite high in the United States. Studies are needed to determine the true prevalence of this disorder in the United States and to assess the factors accounting for the variability in the renal toxicity of these drugs.

Lupus Nephritis

Kidney disease represents one of the most common and serious manifestations of systemic lupus erythematosus, an inflammatory connective tissue disease that affects different organ systems in varying degrees. The majority of patients afflicted with systemic lupus erythematosus are young women, mostly blacks of childbearing age. Women of black and Hispanic origins have both a higher incidence of systemic lupus erythematosus as well as an increased mortality from it. The importance of renal involvement as a major cause of both morbidity and mortality of lupus is well established.[9] Thus, an understanding of the causal mechanisms of lupus nephritis and of the best treatment is of significance for women's health.

Renal Complications in Pregnancy

Normal pregnancy is characterized by dramatic changes in cardiovascular and kidney function, with a marked fall in peripheral resistance and augmentation of renal blood flow and glomerular filtration rate. Preeclampsia, or pregnancy-induced hypertension, is a hypertensive disease that occurs only in pregnancy, complicating almost 10 percent of all pregnancies.

Preeclampsia is associated with disturbance in the normal regulatory adjustments of renal and cardiovascular function. Preeclampsia occurs more often among certain groups of women including women under 20 years of age, minority women over the age of 35 years, women with chronic high blood pressure, women who have had high blood pressure in previous pregnancies, women carrying more than one fetus, and women with diabetes.[10] Characteristic signs and symptoms usually occur after the 20th week of pregnancy and include high blood pressure, swelling of the limbs accompanied by rapid weight gain, and protein in the urine.

Less commonly, a severe impairment of renal function develops in the immediate peripartum or postpartum period, a condition termed postpartum hemolytic-uremic syndrome. This syndrome may develop in women who have experienced normal pregnancies and deliveries. It appears to occur independent of infections, malignancy, or renal injury and may be the result of an altered hormonal milieu. The long-term renal prognosis depends on the severity of the renal damage.

Incontinence

Incontinence has been clinically categorized into three broadly defined groups: stress incontinence (urinary leakage during increased abdominal pressure as with coughing, laughing, and heavy lifting); urge incontinence (inability to suppress the urge to urinate); and overflow incontinence (incomplete emptying of the bladder and subsequent spilling of urine when the bladder reaches capacity). Urinary incontinence is very common. A popular misconception is that incontinence affects only older women, but large numbers of young and middle-aged women also experience this significant problem. Prevalence estimates vary widely. Among the population between 15 and 64 years of age, the prevalence of incontinence in women has been estimated from 10 to 30 percent and in men from 1.5 to 5 percent. For non-institutionalized persons older than 60 years of age, prevalence estimates range from 15 to 35 percent, with women having twice the prevalence of men. Rates among patients in nursing homes are substantially higher, and urinary incontinence is one of the commonest reasons for need for institutional care for the elderly. Despite its prevalence and an estimated cost of more than $15 billion annually,[14] most individuals do not seek medical advice.

Treatments for Incontinence. Development of drugs to affect voiding disorders and treat urinary incontinence is a subject of active investment by the pharmaceutical industry, and a number of promising agents are under development. A number of nonsurgical strategies exist to improve urinary continence. These include the Kegel exercises that strengthen or re-train pelvic floor muscles and urinary sphincter muscles and have been shown effective in reducing or curing stress incontinence. Other investigational strategies to improve bladder function include electrical stimulation to strengthen muscles in the lower pelvis and biofeedback methods. In the interventional arena, a number of innovative approaches have been developed, including the use of artificial sphincters and bulking agents or implants to improve tissue integrity and function. Doctors usually suggest surgery to alleviate incontinence only after other treatments have been tried. Many surgical options have reported favorable rates of success, although in many of these reports the severity of the incontinence prior to surgery is not reported, and the length of followup of the treated patient is not very long.

Pelvic Floor Disorders

Pelvic floor disorders encompass not only genital prolapse but also the consequent urinary incontinence, defecatory disorders, and sexual dysfunction. Annually in the United States, some 400,000 surgical procedures are estimated to be carried out for pelvic organ prolapse, many of these for repeat surgery.[11] Despite the magnitude of this clinical problem, little is known about its etiology and how best to treat it. The epidemiology of these disorders is not well characterized. A strong association with multiple vaginal deliveries is one well established risk factor, but many cases are idiopathic. Overall, whether altered obstetric strategies can reduce this complication is not well established.

Urinary Tract Infections

Urinary tract infections remain a common problem affecting a wide spectrum of the population, especially women. Almost all uncomplicated urinary tract infections occur in women between the ages of 18 and 40. Some infections may occur before menarche, but the incidence increases significantly in late adolescence and during the second and third decades of life. It is estimated that by age 30, half of all women will experience at least one urinary tract infection and about 20 percent of these women will have had one or more recurrences. Each year, infections of the urinary tract are responsible for more than 6 million doctor visits and about $4.5 billion in health care costs.[16]

Interstitial Cystitis

Interstitial cystitis (IC) is a chronic inflammatory bladder condition that affects approximately 450,000 people in the United States, 90 percent of whom are women. It is manifested by mild to severe and unrelenting pain, urgency, and extreme urinary frequency — sometimes up to 60 or more times in 24 hours. Neither a cause nor a uniformly effective treatment have been demonstrated. The symptoms are similar to acute urinary tract infection, but urine cultures are negative for bacteria, and the symptoms do not respond to antibiotics. Not surprisingly, interstitial cystitis confines many individuals to their homes. The pain, frequency of urination, isolation, and sleep deprivation often make it difficult for an individual with interstitial cystitis to function in a work environment outside of the home or to maintain a normal family life, leading to clinical depression.[17]

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Significant progress has been made in many areas of women's renal and urological health since the establishment of ORWH in 1990, although substantial gaps in knowledge remain.

End-stage Renal Disease

Highlights in end-stage renal disease include the following:

- 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.
- Improvement in survival rates for kidney transplant patients, diminished rates of both short-term and long-term graft loss.
- Evidence that angiotensin converting enzyme inhibitors may slow the course of progressive kidney disease in individuals with Type I diabetes. The use of these drugs during the second and third trimesters of pregnancy has been associated with a specific pattern of birth defects.
- Demonstration that production of the active metabolite of vitamin D, (1,25 (OH) 2D3), a compound not made by the failing kidney, is stimulated by estrogens.

> *"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

Kidney Disease of Diabetes Mellitus

In recent years, advances in diabetes research have led to better ways to attempt to prevent and to manage diabetic nephropathy. Major advances include:

- Evidence that intensive management of blood glucose reduces and may prevent development of micro-vascular complications of diabetes.
- Demonstration that angiotensin converting-enzyme inhibitors prevent or delay kidney disease progression and renal failure in people with diabetes.
- 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.

Analgesic Nephropathy

Important advances in analgesic nephropathy include the following:

- Molecular characterization of the probable targets for analgesic effects on renal function, especially characterization of the distribution and regulation of the renal cyclooxygenases.
- Improved characterization of the clinical presentation of analgesic nephropathy and of the specificity of non-contrast computerized tomographic imaging of the kidney for its diagnosis.

Lupus Nephritis

Progress in lupus nephritis has been made in the following areas:

- Identification of a genetic loci associated with an increased risk of kidney disease in murine models of this disease.
- 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.
- Demonstration that intermittent pulse cyclophosphamide therapy has the highest therapeutic index among currently available immunosuppressive drug therapies in the treatment of proliferative forms of lupus nephritis.
- Initiation of randomized controlled clinical trials comparing alternate day prednisone alone or in combination with either pulse cyclophosphamide or low-dose cyclosporin A.

Renal Complications in Pregnancy

Progress areas in hypertensive disorders of pregnancy include the following:

- 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.
- Delineation of the importance of endothelial cell dysfunction in preeclampsia.

Urinary Incontinence

Progress highlights in urinary incontinence include the following:

- Development of treatment guidelines by the Agency for Health Care Policy and Research and the American Urological Association.

- Improved design and an increase in the availability of adult continence products.

- Increased emphasis in patient training for self-management of incontinence.

- Improved coverage in medical texts and journals.

- Knowledge that folate supplementation prior to and during pregnancy prevents neural tube defects, conditions typically causing bladder dysfunction.

Pelvic Floor Disorders

Advances in pelvic floor disorders include the following:

- Diagnostic standards for genital prolapse were 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.

- Acceptance and understanding that preventive measures need to be defined.

Urinary Tract Infections

Highlights in investigation of urinary tract infections include the following:

- 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.

- Advances in the development of vaccination strategies for prevention of urinary tract infections.

Interstitial Cystitis

Progress highlights in interstitial cystitis include the following:

- Increased public awareness.

- Development of a scientific research community.

- Availability of new pharmaceutical treatments.

- Increased neurophysiological research.

- Establishment of the Interstitial Cystitis Database.

GAPS IN KNOWLEDGE

To further the progress in prevention, diagnosis, and management of urologic and kidney conditions, the working group identified the following gaps in knowledge of particular relevance to women's health.

End-stage Renal Disease

Gaps in knowledge about end-stage renal disease of particular concern for their impact on women's health include the following:

- Studies are needed to define the best strategies for reducing the risk of cardiovascular disease mortality in end-stage renal disease patients, including the potential role of hormone replacement therapy.

- Investigation should define the factors that result in an altered hormonal milieu and sub-normal fertility in uremia and mild-to-moderate chronic renal insufficiency, and the effect of dialysis dose on these hormonal factors.

- The issue of whether the preventive management of renal bone disease needs to be different in the two genders needs to be addressed, with particular attention to the role of hormone replacement therapy in prevention of renal bone disease.

- Social and cultural issues affecting referral and access to transplantation need continued study.

Kidney Disease of Diabetes Mellitus

Despite progress in diabetes research in recent years, major deficiencies still exist in many areas. A recent NIH-sponsored symposium on diabetes identified numerous research challenges and knowledge gaps, the scope of which are too broad for this report. The most important highlights, as they pertain to this report, are the following:

- Studies are urgently needed to understand the mechanisms of deterioration of renal function in diabetes, including genetic determinants.
- Studies are need to establish the role of tight glycemic control in prevention of diabetic kidney disease in patients with Type II diabetes.
- The role of lowering blood pressure to levels below standard targets in slowing or preventing diabetic kidney disease needs study.

Analgesic Nephropathy

Knowledge of analgesic nephropathy needs to be improved with particular attention to the following areas:

- Safety of long-term use of high doses of acetaminophen, alone or in combination, needs continued investigation. Of particular concern is the possible effect on pre-existing renal disease.
- Behavioral studies to assess which factors predict heavy analgesic use and long-term evaluation of strategies to alter over-use of these agents are needed.
- Better diagnostic tools to diagnose and monitor analgesic nephropathy are of high priority.

Lupus Nephritis

Understanding of lupus nephritis is lacking in many areas, as highlighted below:

- Etiology of lupus and nature of the genetic determinants that modify the clinical presentation remain unknown.
- Progressive kidney disease results from inflammation amplified by resident renal cells that have been activated in an antigen-independent manner. However, molecular mechanisms of cellular activation continue to elude definition.
- There is a lack of knowledge of the role of cytokines in the pathophysiology of lupus nephritis.
- Studies to examine the reasons for the female preponderance among lupus patients should include examination of the action of estrogens in the pathogenesis of the disease, as well as the examination of X-linked genetic factors.

Renal Complications in Pregnancy

Gaps in knowledge about renal disorders of pregnancy include:

- There are no measures that can consistently distinguish pregnancy-induced hypertension from hypertension due to underlying renal disorders or pre-existing hypertension, hampering research on the etiology of pregnancy-induced hypertension.
- The determinants of and the factors influencing the changes in renal function during pregnancy are still incompletely understood.
- The frequency with which pregnancy results in clinically significant deterioration in renal function in women with pre-existing renal disease and renal transplants is poorly defined. This issue is of substantial importance to women with these conditions who are

contemplating pregnancy. Prospective, observational studies are urgently needed.

Urinary Incontinence and Pelvic Floor Disorders

Understanding of urinary incontinence and pelvic floor disorders is lacking in many areas, as highlighted below:

- The following issues need investigation using the tools of basic science:
  - developmental biology of the genitourinary tract and pelvic structures
  - nature of the anatomical abnormalities of the pelvic floor which underlie prolapse
  - normal physiology and pathophysiology of the bladder and pelvic floor structures.
- In the area of epidemiology, there is a lack of information on:
  - natural history of these disorders
  - prevalence and incidence by sociodemographic factors (specifically minority and younger populations)
  - risk factors including childbirth, exercise, diet, obesity, smoking, hormone deprivation.
- Consistent clinical and research definitions need to be developed, incorporating both subjective and objective measures.
- Awareness of these disorders by physicians, particularly primary care physicians, and allied health professionals need to increase.
- Studies are needed to define the economic, social, and psychological impacts of these disorders.
- Investigation evaluating surgical outcome and comparing alternative surgical interventions for both genital prolapse and urinary incontinence are urgently needed. Studies need to examine long-term recurrence rates.

> *". . . the most common cause of postmenopausal women undergoing gynecologic surgery is for the treatment of urinary incontinence and/or organ prolapse."*
>
> Nicolette S. Horbach, M.D.
> American Urogynecologic Society

Interstitial Cystitis

In the area of interstitial cystitis, the following gaps in knowledge were identified:

- Improved description of the epidemiology of the disorder is needed.
- Further investigation of potential etiologies should occur.
- Studies need to be undertaken to establish markers for the diagnosis of the diseases and for monitoring the efficacy of treatment.
- High priority should be given to continued investigation of therapeutic strategies, both for symptom control and potential cure.

Urinary Tract Infections

Gaps in knowledge regarding urinary tract infections include the following:

- Understanding of the molecular epidemiology of urinary pathogens is needed.
- More complete characterization of factors, such as surface adherence molecules, that make a uropathogen pathogenic may lead to new therapeutic strategies.

- Further studies are needed to understand mechanisms of transmission.
- Investigation is needed into the mechanisms of chronic recurrent infections and the risk factors for recurrence.
- Behavioral risk factors especially in women over 40 years of age and impact of hormone replacement therapy in prevention are topics needing further study.

Overarching Gaps of Special Concern

The working group also identified general gaps in knowledge about urologic and kidney conditions that affect a number of conditions. These include a lack of understanding of:

- Role of hormonal changes in the genitourinary system, and impact of hormone replacement therapy.
- Childbirth effects on the anatomy of the pelvis and bladder.
- Female sexual dysfunction and behavior as it relates to pelvic floor disorders.
- Prepubertal development and relationship, if any, to conditions appearing later in life.

RESEARCH RECOMMENDATIONS

The Working Group on Urologic and Kidney Conditions made the following recommendations for priority areas for future research:

- 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 the short- and long-term renal prognosis, as well as pregnancy outcomes.
- Conduct research to determine the causes of altered renal hemodynamics during pregnancy.
- Conduct studies to establish the optimum approach to hormone replacement therapy in women with chronic renal insufficiency and end-stage renal disease.
- Expand research on the pathogenesis of lupus nephritis to exploit current insights in inflammatory mechanisms and cytokine pathways.
- Undertake investigation to improve strategies for prevention of diabetic nephropathy, particularly that 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.

REFERENCES

1 U.S. Renal Data System. Annual Data Report, 1997. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, USRDS, April 1997.

2 Delano BG, Macey L, Friedman EA. Gender and racial disparity in peritoneal dialysis patients undergoing renal transplantation. *Am Soc Artificial Org J* 1997;43:861-47.

3 Bloembergen WE, Mauger EA, Wolfe RA, Port FK. Association of gender and access to renal transplantation. *Am J Kidney Dis* 1997;30:733-8.

4 Daugirdas JT, Ing TS. *Handbook of Dialysis*, 2nd ed. Boston: Little, Brown, 1988.

5 Allen RD, Chapman JR. *A Manual of Renal Transplantation.* London: Edward Arnold, 1994.

6 Davison JM, Lindheimer MD. Pregnancy in women with renal allografts. *Semin Nephrol* 1984;4:240.

7 Diabetes In America, 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995.

8 De Broe ME, Elseviers MM. Analgesic nephropathy. *New Engl J Med* 1998; 338(7):446-52.

9 Hayslett JP, Kashgarian M. Lupus nephritis. In: Schrier RW and Gottschalk CW, eds., *Diseases of the Kidney,* 5th ed. Boston: Little, Brown, 1993.

10 Management of hypertension in pregnancy. ACOG Technical Bulletin. Washington, D.C.: American College of Obstetricians and Gynecologists, 1994.

11 Jones DC. Pregnancy complicated by chronic renal disease. *Clin Perinatol* 1997; June 24 (2):483-96.

12 Hayslett JP. Postpartum renal failure. *New Engl J Med* 1984;312:1556-59.

13 Jungers P, Chauveau D. Pregnancy in renal disease. *Kidney Int* 1997; October 52(4):871-85.

14 Fantl JA, Newman DK, Colling J, et al. Urinary Incontinence in Adults: Acute and Chronic Management. Clinical Practice Guideline, No. 2. 1996 Update, U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 96-0682. 1996.

15 Ostergard DR, Bent AE, eds. *Urogynecology and Urodynamics,* 4th ed. Baltimore: Williams & Wilkins, 1996.

16 Zamula E. Help for urinary tract infections. FDA Consumer Special Report: Your Guide to Women's Health, 3rd ed. Rockville, MD: Food and Drug Administration, 1997.

17 Hanno P. Interstitial cystitis and related diseases. In: Wash P, ed., *Campbell's Urology,* 7th ed.. Philadelphia: W.B. Saunders, 1998.

CAREER ISSUES FOR WOMEN SCIENTISTS

CAREER ISSUES FOR WOMEN SCIENTISTS

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BACKGROUND

When the Office of Research on Women's Health (ORWH) was created in September 1990, one part of its threefold mandates was "to develop opportunities and support for recruitment, retention, re-entry, and advancement of women in biomedical careers." To that end, ORWH convened a series of meetings, with both female and male participants, to discuss areas of concern and recommend solutions that will assist women scientists in the areas of education and career.

Women in Biomedical Careers: Dynamics of Change; Strategies for the 21st Century met in 1992 and produced a workshop report with recommendations. Nine general issues or barriers were identified that are common to women biomedical professionals regardless of race, ethnicity, culture, or scientific discipline.[1] These are:

- Recruitment
- Role models and mentors
- Career paths
- Re-entry programs
- Family and career conflicts
- Discrimination and harassment
- Research on gender and health
- Gender sensitivity
- Minority women

In November 1997, the Working Group on Career Issues for Women Scientists met in Bethesda, Maryland, where it discussed areas of concern and progress and developed final recommendations for ORWH. Its recommendations are new ideas from this meeting as well as recommendations from the previous meetings.

PROGRESS SINCE ESTABLISHMENT OF ORWH

NIH Programs and Initiatives

In 1991, Dr. Bernadine Healy, then-Director of NIH, established a task force to look at the status of NIH intramural women scientists. The task force found several impediments to career development and proposed the following solutions. They were:

Communication. The task force identified a perception of communication problems on the part of women scientists who feel "out of the loop" with respect to various issues at NIH because so few of them hold senior leadership positions. The task force suggested that every institute elect a woman scientist advisor to meet regularly with the institute's scientific director to discuss issues affecting women scientists. Additionally, the woman scientist advisor attends all laboratory and branch chief meetings. The advisor reports back regularly to the women scientists.

Recruitment and Promotion and Tenure-Track Plan. To facilitate recruitment and promotion of women, the task force recommended that every NIH search committee include at least one woman scientist advisor and, where possible, one minority advisor. All searches are broadly advertised nationwide to minimize the effects of the “old-boy network.”

Visibility. To improve visibility of women scientists, the task force recommended that a lecture series be named after the first woman laboratory chief at NIH, Margaret Pittman. NIH screens prospective speakers to ensure a proportional representation of women and minorities speaking in all NIH lecture series and workshops.

Pay Equity. The Women Scientist Advisory Committee identified sizable disparities in pay between tenured men and women scientists. The Department of Health and Human Services agreed to a one-time pay correction that resulted in pay adjustments for 45 out of 200 tenured women, four minorities, and one man. NIH also adjusted salaries for female and minority postdoctoral fellows in Government positions. For those on “real” fellowships, the pay scale is on tight bands with only a small range between the minimum and maximum pay levels.

Flexible Leave Plan. The Family and Medical Leave Act gave all federal employees access to limited leave for specific family or medical reasons. NIH extended these privileges to postdoctoral fellows (who are not employees by technical definition) for up to 6 weeks of paid leave for maternity. NIH also built into its 6-year term tenure track a “stop-the-clock” mechanism that permits up to 1 year to attend to family matters.

Intramural Career Development. NIH’s Office of Education sponsored an intramural career development program that teaches fellows about job negotiation, presentations, and professional life issues. The office also sponsors a predoctoral internship award for recent college graduates that enables them to spend a year in an NIH laboratory while applying to graduate or medical school.

In addition to these task force recommendations, in 1992, ORWH developed a pilot program, which all the NIH institutes now support, to assist scientists who are re-entering biomedical careers. The program focuses on men and women who withdrew from their careers because of family responsibilities such as caring for children or an ill family member, but who during their time away stayed partially involved in their science careers. Applicants to the program identify mentors with investigator-initiated research grants (RO1s) or other NIH grants who will receive a supplement to their grants to support re-entering scientists for 2 to 3 years of retraining. A 1995 analysis of the program found that the scientists were still employed in research positions 2 years after completion of the program.

Another NIH opportunity is aimed at reaching young women and minority students in the precollege years. Data have established that most young girls leave the fifth grade liking science and considering it as a career. By the time they are in high school, however, the same young women no longer consider science a career option. The NIH Office of Science Education (OSE), with funding from ORWH, is undertaking efforts targeting kindergarten to college-level women to increase their interest in science. OSE is working on a series of posters aimed at middle-school girls that depict women in medical research. OSE also created a web site for middle and high school students. The web site contains “Research in the News,” which provides information on news and breakthroughs in science; “Cool Links,” which points users to other science education resources; and “People Doing Science,” which profiles NIH employees, such as a genetic counselor, a speech pathologist, or a medical librarian.

Non-federal Programs

Because nursing is a profession that has only encouraged research careers in recent years (what is now the National Institute of Nursing Research was only founded in 1986), a number of nursing schools have created inhouse research centers to provide an infrastructure in support of such development. At their best, they make available seed grants and research assistants, provide statistical consultation and editorial assistance, connect faculty with mentors and campus resources, assist in budget preparation, and other help. The staging of mock grant reviews, patterned after the NIH review panels, are used to prepare faculty for the rigors of peer review, and thus improve the quality of grant applications.

Harvard Medical School developed a program in 1995 that provides 10 fellowships a year for junior faculty who want to teach, conduct research, compete for grants, publish, or practice (if a clinical faculty member) at the same time they are assuming increased family or other responsibilities. Faculty may apply for a $25,000 fellowship that will buy protected time for writing a grant application, finishing a research project, preparing a manuscript, or developing a new curriculum. The fellowship also provides funds for additional laboratory assistance. The Office of Faculty Affairs at Harvard intends to continue these fellowships, with a new competition each year, for at least 5 years. In the first year, Harvard granted fellowships to nine women and one man out of 210 applicants.

For women at the associate professor level who want to progress into administration, the Office of Faculty Affairs at Allegheny University of the Health Sciences has developed a program called Emerging Leaders in Academic Medicine. Participants are in residence for two 1-week sessions that include workshops on developing leadership skills and mentoring. Women who participate must show that their university administration is committed to the program, and the dean of the school is required to attend 2 days of the last session.

> *"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

Several organizations have published information on sexual harassment and discrimination. The Council of Graduate Medical Education's *Fifth Report: Women and Medicine* found that the greatest obstacle for women in medicine is sexism. The Association of American Medical Colleges offers a variety of materials on the status of women in medicine — from statistics on women at all levels to a compendium entitled *Building a Stronger Women's Program.* Janet Bickel's book, *Enhancing the Environment for Women in Academic Medicine* (1996), includes chapters on sexism in medicine and on salary-equity programs.

The Department of Surgery at North Shore University Hospital in Manhasset, New York, sends *The Pocket Mentor* to all new interns, particularly women. A good resource for all institutions looking for women candidates is the reference manual that lists women with their subspecialty of medicine. A book by Dr. Deborah Swiss of Harvard addresses "Mommy-track" issues.

GAPS IN ADVANCEMENT OF WOMEN IN BIOMEDICAL CAREERS

The working group discussed common themes and recommendations from the previous ORWH meetings and raised new issues to be addressed.

Data Collection, Monitoring, and Dissemination

Data Collection. As more women scientists acquire leadership positions, they face issues traditionally handled by men. Collecting data is an option for use in supporting and ensuring the success of women leaders. For example, collecting data on women chairs of basic science departments across institutions will facilitate communication among women leaders to enable networking, brainstorming, and discussion of leadership styles.

Few databases are available that contain benchmarking or best practices data that could be used to improve conditions at an institution. For example, identifying the best mentoring programs is difficult because so many are currently available.

Salary Program Monitoring. Some institutions may pay women faculty less than men. NIH should mandate that institutions receiving federal funding make salary information available to ensure equal pay for similar training. Some organizations publish and post their salary information on websites. The IPEDS Interactive Database at Arizona State University (http://ncda.org/ipeds), for example, contains information on faculty salaries, including faculty salary sex differences, for hundreds of institutions.

Dissemination. NIH plans to expand the availability of public information. Any existing databases need to be amalgamated and could, for example, contain information on principal investigators.

Electronic Technology. Women should be encouraged and supported in the use of computers and the Internet. This technology needs to be accessible to all women.

Marketing and Outreach. The lack of sufficient marketing and information outreach regarding women's health is a concern.

Institutional Responsibility, Collaboration, and Partnering

Institutional Responsibilities. The working group identified a number of areas in which institutions should assume more responsibility.

Equal pay for equal work remains a difficulty. Department chairs in state or other institutions work within bureaucracies. The longer a scientist (male or female) remains in a particular grade (and women frequently remain in a grade longer because they leave temporarily for childbearing or other reasons), the less likely he or she will receive a pay raise. Chairs or deans have difficulty giving employees the pay increases they deserve.

Likewise, sponsoring organizations may have trouble identifying an office or a contact person to assist women with disabilities at conferences. This type of information could help disabled people easily specify their needs.

Collaboration and Partnering. Collaboration and partnering among organizations are important, particularly because 50 percent of the biomedical research budget is in industry and many women spend their careers there. ORWH needs to work not only with professional scientific organizations but also with the American Association of University Women (AAUW), the Association for Women in Science (AWIS), and the National Science Foundation (NSF) (which have programs directed at the precollege student), as well as with the major business research organizations. Collaboration would ensure that resources are spread out and do not target the same group. Actions taken in concert and under NIH leadership can catalyze outcomes.

Community partnering depends on links with professional associations, academic health centers, practitioners, and industry. Middle school students who are at risk because of environmental or social circumstances often are creative children with much potential. NSF or NIH scholars and experts should be encouraged to participate in community linking by visiting public schools and speaking with elementary, middle school, and high school students about careers in medicine and the health sciences. Many NIH institutes have adopted local Washington, D.C. schools, and NIH scientists visit the schools throughout the school year to talk with students about science and research at NIH.

Education. Generally, teachers are not prepared for educating and encouraging children in science. On the other hand, most graduate schools are reassessing whether they are producing too many Ph.D.s. Reassessment of graduate education and training needs to take place.

Leadership

Leadership requires more emphasis. Much effort is devoted to attracting young women to scientific careers and keeping them there, but as women gain seniority, few attain leadership positions. Approximately 183 women chair medical school academic departments.[1] Female deans, vice presidents, and department chairs do not necessarily have peers within their own organizations. They need to network for survival in these high-level roles, with the help of data collection, as mentioned earlier.

Mentoring

Mentoring is a major need if we are to lessen the number of women leaving career paths. But mentoring is time-intensive for faculty, reduces time available for research, and is rarely a criterion for promotion. A specific proposal is that success in finding, retaining, and placing women and minority graduate and postdoctoral students should be a major criterion for judging, funding, and renewing training grant applications.

> *"The number of black nurses with earned doctorates represents less than 1 percent of all professional nurses in the United States."*
>
> Linda Burnes Bolton, Dr.P.H., R.N.
> National Black Nurses
> Association, Inc.

There is a need to identify institutions with programs that reward mentoring and offer a flexible schedule. Several medical societies have mentoring programs to attract students at precollege levels. Linking into such programs to a database would benefit women.

Cultural Issues and Social Norms

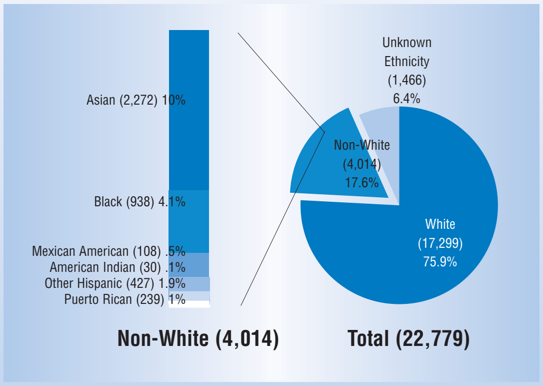
Women are increasing their numbers in medical school — women constituted 43 percent of new entrants and 42 percent of total enrollment in U.S. medical schools.[2] The proportion of women in medical residency programs was 34 percent in 1996, and the highest proportion of women residents was in pediatrics.[2] However, women are leaving because the medical school culture involves such long work hours and large workloads that there is no time for family. Women who stay too often give in to the culture.

How we value the contributions of women as scientists and how we measure that value are of concern. The work of women should not be assessed using male-oriented expectations of behavior, because women often have different working styles due to family constraints. Benchmarks should be developed to evaluate quality of work, regardless of the style used to achieve that work. Some women have assumed particular leadership styles to achieve success, which may be counterproductive to the best strengths and values of women. There are multiple ways to obtain the same goal, and we need flexibility in time, age, and career sequence. Different work styles should be encouraged to accommodate the needs of all women.

Our current education and health care delivery system was haphazardly put together to benefit the social class and gender of the people who traditionally performed this work. We are now trying to fit excluded people into a system that was not designed for them. We need to examine our medical education, working conditions including the lack of sleep for residents, and the timeframe for training in terms of the needs of women. Premedical training, medical school, and residencies make it nearly impossible for women to have children during the ideal childbearing years. This is particularly true of the field of surgery. Women still face discrimination and harassment, most of which occurs in medical school and during residency training. Once women finish training and go into practice, the prevalence of harassment drops substantially. Institutions need to make academic medicine a more secure environment for women.

Women in the health professions face a particular kind of discrimination. Too often those in the traditionally female-dominated professions, nursing and social work, are perceived as not needing to do research to expand their knowledge base, and they are dissuaded from research training. Support for individuals in these professions is further limited by the fact that the questions they study usually exist on the interface between the behavioral and the biomedical sciences (e.g., family adaptation to a child's chronic illness), an area of tremendous clinical importance, but one requiring complicated scientific methods and an interdisciplinary perspective. Thus, scientists in these areas face the added dilemma of feeling not always welcome by the scientific community at the same time that they are struggling to study problems not subject to the rigorous control as bench science, which only reinforces traditional beliefs that they may not belong.

FIGURE 1. Ethnicity of Female Faculty in U.S. Medical Schools



Source: American Association of Medical Colleges (AAMC) Faculty Roster System. Bickel J, Croft K, Johnson D, and Marshall R. Women in U.S. Academic Medicine Statistics 1997, Washington, D.C.: AAMC, 1997. Used with permission.

RECOMMENDATIONS

Overarching Principles

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, including the disabled, all ethnic and racial groups, and those with different sexual orientations. ORWH will need to collaborate with external agencies, associations, academic institutions, and other entities to accomplish these complex tasks.

Data Collection, Monitoring, and Dissemination

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.
- Lend support to 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 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.

> *"We have come a long way from where we were, and we still have a long way to go, but we will get there."*
>
> Carola Eisenberg, M.D.
> Harvard Medical School

- 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
  - 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 OE Scholarship Program for Minority Undergraduates with more vigorous outreach.

- Establish partnership 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. (See Harvard Medical School's 50th Anniversary Program for Scholars in Medicine as one possible model, as described on page 189.)

- Establish collaborative programs with the Department of Education and Department of Rehabilitative Services.

Leadership and Visibility

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, and 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.

- 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 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 in NIH grants enough flexibility to accommodate the transient but compelling needs of women around issues of childbearing.

Note: Although the entire set of recommendations is intended to apply to all women, including women with disabilities and special populations of women, special comment is in order to acknowledge the requests of the disabled workshop members for special accommodations at meetings. Needs for special hotel accommodations, transportation between conference sites, access to meeting rooms, and appropriate seating arrangements should be recognized in all NIH meetings as well as other scientific and medical meetings.

REFERENCES

1 Office of Research on Women's Health. Woman in Biomedical Careers: Dynamics of Change: Strategies for the 21st Century, NIH Publication No. 95-3565, Department of Health and Human Services, 1995.

2 Bickel J, Croft K, Johnson D, Marshall R. Women in U.S. Academic Medicine Statistics 1997, Washington, D.C.: American Association of Medical Colleges, 1997.

SELECTED ISSUES IN RESEARCH DESIGN

HEALTH OF SPECIAL POPULATIONS OF WOMEN

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"Special populations" includes women of different racial, ethnic, and cultural origins; women with disabilities; lesbians; women living in urban and rural settings; and immigrants, among others. In this report, studies dealing with different racial, cultural, and ethnic groups are cited primarily, but health issues for women in the other categories should not be forgotten.

Any one of several data books demonstrates differences in health status and health outcomes among different populations of women. 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 white, black, Asian, and Hispanic women; for American Indian women, however, the third leading cause is accidents and unintentional injuries.[1] Death rates from cancer vary among the different populations. For example, the death rate from breast cancer reported for black 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. Definitions vary among the sources of data. For example, although, beginning in 1976, the Federal Government data systems classified individuals into the following groups — American Indian or Alaskan Native, Asian or Pacific Islander, black, and white — some source books classify Pacific Islanders with American Indians. Prior to 1980, the race of a newborn infant was determined by the race of the father when neither parent was white. If the parents were of different races and one parent was white, the child was classified according to the race of the nonwhite parent. Since 1980, the race of a newborn infant has been recorded according to the race of the mother. Persons of Hispanic origin are defined as persons speaking Spanish or with Spanish surnames, and may be of any race.

Given the variables associated with designation of race, culture, or ethnicity, one might question whether using these designations to examine different populations for study is wise. Should individuals be assigned to certain study groups according to such designations, or should they be assigned based on self-description? Agreement is needed among researchers on a uniform method, so that sound comparisons can be made.

DIFFERENCES IN HEALTH STATUS

Differences in health status and health outcomes among the different populations are known to correlate with educational, cultural, and behavioral variables; 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. Analysis of data over a 24-year period showed that corpus uterine cancer among non-Hispanic white women was twofold higher than for Hispanic women and three times higher than for American Indian women.[2] In this study, as in many, race and ethnicity were self-reported. Prolonged exposure to endogenous or exogenous estrogens and obesity are risk factors for uterine cancer. Although the prevalence of exposure of the three ethnic groups to exogenous estrogen replacement therapy is not known, obesity is more common among both Hispanic and American Indian women and thus exposure to high levels of endogenous estrogen could be presumed more prevalent. Diabetes and hypertension, which are risk factors for uterine cancer, also are more prevalent in Hispanic and American Indian women in New Mexico. These assumptions conflict with the lower incidence rates of uterine cancer in these two groups. Further research should explore instances such as this.

The rate of cervical cancer among Hispanic women in the southwest was found to be almost twice that of non-Hispanic white women. Risk factors including lower income, low education level, and infection with multiple human papilloma virus (HPV) types were similar for both groups, but for Hispanic women, infection with HPV types 16-18 was strongly associated with cervical dysplasia. The odds ratio for a cervical lesion for non-Hispanic white women was 18, whereas for Hispanic women the odds ratio for developing cervical dysplasia was 171. This disparity suggests that environmental, immunologic, or genetic cofactors may play a part in the development of cervical dysplasia pathology and progression to invasive cancer.

In humans, a specific class of human leukocyte antigen regions is associated with a variety of diseases, including some cancers. This prompted researchers at the University of New Mexico to look for an association of an HLA phenotype with invasive cervical carcinoma in a group of New Mexico Hispanic women.[3] The investigators found that DR-13 haplotypes are associated with a strong protective effect against developing invasive cervical carcinoma. On the other hand, a group of DRDQ haplotypes was associated with a strong susceptibility to develop invasive cervical carcinoma in association with HPV-16 infection. These results suggest that the immune response to HPV-16 may be determined in part by specific HLA class II haplotypes and may influence risk of cervical neoplasia. In other words, specific host genotypes may predispose some populations to certain cancers.

Virtually all comparative black/white studies in North America have shown that black women have 5 to 10 percent greater bone mass and 5 percent greater bone density than white women when matched for age.[4] This is the case despite the fact that blacks have been shown to have a significantly lower calcium intake throughout the life cycle. Two possible explanations have been proposed to explain the black/white difference in bone mass. One deals with calcium and bone metabolism and the other with reproductive hormones. A study showed lower urinary calcium excretion among black children compared with white children of the same age. Lower urinary calcium excretion also was found in a population of older black women compared with white women. Although not fully explained, the concept is that lower bone turnover among blacks may contribute to accumulation of greater bone mass. The implications of the differences in steroid hormone levels are not entirely clear, but it is hypothesized that higher estrogen levels among black pubertal girls favor retention of minerals by the skeleton, which is beneficial because of the lifetime priming of bone estrogen receptors. Thus, in this instance a physiologic explanation appears to account for some of the differences, although genetic determinants that increase bone mineral density — independent of dietary intake of calcium — may be a factor as well.

Bone mineral status among Asian populations has been studied only recently. There is some indication that bone mineral content and bone mineral densities are similar in Asian and white children. Japanese women are thought to have lower calcium intake, yet for elderly Japanese women living in Japan, hip fracture rates are significantly lower than for Caucasians living in the United States. For Japanese women in this country, the prevalence of hip fracture approaches that of white women. The degree to which acculturation and changing lifestyles affect health should be determined.

A common belief is that incontinence and pelvic organ prolapse occur less frequently among black women than among white women. Until the NIH consensus development panel on urinary incontinence in adults in 1989 emphasized the importance of gathering data regarding incontinence in nonwhite ethnic groups, most studies of incontinence were done on white women. In 1993, a group of black women with incontinence were studied, and the findings were compared with those of a group of white women.[5] Urodynamic assessments showed that black women were more likely than whites to have motor instability as a cause of their incontinence and less likely to have genuine stress incontinence. Thus, black women presenting with incontinence require more accurate and sophisticated urodynamic testing before they undergo treatment. Continued study of a larger population and of different subgroups is needed.

The fact that blacks have a greater prevalence of hypertension than whites is well known, but they also have increased morbidity. Obesity is more common among black women than Caucasian women, 20 percent of black women over the age of 18 are smokers, and, as a group, black women are less likely to engage in regular physical activity, which puts them at greater risk. But there are physiologic reasons that increase risk and serious sequelae. Fifty-one percent of black women have undesirably high serum cholesterol levels and lipoprotein-A levels, which correlate with increased risk of coronary heart disease. Diabetes is more prevalent among black women. Blacks are more sensitive to sodium loading and exhibit a less marked reduction in blood pressure at night. The constant increased pressure load has obvious implications for the development of organ damage and thus increased morbidity.

Differences in infant mortality rates have been known for a long time. Elevated infant mortality rates have been attributed to adverse sociologic factors, including poverty, alcoholism, inadequate parenting skills, and inadequate prenatal care. But, even correcting for socioeconomic risk factors, blacks still have greater risk for infant mortality.[6,7] On the other hand, favorable birth weight and low infant mortality rates have been reported more consistently for Hispanics of Mexican descent, despite the lower socioeconomic status. An explanation was that Hispanics of Mexican origin have a higher rate of fetal loss, which eliminates the biologically weaker fetuses. This does not seem to be the case, however. A study evaluating fetal deaths in Mexican American, black, and white non-Hispanic women who receive government-funded prenatal care did not substantiate an increased fetal death rate among Mexican-American women. Many think that the traditional family attitudes of Mexican-American women influence their health and the health of their newborn infants.

> *". . . 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

"Studies that investigate how exercise can promote healthy aging in women are especially indicated."

Andrew A. Guccione,
Ph.D., P.T.

CULTURAL AND BEHAVIORAL DIFFERENCES

Maintaining health is essential for preventing disease. The roles of traditional cultural values and sociologic and behavioral factors in health maintenance must be recognized. Among a group of women studied at Denver General Hospital, for example, the major reason for lack of prenatal care was attitudinal: Most pregnancies were unplanned, and feelings of depression, ambivalence about the pregnancy, and having to deal with other problems were the most common reasons cited for lack of prenatal care.[8] Among the Hispanic women, a common reason for not getting prenatal care was, "I was getting good advice from family and friends." Among blacks, the reasons were "I didn't think it was important," and "I didn't want to think about being pregnant." White women were more likely to identify financial reasons and problems with access than were black and Hispanic women. Nearly all women (88 percent) thought they were pregnant by the fourth month of pregnancy, but by the end of 6 months one-third still had not seen a professional.

Analysis of 19,027 females (56 percent black, 44 percent white) showed that black women were less likely to exercise, more likely to be overweight, and less likely to be nonsmokers.[9] Explanations included lack of personal control over their lives and having to deal with a myriad of other issues. On the other hand, black women were more likely to obtain a Pap test and breast exam than white women, which may be explained by the fact they commonly live in urban settings, where they are screened when entering the health care system for other reasons and where there is higher availability of medical services.

Hispanic women are less likely to obtain Pap smears or to have had a mammogram in the past 3 years.[10] Access to care, the importance of a family member to accompany them to the hospital setting, transportation, and so on, play a role. The effect of acculturation on health-seeking behavior has been examined. A group of Mexican-American women age 40 or older living in El Paso were studied to determine the effects of acculturation in cancer-screening behavior.[11] Acculturation was measured by English proficiency, English use in the family setting, value placed on culture, traditional family attitudes, and social interaction. The researchers found that the strongest independent factor affecting mammogram screening was insurance, but after they adjusted for socioeconomic factors, a woman with a positive attitude toward traditional family values was more likely to have undergone a mammogram.

PROVIDER ATTITUDE DIFFERENCES

One cannot examine differences in health outcomes among special populations of women without addressing physician attitudes and practice. Several studies indicate that less than 50 percent of primary care physicians take a sexual history from patients. Failure to inquire about the possibility of abuse — physical or sexual — is frequent. There is ample evidence in the literature that many lesbians avoid medical care because of fear of discriminatory practice, thus decreasing the likelihood of obtaining routine screening. 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. Women with developmental disabilities frequently are treated as children — because of an incorrect assumption that they cannot understand adult discourse.

Differing practice patterns may relate to patients' race. One study found an association between race and likelihood of screening for diagnosis of hypercholesterolemia in an office-based family medicine residency training program in Rochester, NY.[12] Of the group with identified race or ethnicity, approximately 23 percent were minorities, of whom 80 percent were black. Female sex, age less than 45, receiving Medicaid, not having insurance, and being a minority were associated with reduced likelihood of screening. Minorities were less likely to have a diagnosis of hypercholesterolemia on the medical record even though cholesterol levels were comparable to those of whites. The authors concluded that this underdiagnosis of hypercholesterolemia in minority patients suggests a difference in the behavior of health care providers toward white compared with black patients.

In another study, of a group of Medicare beneficiaries including 24 million whites and 2 million blacks, the black beneficiaries and low-income beneficiaries had fewer visits, fewer mammograms, and fewer immunizations against influenza, but were hospitalized more often and had higher mortality rates.[13] They also had higher rates of amputation of the lower limbs, suggesting that black beneficiaries were less likely than whites to have leg-sparing surgery and more likely to undergo amputation. The rates for angioplasty and coronary artery bypass surgery were substantially higher among white than black beneficiaries. Although the authors invoked many reasons for these differences, including educational, cultural, and behavioral variables, individual preference, and differences in treatment of disease, other barriers to elective health maintenance care such as race, low income, and physician attitude may exist.

> *"We want to be assured that diseases and ailments that so disproportionately affect minorities and women — diabetes, hypertension, teenage pregnancy, low-birthweight babies, heart attacks, strokes, sickle cell anemia, kidney failure — are given adequate attention and funding."*
>
> Jann Primus, Ph.D.
> Spelman College

In summary, health status and health outcomes vary among different populations of women. It is important to explore the reasons for the differences and to utilize the knowledge to influence the health of women.

REFERENCES

1 National Center for Health Statistics. Leading causes of death by race and ethnicity, 1993. Health, United States, 1995. Hyattsville, Md: Public Health Service, 1996. p. 114.

2 Becker TM, Wheeler CM, McGough NS, et al. Sexually transmitted diseases and other risk factors for cervical dysplasia among southwestern Hispanic and non-Hispanic white women. *JAMA* 1994;271:1181.

3 Apple RJ, Erlich HA, Klitz W, et al. HLA Dr-DQ associations with cervical carcinoma show papillomavirus-type specificity. *Nat Genet* 1994;6(2):157-62.

4 Anderson JJ, Pollitzer WS. Ethnic and genetic differences in susceptibility to osteoporotic fractures. *Adv Nutr Res* 1994;9:129-49.

5 Bump RC. Racial comparisons and contrasts in urinary incontinence and pelvic organ prolapse. *Obstet Gynecol* 1993;81(3):421-5.

6 Kerr GR, Ying J, Spears W. Ethnic differences in causes of infant mortality: Texas births, 1989 through 1991. *Tex Med* 1995;91(9):50-6.

7 Guendelman S, Chavez G, Christianson R. Fetal deaths in Mexican-American, black, and white non-Hispanic women seeking government-funded prenatal care. *J Community Health* 1994 Oct;19:319-30.

8 Meikle SF, Orleans M, Leff M, et al. Women's reasons for not seeking prenatal care: racial and ethnic factors. *Birth* 1995 Jun;22(2):81-6.

9 Duelberg SI. Preventive health behavior among black and white women in urban and rural areas. *Soc Sci Med* 1992 Jan;34(2):191-8.

10 National Institutes of Health, National Cancer Institute. Seer Cancer Statistics Review: tables and graph. Bethesda, Md; 1989. NIH Publication no. 89-2789.

11 Suarez L. Pap smear and mammogram screening in Mexican-American women: the effects of acculturation. *Am J Public Health* 1994;84(5);742-6.

12 Naumburg EH, Franks P, Bell B, et al. Racial differentials in the identification of hypercholesterolemia. *J Fam Pract* 1993 Apr;36(4):425-30.

13 Gornick ME, Eggers PW, Reilly TW, et al. Effects of race on mortality and use of services. *N Engl J Med* 1996;335:791-6.

SEX AND GENDER DIFFERENCES

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BACKGROUND

With the founding of the Office of Research on Women's Health and the enacting of the mandate that women and minorities be included in clinical studies, NIH has responded to the issues raised about sex and gender in medical research. The Food and Drug Administration (FDA) has echoed this concern about gender in medical research by changing its policy on the study and evaluation of drugs in women. These policy changes by NIH and FDA reflect the growing concern for women's health, and have also opened the door to other issues regarding clinical studies, sex and gender differences, and new approaches to medical studies.

CLINICAL STUDIES

Designing Clinical Studies

The NIH guidelines are still evolving; many in the medical community view them as a starting point in the discussion of sex and gender and clinical studies. For example, one issue mentioned by the working group concerned the implication of the semantics of the NIH guidelines on "inclusion" of women and minorities in clinical studies. That 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. The design of the research study must derive from the question being asked. Designs will differ according to the questions being asked — for example, whether there is a difference between men and women in response to a drug and whether the drug works in women. Even when women are included in clinical trials, the data may be aggregated in such a way that investigators analyze the data overall and not by sex.

Many researchers have noted that politics can prevent or hinder the study of sexual differences in clinical trials. For example, until recently, it was difficult to publish a paper with the words "sex differences." The paucity of studies on neuroendocrine aspects of female functions may be attributable to a belief that it was not politically correct to acknowledge different functioning at different times of the month or to a fear of discrimination based on the differences.

Socioeconomic factors applicable to women can complicate research design. Socioeconomic differences cannot be measured in the same way in men and women because there are no good sex- and gender-neutral measures of socioeconomic status. Three basic measures of socioeconomic status are income, occupation, and education. These factors tend to correlate better in men than in women. A woman can be highly educated, have a low household income, and be in a pink-collar job.

Finally, there is a lack of studies on healthy people, an area for which research designs must be unique to healthy women. For example, the effects of the menstrual cycle on drugs and other therapies should be analyzed in clinical trials.

Although incorporating women into the designs of clinical studies may create logistical issues, it may result in new areas of research, innovative research designs, and cost-effective options. A well-designed and well-conducted study involving women and minorities can provide information about treatment and care of direct benefit to men and women alike. In addition, results from such studies can enable policymakers to make decisions that will improve the overall health of the nation.

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. “All of our costs in industry have been cut, are being cut, and will be cut in the future. What this means is that any increase in cost in any area of drug development will be carefully considered.”[1] Although the inclusion of women as research subjects may initially cost more, the savings will be realized in the longer term. Excluding women from trials would result in inadequate data, which could lead to inappropriate treatment, added risks for women, and increased costs to society.

How can clinical trials be conducted at minimum cost and still include women participants? One possibility is for investigators to do multi-institutional, collaborative studies. Another possibility is for investigators to ask smaller questions and be willing to be patient to get meaningful answers. The focus of research should be on clinically significant questions, and the answers will change how health care providers take care of their patients, whether women or men.

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. However, the role of MCOs in women’s health research is more extensive than just as a data source — MCOs could significantly affect clinical research in general.[2] At the Society for the Advancement of Women’s Health Research Annual Corporate Advisory Council Conference in 1996, attendees generally agreed that MCOs could have a negative effect on traditional clinical efficacy research because of financial, political, and operational concerns. These concerns require that knowledge be practical and that practicality be incorporated into research design, costs, measurement, and potential application.[2] MCOs that perceive research as increasing costs, rather than generating profits, have been reluctant to become involved in research.[2] The trend of MCOs and women’s health research is “improved processes for providing care, but reduced technologies for implementing cures. The challenge for the research advocacy community will be to ensure the former without sacrificing the latter.”[2]

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. For example, women generally do not use the health care system for menopause, unless they need a hysterectomy. This absence creates difficulties for capturing an accurate picture of women and menopause, and is one of numerous barriers to addressing the health issues of women: “Access to health care, mistrust of the medical system, language barriers, cultural beliefs, and even transportation and child care are all issues that must be addressed to ensure that women are able and willing to participate in clinical studies."[3]

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. On some occasions, when pharmaceutical companies opened trials to women, they did not come forward to participate. In such cases, investigators may be inclined to assume that women do not wish to participate and may wish to proceed with the trial as before. Thus, there is a need to train investigators to use different strategies to increase women's participation. For example, typically the first step in recruiting potential participants is to advertise in newspapers. Whereas newspaper advertisements may be effective in recruiting men, studies indicate that women are more likely to respond to radio messages or television advertisements. In recruiting women for some AIDS trials, investigators found that they had to offer incentives, such as transportation and day care, to enable women to participate.

Informing the appropriate people is key to recruiting for clinical trials, and yet two major considerations are often overlooked. First, although physician referrals can be crucial to successful recruitment, many physicians are not informed about clinical trials. Second, if the potential population to be recruited includes women whose native language is not English, the recruitment plan should include disseminating information in languages other than English.[3]

Once informed about a study, whether a woman decides to participate may depend on their attitudes toward the medical profession, research team members, and clinical studies in general. Participants' confidence in those conducting the research, and even their opinions about the quality of study design, can be important determinants of enrollment and retention. The recruitment and implementation plans should consider establishing one-on-one relationships between research staff and study participants, having as many women as possible be members of the clinical staff, encouraging joint decisionmaking and informed consent, and establishing educational and support networks of former and current study participants.[3]

The relation between the research institution and the community participating in the study should be considered when recruiting participants. Clinical studies may fail if the researchers and community do not have common goals or a shared recognition of the needs of the community. Trust should be established between the research institution and the community, along with a partnership approach. Partnerships can be established by having members of broad-based groups, such as religious groups, participate as early as possible in the recruitment process, preferably at the planning stage. Partnerships that create strong personal relationships between participants and clinical staff can lead to such benefits as higher participant retention and compliance with study protocols: "An attitude of caring and assistance on the part of investigators and staff may keep participants returning to the facility not only to participate in the study, but also for the personal and social contacts."[4]

When recruiting and retaining women in clinical trials, investigators need to consider all the above-mentioned concerns, but these concerns should not be viewed as absolute obstacles to having women participate in studies — the obstacles can be overcome with careful planning and persistent efforts.

Ethical and Liability Considerations

A major ethical and liability consideration is the inclusion of women of childbearing age in clinical trials. In particular, pharmaceutical manufacturers worry that including women of childbearing potential in clinical trials can make manufacturers vulnerable to lawsuits. The NIH and FDA guidelines address this issue. In 1993, the FDA reversed its recommendation that women of childbearing potential be restricted from participating in drug trials. FDA issued new guidelines about including both sex and gender in drug development, analyzing clinical data by sex and gender, assessing potential pharmacokinetic and pharmacodynamic differences between sex and gender, and conducting specific studies in women. 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.

Scientists, pharmaceutical companies, and the FDA emphasize the problems of testing pharmaceutical agents in pregnant women. They are concerned about protecting fetuses from potential toxic therapies as well as the possibility of liability and lawsuits.

During pregnancy, physiological changes occur in the cardiovascular, renal, gastrointestinal, pulmonary, and hepatic systems. These changes can affect how a drug is absorbed, distributed, metabolized, and eliminated. According to a white paper by the American College of Clinical Pharmacy, pregnancy significantly influences the pharmacokinetics, and possibly pharmacodynamics, of various compounds.[5] The fetus and placenta should be regarded as different compartments in the pharmacokinetic model in pregnant women.

Although pregnant women have been excluded from clinical trials in the past, they use drugs during pregnancy. Companies have marketed drugs used by pregnant women without having knowledge about the maternal and fetal effects of the drugs. An Institute of Medicine report states that 75 percent of pregnant women use prescription and over-the-counter medications.[6] In 1992, investigators discovered that pregnant women with hypertension who used angiotensin-converting-enzyme inhibitors during the second and third trimesters sometimes experienced fatal neonatal renal problems.[7]

The FDA is examining the issues surrounding participation of pregnant women in clinical trials of new drugs and biological agents. The agency has acknowledged the importance of including pregnant women in trials that use experimental therapies for life-threatening conditions, such as new therapies for AIDS. New models are needed, including animal models, and followup procedures, such as postmarket surveillance for drugs.

Animal Studies

Research on animals can lay the foundation of progress toward developing research designs for clinical trials, yet female animals are generally not used in research because of the rate and complexity of the estrous cycle. Few animal models mimic the menstrual cycle and when they are used it is almost exclusively for contraceptive research. Otherwise, if a study uses female animals, the animals are basically “castrated” before being studied. Investigators should investigate the use of female as well as male animals and differences in the hormonal milieus in these animals and consider looking at several animal models, not just a rodent model.

SEX AND GENDER DIFFERENCES

Women and men are obviously different in regard to the presence of hormones, such as testosterone, estrogen, progesterone, and prolactin. Since these hormones affect sex- and gender-dependent physiological characteristics, they may also modify the pharmacokinetics and pharmacodynamics of selected drugs. Yet the scientific knowledge base does not provide information about sex and gender differences in responses to drugs. It is vital that investigators determine under what conditions sex and gender differences happen and design clinical studies appropriately to examine these situations.

Women and men also differ biologically in body composition, size, and metabolism. These factors may influence the dosage, disposition, and metabolism of drugs. Therefore, when determining drug dosing it may be appropriate to consider these differences, especially body size and composition, instead of using standard fixed doses.

The design of diagnostic technology and medical devices poses concerns. Most medical diagnostic technology is built with a man in mind; and, because some medical devices are designed for men, women are often too small for the use of the devices.

Differences between women and men are more than just biological. There are also behavioral and psychosocial differences between the sexes. Differences in lifestyle, such as exercising, alcohol consumption, and cigarette smoking, affect health. Women and men perform different roles in society, which influence their health. Women are more often the victims of domestic violence and have higher rates of depression and eating disorders.

Another important sex and gender issue is aging. On average, women live 7 years longer than men; they constitute the majority of the population over 65.[6] Therefore, research on the aging process should include women. Women and men are affected by different diseases and conditions. Rheumatoid arthritis and osteoporosis are more common among women than men, whereas more men than women suffer from gout. In addition, older women tend to experience more adverse reactions to medications than do men.[6]

In 1994, the Institute of Medicine Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies concluded that sex and gender differences are relevant to design of clinical drug trials. They summarized that “differences in size, fat ratios, and metabolic rates are associated with differences in drug concentration, metabolism, and response. Psychosocial differences are associated with differences in risk factors and, more important, in adherence to experimental protocols. These differences can change over time, both in the short term (during menstrual cycle) and the long term (with pregnancy, lactation, and aging).”[6]

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. These stages influence the development of diseases such as myocardial infarction and osteoporosis. Thus, a study in which only premenopausal women participate may not reveal findings that are applicable to postmenopausal women. If women participate in pharmacokinetic and pharmacodynamic studies, it is vital to establish whether they are premenopausal or postmenopausal and whether they are receiving hormone replacement therapy or oral contraceptives.

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. This was not done in breast cancer screening trials. In these trials, women were grouped by age, instead of by pre- or postmenopausal status.

Research designs and study instruments should be developed that describe the menstrual cycle longitudinally and assess hormone differences across menstrual cycles. Clinical trials that include premenopausal women should study changes not only month to month, but also week to week, plotting information over two or three menstrual cycles. A single blood level is not helpful, because it represents a single point in time, instead of a view of dynamic change. New technologies may be needed to perform population-based studies: instead of blood measurements, investigators should explore less intrusive measures such as those using saliva and urine samples.

INSTITUTIONAL REVIEW BOARD SHOPPING

Before conducting research, some pharmaceutical companies go "institutional review board (IRB) shopping," looking for the appropriate IRB for the investigation. IRBs may find equitable selection criteria confusing if the private and public sectors present conflicting policies. Sometimes IRBs get requests from pharmaceutical companies to do research that specifically excludes women. When an IRB questions a protocol or tells a pharmaceutical company to change the protocol to allow women in the studies, the company may threaten to take their studies elsewhere. Money for research is at such a premium that if a pharmaceutical company has any conflict with an IRB, the company can move the study elsewhere.

To deal with IRB shopping, IRB chairs have proposed establishing a network of IRBs so that IRBs can communicate with each other to stay abreast of pharmaceutical companies' studies and activities. Another way to avoid IRB shopping is to have pharmaceutical companies contribute to a pool of funds (perhaps managed by NIH), which would separate research money from pharmaceutical companies' perspectives. Such a pool could also be established with funding from MCOs.

Another concern with IRBs is that the boards do not learn about the population composition of the study until the annual or interim project review, which restricts an IRB's capability to secure a balanced population study. Involving IRBs in the early design phases of research would help to ensure that there is an equitable representation of study subjects.[8]

IN SEARCH OF A NEW PARADIGM

In 1995, Gerhard Levy wrote about patient-oriented pharmaceutical research that focuses on the individual. This research would extend beyond pharmacokinetics, pharmacodynamics, and medication adherence to include the behavioral sciences.[9] In a similar vein, the World Health Organization's Tropical Diseases Research program uses a multidisciplinary approach that views women's health as a result of sociocultural interactions and economics.[10] A framework for health research is supported that would create a sex and gender framework that incorporates research from such diverse fields as medicine, pharmacy, public health, epidemiology, anthropology, economics, entomology, agriculture, environmental engineering, ecology, and health education. In this approach, women and men are seen as principal agents of their own health, with personal needs, priorities, and preferences.

EDUCATION

The issues discussed above all require education. The general public needs to learn more about women's research issues and about participating in clinical trials; pharmaceutical companies about inclusion of women in trials; and investigators about how to design trials for women's participation, and how to create new research models based on women. Moreover, society, the medical establishment, and investigators should be educated on the importance of having more women investigators.

CONCLUSION

Scientists will continue to struggle with the fact that they serve a diverse society — diverse in sex, size, age, culture, and income. The population is not only diverse, but dynamic. Given the nature of society, it is vital to recruit, retain, and observe diverse populations in an ethical manner. The public needs to be informed and educated about medical studies and their importance. Ultimately, scientists must search for the most significant findings, those that will affect the practice of medicine. Part of science's responsibility is to serve all; yet science must also focus on the most meaningful issues, and not be diverted by simplistic academic issues.

REFERENCES

1 Bush, J. The industry perspective on the inclusion of women in clinical trials. *Academic Medicine* 1994;69:712.

2 Moore D, Bernard S. The impact of managed care on women's health research. *J Women Health* 1996;6:197-202.

3 Kaufman B, Rodriguez-Trias H. Participant and community issues in the recruitment and retention of women in clinical studies. In: Recruitment and Retention of Women in Clinical Studies. NIH Pub. No. 95-3756. Office of Research on Women's Health, National Institutes of Health, 1995. p. 17-19.

4 Kuller LH. Current experiences in women's health research. In: Recruitment and Retention of Women in Clinical Studies. NIH Pub. No. 95-3756. Office of Research on Women's Health, National Institutes of Health, 1995. p. 27.

5 Sagraves R, et al. Women as research subjects. American College of Clinical Pharmacy White Paper. *Pharmacotherapy* 1993;13:534-42.

6 Mastrianni A, Faden R, Federman D, eds. Women and health research: Ethical and legal issues of including women in clinical studies. Washington, D.C.: National Academy Press, 1994. p. 93.

7 Merkatz R, et al. Women in clinical trials of new drugs. *N Engl J Med* 1993 (Jul 22);329:295.

8 Henderson M, Lee MM. Investigator and institutional issues in the recruitment and retention of women in clinical studies. In: Recruitment and Retention of Women in Clinical Studies. NIH Pub. No. 95-3756. Office of Research on Women's Health, National Institutes of Health, 1995. p. 11, 14.

9 Levy G. Patient-oriented pharmaceutical research: Focus on the individual. *Pharm Res* 1995;12:943-4.

10 Rathegeber E, Vlassoff C. Gender and tropical diseases: A new approach. *Soc Sci Med* 1993;37:513-20.

RACIAL, ETHNIC, AND CULTURAL DIVERSITY

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BACKGROUND

American women come from and continue to live in diverse racial, ethnic, cultural, and socioeconomic backgrounds. A growing number belong to groups commonly referred to as minorities — black, American Indian, Alaskan Native, Asian, Pacific Islander, Hispanic. To a large extent, a woman's health status may depend on the group or subgroup to which she belongs, as is apparent in the following statistics:

- In 1993, life expectancy at birth was 79.5 years for white women and 73.7 years for black women.[1]
- In every year from 1970 to 1993, heart disease was the leading cause of death for all women living in the United States. However, between 1970 and 1980 the age-adjusted death rate for heart disease was about 50 percent higher for black women than for white women. Between 1980 and 1993, the heart disease mortality differential between white and black women widened to 67 percent, due to a more rapid decline in heart disease death rates for white women (26 percent) than for black women (18 percent).[2]
- In 1993, the age-adjusted death rate from heart disease was 24 percent lower for American Indian and Alaskan Native women and 43 percent lower for Asian and Pacific Islander women than for white women (99.3 per 100,000), and the rate was 29 percent lower for Hispanic women than for non-Hispanic white women.[2]
- In 1993, black women were 28 percent more likely than white women to die of breast cancer.[3]
- Since 1973, the age-adjusted incidence rate for ovarian cancer, the most common female reproductive malignancy after breast cancer, has been about 50 percent higher among white women than among black women.[4]
- Most of the women diagnosed with AIDS during the 12 months ending June 30, 1995, were black or Hispanic women (59 percent and 17 percent, respectively).[5]
- Between 1988 and 1991, the age-adjusted prevalence of hypertension was higher for non-Hispanic black women (31 percent) than for non-Hispanic white women (21 percent) or Mexican-American women (22 percent).[6]
- Between 1988 and 1991, being overweight was more common among women whose family incomes were below the poverty line than among those with higher incomes. Among all women 20 years of age and over, the age-adjusted prevalence of overweight was 47 percent for women below the poverty line and 32 percent for those at or above the poverty level.[7]

- In 1992-93, women were 6.6 times as likely as men to experience violent crimes by a spouse, ex-spouse, or partner. However, the rate of violent attacks by intimates among women in families with annual incomes of less than $10,000 was 19.9 per 1,000 women, compared with 4.5 per 1,000 women among those with annual incomes of $50,000 or more.[8]

- In 1993, women below the poverty line were 3.2 times as likely to be uninsured as women above the poverty line (36 percent and 11 percent, respectively).[9]

- In 1993, women who lived below the poverty line were 57 percent more likely to lack a regular source of medical care than women whose family income was at or above the poverty line (16 percent and 10 percent, age-adjusted).[10]

- For women admitted to substance abuse treatment in 1993, the type of substance abuse correlated with race and ethnicity. Alcohol, and alcohol combined with another drug, were the primary substances of abuse among non-Hispanic white women, while cocaine was the predominant substance of abuse among non-Hispanic black women, and heroin among Hispanic women.[11]

Despite these and other 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 white, middle-class, heterosexual, able-bodied women. This focus on the majority group retards the advance of biomedical information about minority groups, who make up more than 25 percent of the population in the United States (see Table 1), and who are different not only in biological factors but also in cultural and behavioral factors that are associated with health. 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 in some cases remains large.[12]

To develop the knowledge base that will yield benefits for minority women, enabling them to access the remarkable advances in medicine and health care, population diversity must be ensured in all aspects of research, including training minority researchers, awarding grants for research that includes diverse populations, designing research models to evaluate the differences among population groups, retaining study participants from diverse populations, and publishing results so that the appropriate caretakers have access to the information.

TABLE 1. Detailed Race and Hispanic Origin of U.S. Women, 1980 and 1990-1993, *Numbers in Thousands*

RACE/ORIGIN	1980	1990	1991	1992	1993
All Persons	226,546	248,710	252,177	255,078	257,783
Women					
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.

The study of the health problems in diverse subgroups could also increase the knowledge base about how to prevent and survive disease, with applications for the entire population. Research models that study the assets on resiliencies of specific groups and individuals might reveal the adaptive mechanisms that make them healthy despite adverse environments. For example, the study of heart disease among Asian-American women, who have a much lower incidence of heart disease than women from any other racial or ethnic group, might provide insight into the resiliency factors and behaviors that protect from heart disease. An examination of beneficial dietary or exercise patterns might suggest preventive strategies for all women.

NIH GUIDELINES ON INCLUSION OF WOMEN AND MINORITIES IN CLINICAL STUDIES

In the past 5 years, the National Institutes of Health (NIH) has taken several steps to increase the participation of women and minorities in clinical studies. Most notably, early in 1994, the agency published its *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research,* which require that researchers receiving NIH support include women and members of minority groups and their subpopulations, when appropriate, in biomedical and behavioral research projects involving human subjects.[13] NIH issued these guidelines in response to the NIH Revitalization Act of 1993 (P.L. 103-43), which directed that "the Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in projects of clinical research." The goal of this requirement is to increase the opportunities for obtaining critically important information with which to enhance health and treat disease among all Americans, and to detect and account for significant differences between genders or racial and ethnic groups where they exist.

> *"Each ethnic group has certain values, beliefs, symbolic meanings, and sense of spirituality that guide our family, close interpersonal relationships, choices, and decisions."*
>
> Wes Sagawa
> Hawaii—Caring for
> Women Project

The guidelines also strengthened the previous policies published in the *NIH Guide for Grants and Contracts,* 1990, which required that NIH staff and peer advisory groups "ensure that applications/proposals for extramural support for clinical research studies involving human subjects include appropriate representation of women and minorities, unless a compelling justification is made for their exclusion or inadequate representation."[14] The guidelines required NIH to take three additional actions: (1) to ensure that women and minorities and their subpopulations are included in phase III clinical trials in a way that differences in intervention effect can be analyzed, (2) to reject cost as an acceptable reason for excluding these groups, and (3) to initiate programs and support for outreach efforts to recruit these groups into clinical studies.

ETHICAL ISSUES FOR INSTITUTIONS AND IRBS TO CONSIDER

The importance of including women and minority groups in health research must be balanced against the right of individuals to refuse to participate in research. To facilitate that process in 1994, NIH's Office of Protection from Research Risks issued a report outlining the responsibilities of institutions and institutional review boards (IRBs) that are responsible for protecting the rights of study participants in their consideration of ethical issues surrounding the inclusion of women and minorities in research.[15] The report lists seven key responsibilities:

1. To provide investigators with written guidance clearly delineating expectations for inclusion of both genders and minorities in the design and conduct of research.
2. To specify that, when scientifically appropriate, investigators show how the research will address any difference in the way a health situation or intervention in the proposed research may affect one gender or minority group. Investigators should be prepared to describe the extent to which both genders and minority groups have been involved in similar research.
3. To review the extent to which investigators are collaborating with researchers at other institutions to ensure representation and sufficient involvement of participants of both genders from minority groups. The review of such information is particularly important in phase III clinical trials.
4. To consider whether cash or material reimbursements are appropriate to the educational level and socioeconomic status of the study participants and to ensure that these reimbursements do not promote coercion or undue influence to participate or remain in the study.
5. To ensure that consent documents have been translated appropriately or that translators are available when the study participants include speakers of foreign languages or those who are illiterate.
6. To include women and members of minority groups on the IRB, especially if the nature and volume of the research to be conducted at the institution routinely includes these populations. IRBs should also consider consulting ad hoc advisors who could help with understanding the perspectives of various groups. Also, institutions and IRBs can encourage investigators to seek out such perspectives during the planning of research protocols.
7. To require that NIH-supported investigators specify the gender and racial or ethnic composition of the subject population, as well as their criteria for including or excluding any subpopulation, or to provide a clear rationale for excluding such information from the background data for the protocol.

TRAINING OF MINORITY RESEARCHERS

The diverse views that women and minorities could bring to bear on the research agenda have been significantly absent. Diverse populations pose diverse and challenging issues that can be better researched and understood only by a creative variety of research approaches. Researchers who are homogenous in culture and experience are less likely to generate rich and varied research concepts than researchers who are diverse. Many people believe that clinical research to date has focused on the health status of white men because most investigators are themselves white men. One of the best ways to improve the quality and quantity of research and alter its focus is to increase the number of women and minority investigators. An additional advantage to cultural diversity among researchers is the enhanced effectiveness of recruiting the participation of women from minority communities.

Since 1989, NIH has encouraged the training of minority researchers through such programs as its Minority Research Supplement Program, which provides supplements to minority high school and college students, graduate research assistants, individuals in postdoctoral training, and investigators. In fiscal year 1990, NIH provided minority supplements to 376 members of ethnic groups: black (226), Hispanic (114), American Indian (20), Pacific Islander (10), and unknown (6).[16]

Collaborative programs between majority and minority institutions can provide important training opportunities for the students at both institutions. A program established between Tulane University and Xavier University, a black university in New Orleans, provides a model for other institutions who want to increase the number of minority investigators. The two universities have established the Center for Bioenvironmental Research (CBR), which investigates the causes and effects of environmental problems and devises practical solutions for them.[17] One way in which the CBR fosters training for minority researchers is by offering fellowships to minority students of outstanding academic achievement and scholarly promise who have been formally admitted to a doctoral program and whose research topic is environmentally related. For the academic year 1996-1997, two minority women were among the six recipients of fellowships. Both women are graduate students in the molecular and cellular biology program. One will study the identification of phytosterols that have anti-estrogenic activity in breast and endometrial cancers. The second will investigate mechanisms of lung injury induced by environmental agents such as air pollutants and allergens.[18] The CBR also provides opportunities for investigators to work with minority communities. For example, CBR members provide an ongoing occupational health research and advisory function for the Southern Louisiana Industry Council, placing special emphasis on minority health. CBR's Coping with Community Stressors Program examines minority community responses to environmental risks, and the Environmental Justice Partnership Project addresses the environmental research, education, and outreach needs of community groups along the Mississippi River chemical corridor. Also, in cooperation with the U.S. Department of Housing and Urban Development, CBR members are working with residents of a public housing community in New Orleans to identify and act on environmental health issues.

DESIGNING STUDIES TO INCLUDE MINORITY WOMEN

In planning clinical research, the NIH guidelines encourage investigators to first consider whether their scientific questions or hypotheses make the inclusion of minority women in the study appropriate. Investigators may limit the population to women from a single minority group if their scientific questions or hypotheses apply to majority women as well, and if the condition to be studied is more severe or prevalent among a particular group of minority women than among majority women, or if less is known about the disease or treatment in minority women than in majority women.

For an NIH-defined phase III clinical trial, the investigator should determine whether important minority differences are to be expected in the intervention effect. (NIH defines a phase III clinical trial as a broad-based clinical investigation to evaluate an experimental intervention in comparison with a standard or control intervention or to compare two or more existing treatments.) If so, the investigator should design the trial so that the intervention effect can be tested for minorities or their subpopulations.

UNDERSTANDING THE STUDY POPULATION

To obtain valid data, researchers must clearly define the populations they are studying. Countries of origin, immigration status, level of acculturation, socioeconomic status, and cultural and linguistic characteristics vary widely. A cultural or racial label for a minority group may fail to reflect the heterogeneity of individuals or groups to which the label is applied. For example, the label “Southeast Asian” refers to Philippine, Hmong, Laotian, Vietnamese, and Cambodian peoples, and the term “American Indians” is used to describe more than 500 federally recognized tribes. Similarly, “Hispanic/Latino” populations include Mexicans, Puerto Ricans, Cubans, and other Central and South Americans, whose ethnic origins and racial characteristics are varied. Yet, health studies on “Hispanics” commonly include a larger number of Mexican Americans (who constitute almost 65 percent of the Hispanic population in the United States) than members of any other Hispanic subpopulation. Generalizations based on data from these participants may be valid for Mexican Americans, but invalid for Hispanics of other origins.

An understanding of cultural and linguistic differences is essential to ensuring that methods used in screening and interviewing are culturally sensitive. For example, the Hmong have views regarding blood that prohibit its sampling. Some groups take offense at questions about sexual issues. One recent recruitment effort among black women students at Howard University failed because the women thought that the questions about sexual behavior were inappropriate, and they simply refused to answer them. In addition, important linguistic differences often exist among speakers of the same language who come from different countries; an inoffensive word for a Puerto Rican, for example, may be an obscenity for a Mexican.

COLLABORATION WITH THE COMMUNITY

Successful research efforts in minority communities depend on collaboration with members of the community at every phase of the research. Community leaders and other residents, as well as the study participants themselves, should be involved in setting research goals, designing appropriate methods for informing the target population about the planned research, determining appropriate instruments for collecting data, and evaluating outcomes.

A major barrier to recruitment in many minority communities might be distrust of scientific researchers because of historical incidents of abuses of research by outside organizations and researchers, or because they may feel that the researchers have been insensitive to the health concerns of their community. Therefore, enlisting the support of community leaders may be essential to gaining access to a community. Researchers who meet with community leaders to define the health or disease problems they want to study and to explain the benefits and risks of the research are likely to find that the leaders are eager to provide a perspective on the cultural, behavioral, social, and economic factors that may contribute to or interfere with the research protocol. The community leaders can also help researchers form networks with other community organizations that will facilitate development and acceptance of the planned research.

Collaboration with religious leaders has been found to be especially useful for several reasons. First, churches are usually interested in participating in primary prevention efforts, operating health care and wellness programs of their own. Also, since churches serve as natural community centers, establishing the church as the place of contact between researchers and participants partially eliminates the transportation problems that constitute a barrier to participation in studies. Furthermore, churches tend to involve entire families. The importance of the family among many minority groups makes the inclusion of the individual’s family desirable in dealing with the individual’s health problems. For example, smoking cessation research shows that Latino men are more likely to stop smoking if they are encouraged to do so to benefit their wives and children. In the black community, too, a health care project is always a family project.

Ministers and other community leaders may also be able to help researchers gain access to those populations who can most benefit from the research effort, such as those minority women who never use the health care system or who use it only at times of crisis. Too often, researchers in minority communities have had to select their samples from the people who have access to health care, simply because they had no access to those who most needed health care.

Community leaders and other members can also help define the problem to be studied, ensuring that the priorities of the researchers pose no conflict with those of the participants. For example, a community concerned with alcoholism, drug abuse, and AIDS may have little interest in participating in a study on dietary cholesterol.

Recruitment and retention efforts are much more likely to be successful if the recruiters are local residents of the same race and ethnicity as the defined study population. At one West Philadelphia clinic, for example, nurse practitioners are collaborating with the principal investigators from the university in a highly successful weight loss program for black women. Also, a study on how to reduce prenatal transmission of AIDS in southeastern Pennsylvania is using HIV-positive women as part of the investigative team. The researchers trained the women how to gather data through personal interviews and telephone conversations. As a result, the women have a sense of accomplishment, and the project has reported a tenfold improvement in access to information.

Local residents may also have better insight into the problems that are causing participants to drop out of a study. For example, researchers assume that low retention is the result of child care and transportation problems, only to find out that the real reasons are quite different. Community residents may be able to suggest ways to retain participants in the study, such as by setting up a network relationship among the participants so that they will remind each other to visit the clinic at the appointed time.

GIVING BACK TO THE COMMUNITY

Researchers in minority communities have a moral obligation to give something back — whether that return be health care, education and training, or even employment. Several institutions have established programs that can serve as models for a reciprocal relationship between researchers and the communities in which they work:

- The Emory School of Nursing has opened clinics in so-called “undeveloped” poor neighborhoods.
- At the University of Wisconsin, professors from the School of Nursing and health professionals donate their time on evenings and weekends to a community center. They also do intensive community education. In return, they ask the community to participate in their research projects.
- In setting up the Navajo Research Program in early 1996, an institutional review board was first established to ensure that researchers would benefit the health of the Navajo people. The board asks researchers (1) to provide educational materials to help the people or the Navajo service providers, (2) to train the Navajo staff in existing health care facilities and programs, and (3) to return to the reservation when the research is completed to explain the results of their studies in layman’s terms and to explain the significance of those studies for the Navajo people.

PUBLICATION OF RESEARCH RESULTS AND EXPERIENCES

Published research data should show results by gender and minority group status. In spite of the general recognition of the importance of including minority women as study participants, journals still frequently publish studies that give no information on the race or ethnicity of the populations studied. For example, a recent survey of all the articles published in the *New England Journal of Medicine* in 1995 revealed that 80 percent of the articles gave no information on the race or ethnicity of the populations studied.

Biomedical science would also benefit from increased reporting of research outcomes, successful and unsuccessful, involving minority groups. Although many research institutions have developed excellent relationships with minority communities, they have not published these experiences, which would be useful to other investigators.

SOCIAL, CULTURAL, AND PSYCHOLOGICAL ISSUES

Clinical research is needed that takes into account the social, cultural, and psychological issues relevant to health, especially in the study of health problems of minority women. More studies are needed on the ways that the cultural and social environments of minority women, and their perceptions of these environments, influence their health and quality of life. Working group members felt that progress in minority health research depends on developing and applying research models that integrate quantitative and qualitative methods to study the social, economic, and biomedical determinants of health. A holistic approach that overcomes the false dichotomy between body and mind is needed. In that vein, a study of black working class women and black professional men conducted by epidemiologists at the Harvard School of Public Health and the Kaiser Foundation Research Institute found a link between hypertension and race, gender, and socioeconomic class, and between hypertension and the way in which an individual reacts to the perceived discrimination.[19] More research of this type is needed to understand how the variables of race, class, and gender affect health.

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 their 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: handicapped women 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 church groups in planning, conducting, and evaluating research.
- Collaborate with churches on research in minority communities where appropriate.
- Include the participants' families when the participants belong to minority groups where family is of great importance.
- 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 as to what the barriers are.
- 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 in some situations 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.

REFERENCES

1 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 17.

2 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 21.

3 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 22.

4 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 25.

5 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 26.

6 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 34.

7 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 39.

8 Bachman R, Saltzman LE. Violence against women: Estimates from the redesigned survey. U.S. Department of Justice, Office of Justice Programs, Bureau of Justice Statistics, 1995.

9 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 45.

10 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 46.

11 National Center for Health Statistics. Health, United States, 1995. Hyattsville, MD: Public Health Service. 1996. p. 55.

12 Council of Economic Advisers for the President's Initiative on Race. Changing America: Indicators of Social and Economic Well-being by Race and Hispanic Origin. September 1998. pp. 4, 40.

13 NIH guidelines on the inclusion of women and minorities as subjects in clinical research. *Federal Register*, March 1994.

14 *NIH Guide for Grants and Contracts*, 1990.

15 Office of Protection from Research Risks (OPRR). Inclusion of women and minorities in research. OPRR Reports 94-01, Bethesda, MD: OPRR.

16 Rene A, Fakunding J. Support of minority training and career development in the biomedical and biobehavioral sciences by the National Institutes of Health. In: Health behavior research in minority populations: Access, design, and implementation. Washington, D.C.: National Institutes of Health. NIH pub. no. 92-2965. 1992.

17 Allen A. The synergy of Tulane and Xavier Universities. *Environmental Forum* 1996;l,5; no 1.

18 Gresh C. CBR Scholars program. *Environmental Forum* 1996;l,5; no 1.

19 *American Journal of Public Health*. October 1996.

MULTIDISCIPLINARY PERSPECTIVES

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Research aimed ultimately at improving the health of women and subpopulations of women across the life span focuses on a broad spectrum of factors. Investigations may examine basic, molecular, genetic, immunologic, and other mechanisms in the etiology and pathogenesis of disease, thus contributing to the biomedical knowledge base or to the development of innovative therapies. At the same time, psychosocial research seeks to improve understanding of the cultural, lifestyle, personality, cognitive, affective, motivational, social support, and other factors associated with women's decisions to adopt or maintain healthy behaviors, or seek health care services. In addition, socioeconomic research seeks to better understand the effects of such variables as employment status and income on women's health.

Much of the research on women's health conducted in the past, and even today, addresses questions from a specific, singular perspective rather than from a range of biomedical, psychosocial, and socioeconomic points of view. Research projects involving investigators from multiple disciplines are not usually the norm. However, as available research dollars shrink, innovative integration of expertise from various disciplines may become an increasingly important strategy for maximizing funding potential. During the past several years, a growing number of funding opportunities made available through NIH have specifically encouraged or called for multidisciplinary research teams.

Research on women's health, because of the encompassing nature of this area, 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. It must be noted that multidisciplinary research should not replace single-discipline research but should supplement it, thereby enriching understanding and permitting the development of broad-based knowledge.

Barriers to conducting multidisciplinary research on women's health issues prevail. For example, academic systems typically have fewer means of rewarding or recognizing multidisciplinary efforts. Furthermore, there are still few funding mechanisms that focus on multidisciplinary research. In addition, researchers have limited firsthand experience or training in building and working as part of multidisciplinary teams. This inexperience is also sometimes reflected in the evaluation of study sections. Clearly, some changes within NIH and academic institutions are required if synergy between disciplines is to be achieved. Overarching issues and specific recommendations that would encourage multidisciplinary research on women's health are discussed below.

STRUCTURE OF NIH FUNDING SHOULD ENCOURAGE MULTIDISCIPLINARY RESEARCH

Women's health provides a unique, cross-cutting research realm in that it is multidisciplinary by definition, offering important opportunities for simultaneous study of biomedical, psychosocial, and socioeconomic variables. While opportunities for multidisciplinary research with NIH funding do exist and are expanding, further progress in this area should be encouraged. In addition, coordination among the NIH institutes, centers, and divisions (ICDs) should be heightened in support of multidisciplinary research activities, and NIH communication about these opportunities should be enhanced. The following recommendations are proposed in support of these goals.

Identify Multi-institute Issues

Issues that cut across research disciplines and across the missions of the NIH ICDs should be identified, and funding for multidisciplinary research should be made more readily available.

Multidisciplinary research has been developed for chronic fatigue syndrome with studies on searches for a wide range of infectious agents, on different aspects of the immune system and neuroendocrine function and use of antidepressants to relieve symptoms of fatigue, sleep disturbance, and chronic aches and pains.

Encourage Inter- and Intra-institute Multidisciplinary Research

The NIH should encourage the promotion and development of multidisciplinary research, both within individual ICDs and across ICDs. Program offices within the Office of the NIH Director and directors of individual ICDs can play a vital role in stimulating cross-cutting research by promoting research policies and funding in support of mechanisms for multidisciplinary research. The Office of Research on Women's Health (ORWH), the Office of Research on Minority Health, and the Office of Behavioral and Social Sciences Research are already engaged in working closely with all of the NIH ICDs to enhance their respective portfolios in behavioral and social sciences research and to identify research opportunities that foster trans-NIH collaborations.

Use RFA and RFP Mechanisms To Support Multidisciplinary Research

Despite philosophical support, NIH-funded multidisciplinary research will not be enhanced unless funding mechanisms are made available for such research. Requests for application (RFA) and requests for proposals (RFP) should be developed that specifically seek multidisciplinary women's health-related investigations. Furthermore, the timelines for application submissions must account for the complexities of developing collaborations among researchers from different backgrounds and perspectives.

Establish ORWH as a Broker

ORWH is in a unique position to function as a "broker" and advocate for funding multidisciplinary women's health research across the NIH ICDs. This broker/advocate role would be in keeping with the ORWH mandate "to strengthen and enhance research related to diseases, disorders, and conditions that affect women and to ensure that research conducted and supported by NIH adequately addresses issues regarding women's health." In a leadership role, ORWH could provide a pivotal point for communication among the ICDs regarding multidisciplinary research on women's health and could proactively develop multidisciplinary research opportunities. In addition, ORWH could serve as a resource for investigators wishing to explore or develop linkages with other investigators and research programs concerned with similar research topics.

ORWH Funding Priorities Should Explicitly Encourage Multidisciplinary Research

Today, ORWH vigorously implements its mandate to strengthen and enhance research on women's health, in part by providing cofunding to ongoing NIH grants and special initiatives that have gender-specific research objectives. In planning for the 21st century, ORWH should identify as a priority research that cuts across disciplines, and then should emphasize cofunding of investigations that cut across biomedical, psychosocial, and sociocultural perspectives.

Establish Multidisciplinary Coordinating Groups

Communication across the NIH ICDs and within the extramural research community is vital to increasing opportunities for multidisciplinary research and to building multidisciplinary teams of investigators. Coordinating groups, committees, and task forces comprising program-level IC staff with common interests should be established to identify shared goals and act upon priority women's health research areas. For example, the Coordinating Committee on Research on Women's Health, coordinated by ORWH, brings together representatives of the NIH ICs to discuss directions for research on women's health and to provide direction to the ORWH director. Similar groups could be established to discuss multidisciplinary research addressing specific disease topics that affect women, such as HIV/AIDS, autoimmune diseases, or heart disease.

Other examples of multidisciplinary groups are both a PHS and an NIH coordinating committee for chronic fatigue syndrome (CFS). Currently CFS has no definition that can be measured by objective criteria. Epidemiological research can help guide hypothesis generation and testing. Research needs to examine prospectively the long-term prognosis of CFS, the patterns of disease, its prognosis in adolescents and children as well as in adults, and the cause — all of which will help lead to better methods of diagnosis, treatment, and prevention. Careful blinded therapeutic trials are also needed.

Convene Multidisciplinary Conferences

Conferences, workshops, and symposia should be convened to discuss research topics on women's health from multidisciplinary perspectives. Such meetings are important in examining current knowledge, as well as theoretical and methodological issues. The Women's Health Seminar Series, sponsored annually by ORWH, serves as a model for such conferences, with topics addressing such issues as genetic testing, hormone replacement therapy, breast cancer, and domestic violence. The series is planned and implemented in conjunction with the NIH Coordinating Committee on Research on Women's Health, ensuring that numerous perspectives are addressed.

Create Core Centers

The funding of "core centers" for research on women's health could be a method to encourage close cooperation, communication, and collaboration among investigators with similar interests who are conducting individual research projects. The core center serves as an identifiable organizational focal point within a single university medical center or among a consortium of cooperating institutions. This concept fosters interdisciplinary cooperation and the sharing of resources, such as instrumentation or assays, thus enabling more efficient and productive work. Core centers for research on women's health would not supplant investigator capabilities but would enhance investigators' opportunities to learn and advance. Core centers may also provide funding for seminars, visiting scientists, or other program-enrichment activities.

MULTIDISCIPLINARY RESEARCH SHOULD BE REWARDED WITHIN ACADEMIC INSTITUTIONS

NIH and academic institutions should collaborate to increase the amount of multidisciplinary research conducted on women's health issues. Institutions should provide both philosophical support and advancement opportunities for those who build bridges across biomedical, psychosocial, and socioeconomic research domains. In addition, academic structure should follow, not dictate, research needs. Matrices that match the multidisciplinary interests and expertise of individual faculty members provide one model for encouraging cross-cutting research within academic institutions. The following recommendations may assist institutions and faculty members in shifting toward a new way of thinking.

Encourage Promotion Criteria that Stimulate Multidisciplinary Research

Professional advancement in academic settings today generally hinges on success in one's discipline. However, especially as federal research resources constrict, the academic environment should not discourage but should reward faculty investigators who seek out and develop multidisciplinary research programs. Promotion criteria should incorporate faculty members' initiative and success in this regard.

Encourage Scientists To Learn How To "Package" Multidisciplinary Careers

If efforts related to research on women's health are to be successful, investigators need to increase their willingness to cross academic and disciplinary boundaries. Individual investigators need to learn to channel their research to fit current models and should draw on their multidisciplinary research abilities in developing their careers.

Encourage NIH-funding Mechanisms that Support Multidisciplinary Research and Training at Academic Institutions

Academic institutions are more likely to encourage multidisciplinary research on women's health if NIH supports such research. Therefore, NIH-funding mechanisms should encourage multidisciplinary research and investigator training. Furthermore, NIH training and career development grants should also emphasize the importance of applications proposing multidisciplinary work.

TRAINING SHOULD BE MULTIDISCIPLINARY, AND RESEARCHERS NEED TRAINING IN MULTIDISCIPLINARY RESEARCH

The environment in which researchers are trained is a critical influence and often determines professional directions and interests. In the past, students of medicine, nursing, and other professional disciplines participated in core courses together, providing opportunities to share ideas and develop an awareness of varied perspectives. Today, the academic environment may often segregate the disciplines, thereby creating barriers to the cross-pollination of ideas. In addition, NIH research training and career development programs tend to be discipline-specific and organ-specific. Training mechanisms, some believe, are equal to or more important than funding mechanisms in determining the amount of multidisciplinary research conducted. The following steps are recommended to enhance integration of disciplines during crucial training years, as well as during the course of the research career.

Establish Multidisciplinary Training Programs

First, professional training programs that require or encourage cross-disciplinary study should be established or reestablished. Such programs would shift the learning process away from professional separatism and toward broad-based learning. Cross-disciplinary study would encourage students to consider the spectrum of biomedical, psychosocial, and socioeconomic concerns that may interact to affect women's health.

Publicize Effective Individual and Institutional Role Models

Individuals and academic institutions that serve as exceptionally effective models for multidisciplinary training in the field of research on women's health should be recognized and publicized. Information about model training initiatives that cross disciplinary and departmental boundaries within medicine and other disciplines should be disseminated widely through professional meetings, journals, professional organization publications, the Internet, and other print and electronic media.

Publish and Publicize the Process of Putting Together Multidisciplinary Teams

The process of building successful multidisciplinary teams for research on women's health should be documented and disseminated to encourage and teach others to follow suit. Only through the sharing of ideas about the team development process will these programs effectively serve as models. Information should be disseminated widely at professional meetings, in journals and the publications of professional organizations, on the Internet, and in other print and electronic media.

Recognize Mentors

Mentors play a vital role in the career development of professionals in any field. This role is even more crucial in the relatively new field of women's health. Mentors who successfully build collaborative teams and are involved in multidisciplinary training and research efforts should be recognized and rewarded.

Encourage and Provide Funding Mechanisms for Continuing Education in Fields Other Than One's Area of Primary Expertise

Scientists wishing to pursue research careers in women's health that traverse scientific and disciplinary boundaries must possess a practical understanding of the concerns, science, and methodologies of fields other than their own. Continuing education provides a formal means of developing this understanding, although funding mechanisms are needed to encourage and support researchers who wish to maximize their capabilities in conducting multidisciplinary research. NIH training and career development grants specifically designed for researchers wishing to study outside of their traditional disciplinary realms may be one mechanism to provide such support.

Encourage NIH Institutes To Fund Multidisciplinary Training

To maintain a cadre of well-trained investigators in research on women's health, the NIH ICs should be encouraged to fund research training and career development efforts that go beyond specific disciplines. Investigators-in-training with interests in cross-cutting research should be considered for support through National Research Service Awards, whether individual or institutional, career development awards, and fellowships.

Develop Inter-institute Review Processes and Funding for Training Awards

The process of reviewing and funding applications for research training and career development often fosters single-discipline and single-organ system approaches. If investigators-in-training in the field of women's health are to develop interests in multidisciplinary work, then application review policies and procedures should ensure review by appropriate multidisciplinary review groups that are also representative of multiple NIH ICs.

MULTIDISCIPLINARY RESEARCH PROPOSALS ARE OFTEN REVIEWED BY SINGLE-DISCIPLINE INDIVIDUALS

The number of NIH-funding opportunities that invite or require multidisciplinary research has increased noticeably. However, there is also a belief within the research community that application review committees evaluate applications for multidisciplinary projects from single-discipline perspectives and represent the review committee's purview. Anecdotal accounts indicate, in some instances, a lack of understanding on the part of reviewers that multidisciplinary projects can truly represent high-quality science, especially if the projects are innovative and methodologically sound. Therefore, the NIH review committee structure should be examined for its ability to ensure that multidisciplinary research applications are evaluated by individuals who possess a clear understanding of the disciplines and concerns involved in multidisciplinary research projects. This issue may be addressed through the following recommendations.

Expand Use of Ad Hoc Reviewers on Standing Committees

For most applications, the initial or first level of review involves panels of experts established according to scientific disciplines or medical specialty areas. The function of these scientific peer review groups is to evaluate the scientific merit of grant applications. Expanding the use of ad hoc reviewers who represent the behavioral and social disciplines on these standing research review committees would help to ensure that high-quality, multidisciplinary research projects on women's health are evaluated appropriately.

Use Ad Hoc Review Committees

Ad hoc review committees should also be considered for the review of multidisciplinary grant applications. Such committees would comprise representatives of multiple disciplines that cut across the biomedical, behavioral, and social sciences, depending on the application topic.

Solicit Reviewers with Appropriate Multidisciplinary Expertise

Selection of reviewers sitting on scientific peer review groups is based in part on their expertise, experience, and knowledge of specific disciplines. Individuals with multidisciplinary expertise should be identified and made known to those scientific review administrators who determine the composition of review committees.

Inform Applicants How To Use Existing Review Structures

NIH grant applicants must learn as much about the grant application and review process as possible. Increased communication with applicants regarding the existing review structures could be accomplished through the NIH Division of Research Grants home page or by other means.

Identify and Publicize Successful Models

Research review committee structures that serve as successful models for the review of multidisciplinary grant applications should be identified and their successes publicized so that they might be emulated within the NIH review structure.

SELECTED TOPICS IN HEALTH IMPACT AND HEALTH OUTCOMES

SELECTED TOPICS IN HEALTH IMPACT AND HEALTH OUTCOMES

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The sections in this chapter represent selected topics in health impact and health outcomes that 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. The topics addressed are: Gender Considerations in Therapeutic Advances, Clinical Trials and the FDA Approval Process, Communications and Outreach, and Patient Care.

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: these 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.

Therapeutic products are the result of a lengthy process that most often begins as a new idea is conceived, is developed in the laboratory, continues through various clinical research stages, receives approval for clinical care applications, and ultimately reaches the marketplace and the consumer. The extent to which this process is powered to detect gender-specific efficacy endpoints and safety signals before approval and is sensitive for monitoring gender-specific safety signals after approval, has important ramifications for women's health. To keep consumers safe, it is important to have in place sensitive data collection and analysis methods that enable the efficient detection of gender-specific signals not only of new but also of old products currently in the marketplace. Technologies that are gender neutral may not look as advantageous to women once the data is accessed and analyzed by gender. The recommendations presented in this chapter are intended to integrate and focus attention on women's health, but all segments of the population can benefit from these proposals.

Concept to Marketplace

Technology transfer has been defined by NIH as "the process by which the fundamental discoveries of laboratories are brought forth into practical knowledge and useful products for the benefit of humanity." The Federal Government, particularly the Public Health Service, including CDC, FDA, and NIH and its grantee institutions, plays a major role in biotechnology transfer. The Bayh-Dole Act of 1982 and the Federal Technology Transfer Act of 1986 encourage greater interactions between the Federal Government and universities, foundations, and industry through cooperative research and development agreements and through the licensing of patented inventions developed by public health agencies or by researchers at universities and not-for-profit institutions funded by NIH.

Mechanisms for determining the safety and effectiveness of new and old therapeutic products are evolving. Traditional methods based on peer review are being transformed by advances in information technology and data manipulation, which simplify the collection, access, exploration, evaluation, and understanding of the safety and efficacy data generated on therapeutic products. The criteria for such assessments are being debated. Although "safety and effectiveness" and "risk/benefit" are important, these concepts mean different things to different people — clinicians, manufacturers, staff of health care institutions, and consumers. Disagreements persist about what level of risk to the individual is acceptable. How are benefits of the individual weighed against benefits to society? Advances in information technology and data manipulation can provide objective measurements for determining safety, efficacy, and risk/benefit, including these determinations for subpopulations at a high risk. Information technology can also provide substantial evidence of the public health benefits and risks of therapeutic products to society as a whole.

The practical business and economic implications of new product development must be recognized as well. Companies traditionally have looked at new technologies and asked how they could make a profit. Some companies are now looking at unmet needs and at populations with large market shares and considering how to respond in a profitable way.

The commercial introduction of a new product or procedure, however, is not the end of the process. After a technology has been introduced to the marketplace, continual assessment is needed to ensure that the product remains safe and efficacious and does not become obsolete. Prenatal ultrasound testing is one example of the need for such assessment. The National Institute of Child Health and Human Development, along with the NIH Office of Medical Applications of Research, sponsored a workshop titled Ultrasound Screening: Implications of RADIUS (Routine Antenatal Diagnostic Imaging Ultrasound Study). RADIUS, a large, randomized clinical trial, assessed the effectiveness of routine ultrasound screening for pregnant women at low risk for poor pregnancy outcomes. Although the study results indicated no real medical value of ultrasound for this population, practitioners have continued to use the technology. This is an example of an adaptation of a technology from an original application in high-risk situations to an entirely different situation, the efficacy and cost effectiveness of which may be questionable. Another example of a reassessment that brought about significant change was reducing the dosages of oral contraceptives because of safety considerations.

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 AND FDA APPROVAL PROCESS

Clinical trials are usually undertaken as a three-phase activity. Clinical research may be sponsored and funded by the Federal Government and by private industry. Participation in clinical trials is voluntary and offers individuals who meet the specific medical criteria access to promising drugs, devices, and treatments long before they are approved for general use. Institutional Review Boards seek to protect participants' rights and safety by ensuring minimal risk, potential benefit, appropriate recruitment strategies and thorough informed consent procedures. Participants should also be provided medical care throughout the investigation.

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?

> *"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

Ensuring diversity and pluralism is part of the challenge. The involvement of communities in research design, implementation, and recruitment must be encouraged. For example, the HIV/AIDS and breast cancer activist communities have been heavily involved in the clinical trials process.

In addition to research design and implementation, questions arise about what constitutes "safe and efficacious" drugs, biologics and devices, and about the necessary level of regulation. The FDA regulates medical devices based on their degree of risk to the public. Devices that are life-supporting, life-sustaining, or implanted must receive the agency's most stringent approval before they can be marketed. But what level of certainty should be required? What are appropriate endpoints? Should there be standards for performance?

Research on technology applications in the area of prevention also deserves greater attention. Traditionally, prevention has been underfunded relative to other categories of research. Two such areas that have and will continue to have a major impact on women's health are contraception and prevention of sexually transmitted diseases. However, other areas of prevention need our attention as well. The analyses of clinical trial and postmarketing data present opportunities and challenges for identifying adverse events and deaths that are potentially avoidable and for discovering new toxicities that have not been described. Many products are still in the marketplace that cause side effects that are not properly appreciated. Once the source of these problems is identified, the toxicities might be prevented. One example is drug-related torsades de pointes. This serious cardiac adverse event occurs mostly in women, and can be caused by overdosage with terfenadine or astemizole or with recommended doses of these and concomitant administration of other drugs that inhibit P-450 metabolism.

Recommendations to improve the process include the following:

- Reassess 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 reanalysis 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

Identification and quantification of risks associated with use of therapeutic agents is among the most pressing problems of all research priorities, and affects the basic quality of health care for the entire population. Although the scope of the problem is extremely broad and its potential solution difficult, many fundamental steps can be taken, both short and long term, to broaden our understanding of these risks. 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, improving the consistency and interpretation of collected data, and expediting 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.

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

Limitations of Clinical Trials

Drugs, biologics, and devices that are tested for safety and efficacy in clinical trials are generally administered only to a small number of people before being released into the general population. Even large trials, however, may be too small to pick up rare side effects. A great deal can be learned about a product after it is approved and released in the marketplace. In the general population, discovery of adverse events caused by therapeutic agents is difficult unless a large number of people are affected, or if the adverse event is very unusual.[1] Discovery of adverse events may take years. Factors that increase the difficulty in recognizing adverse events include the degree to which clinicians are adequately trained or prepared to recognize signal ("red flag") cases, the extent to which clinical and pharmacologic factors responsible for adverse events are understood, the degree of knowledge of risk factors for individual susceptibility, and the presence of many confounding factors that may obscure identification of toxic drug effects,[2-4] and the quality of the processes of data collection and cleaning.

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.[5,7,8] Thus, an adverse event that shows up once per thousand persons may not appear at all in a trial of only several hundred people. Additionally, estimates of measures of central tendency are inappropriate for identifying uncommon responders. The safe use of a drug or biologic agent may be determined by multiple and complex interdependent factors. These factors include 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

The lack of uniformed standardized data structures is a critical and almost uniformly ignored problem and presents a major impediment in the ability to accurately access and interpret vital data in basic and applied clinical research. This problem, which applies to clinical data collected during clinical trials, as well as from medical claims databases, longitudinal electronic medical record databases, hospitals, and HMOs, unnecessarily complicates retrieval of information.[6-8]

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. In clinical trials, for example, data are often derived from multiple, independent research groups (e.g., groups and separate projects within a pharmaceutical company; contract research organizations; academic institutions; and government agencies, such as NIH), each of which designs studies and collects and processes information independently. The processes of these stand-alone systems are often not consistent from project to project or group to group. Thus, it is difficult, if not impossible, either to compare results or to merge data sets in order to increase statistical power. Examples of inconsistencies that hinder the data merging process include using different variable names for the same parameters, different names for the same drug, different formats for data values (even for dates), and several units of measurement for the same analytes.[6] As a result of these differences, clinical trial data require extensive "cleaning" before such data can be extracted for analysis.[11] This lack of standardization also means that the software programming generated to review one study often cannot be applied to the next study, or to the next project, and that collected data are not readily available for analysis. To date, uniform standards for collection, representation, and organization of clinical safety information have not been developed.

> *"A society of active individuals begets a healthy nation, which can recognize real savings in health care costs through the fitness of its citizens."*
>
> Mary Lloyd Ireland, J.D.
> Ruth Jackson Orthopaedic Society

Voluntary Reports of Adverse Events

Currently, FDA uses a system called the Adverse Event Reporting System (AERS), which is based on reports received from health care providers. The primary purpose of AERS is to provide signals of the existence of serious, unexpected adverse events and to aid in the further assessment of associated risk factors. The voluntary nature of such reports tends to result in under-reporting and underestimating the actual frequency of occurrence of adverse events. In one study, for example, it was demonstrated that the reported rate of an adverse event was 300 times higher when prescribers were asked if they had observed a specific adverse event.[12] Another complication factor is that serious omissions often occur in these spontaneous reports, such as missing data on gender and race, on daily dose, form and duration of the reported drug, on concomitantly used drugs (thus making it difficult to assess drug-drug interactions), and on concomitant medical conditions. As new drugs, new drug combinations, and untested dietary supplements enter clinical use there is always the possibility that new adverse effects will go unrecognized.

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.[13] 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. Their findings point to the possibility that fatal ADRs could be between the fourth and sixth leading cause of death. 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. The authors noted that, although their results "must be viewed with circumspection because of heterogeneity among studies and small biases in the samples, these data nevertheless suggest that adverse drug reactions represent an important clinical issue."

Recommendations for clinical trials follow:

- 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 record keeping 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

- It is strongly recommended that a common standardized database structure for clinical trial data from research to clinical practice be developed and implemented throughout the health care system to improve the quality of data and to simplify timely data retrieval and signal generation analysis. This could also extend the capability of searching across studies and across drugs for information required to understand drug safety issues in women. For example, such a common structure would allow rapid access to safety information related to concomitant use of hormonal replacement therapy with other medications and be used for efficient identification of previously undetected safety signals and for identification of dose reduction needs.

A potential starting point might be standardization of nomenclature of diagnostic entities. Starting with one discipline, such as obstetrics, and a small number of clinical entities, such as hypertensive disorders and labor abnormalities, a consensus process could be developed. This process could be based on existing consensus groundwork created under the International Conference for Harmonization of Drug Development (ICH). Because listing all terms will be difficult, techniques/systems capable of text searching need to be developed.

- Develop strategies to improve the quality of reporting adverse events. Determine the best way(s) to improve the acquisition of adverse events reports after use of pharmacologic and biologic agents and devices in the general population. Determine how the reporting of serious adverse events can be increased on the part of individuals from the pharmaceutical industry, HMOs, pharmacies, and physician practices. Most important, develop effective implementation strategies to achieve these objectives.
- 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 functioning either independently or within managed care organizations.
- Develop systems for analyzing large amounts of data in order to detect differences by gender, age, and race in rates of serious adverse events caused by therapeutic agents used either alone or in combination. This includes identifying (a) subpopulations of women who may be at a higher risk of developing serious adverse events and (b) the complex web of drug interactions that may lead to serious adverse events in women, including the influence of exogenous sex hormones. It may be helpful to consult with other agencies that process massive amounts of data, such as those involved with the space programs (e.g., NASA, NSF) to determine if their data collection and processing technologies can be transferred and adapted to this part of the health care sector.
- 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/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.

> *"Perhaps if we changed our conceptual framework to one of "caring" rather than one of "curing" we could all expect a better death."*
>
> Janet Heald Forlini, J.D.
> The Center to Improve Care of the Dying, and
> Institute of Medicine

- Implement prospective methods for collecting data on drug use in pregnancy. Measure outcomes such as spontaneous abortion and followup of live births at different time points. This could be done through establishment of a prospective birth registry at academic centers or through funding of other organizations interested in developmental toxicology, such as the Organization of Teratology Information Services. To successfully accomplish this, it is very important to develop a method for linking mothers and their infants' data records.
- Conduct research to assess potential adverse effects on mother and fetus of dietary supplements taken most frequently by pregnant women.

COMMUNICATION AND OUTREACH

On matters pertaining to therapeutic and diagnostic advances, communication and outreach to health care providers, health professionals, and the public remains an enormous challenge. What are the best ways to disseminate objective information on therapeutic advances after they reach the marketplace? How can practitioners 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. The role of the media in this process is also a factor. How do you create responsible media?

Identifying mechanisms by which new therapeutic advances may be integrated into the education process for practitioners is critical. For example, how can state-of-the-science information on such complex and dynamic topics as genetics be incorporated into medical school instruction? Epidemiologic and biostatistical training and education also are lacking despite the fact that these skills are fundamental to medical, nursing, and other disciplines.

Seeking input from the populations affected by a disease on their most pressing needs should be an ongoing process. How can we ensure that the interests of those outside the scientific and business worlds are taken into consideration and served? For example, the HIV/AIDS and breast cancer advocates represent a new level of involvement by nonscientific communities. How can meaningful forums be developed for the exchange of information between and among scientists, practitioners, and consumers?

On a related topic, an important part of communication is listening. Every clinician knows the value of listening to patients to obtain useful histories. It is equally compelling for clinicians to hear their patients' reports of problems with drugs. Women trying to report side effects are frequently dismissed. It is important for clinicians to listen to reports of adverse events from both men and women and to respond appropriately to these signals.

Recommendations to improve these channels of communication are as follows:

- 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 the safety profile of the drug.
- Determine the best way to inform both health care providers and consumers about risks and side effects.

Education of Health Care Providers about Pharmacologic Agents

Scientific advances have enhanced our ability to understand how gender-specific factors influence the action of drugs and modulate their effective use as pharmacologic agents. However, 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.

It is important to emphasize that more coursework in pharmacology is not needed, but rather an integration of clinical experience for dentistry, medical, nursing, and pharmacy students. Many health science centers have clinical rotations that combine some or all of these students. These rotations optimize the knowledge from each discipline and teach the students a team approach to health care that they take with them into their practices or research.

Optimal drug therapy; counseling patients; monitoring response to therapy; anticipating and reporting adverse drug reactions; and understanding individual variations due to race, age, gender, drug-drug interactions, potential drug-food interactions, and drug-dietary supplement interactions are components of education important to all health care professional students, including dentists, physicians, pharmacists, physician assistants, and nutritionists. Ideally, education will include interdisciplinary components that foster cooperation among the health care disciplines and further promote the best interests of patients.

> *". . . based on current research, it appears that relative to men, smoking behavior of women is reinforced less by nicotine intake and more by other, non-nicotine factors. If confirmed, these sex differences would have important clinical implications; nicotine replacement may warrant a less important role in smoking cessation while interventions to counter non-nicotine aspects of smoking may need to be emphasized."*
>
> Kenneth A. Perkins, Ph.D.
> University of Pittsburgh
> School of Medicine

Additional education regarding the proper prescribing of medications is needed for nurse practitioners, physician assistants, and pharmacists. In addition to their varying levels of prescriptive authority (nurse practitioners and physician assistants have prescriptive authority in 49 states; pharmacists have prescriptive authority in 18 states) these health care providers spend considerable time talking to patients regarding their medications and are often the first to observe or hear about adverse events that may be due to such medications. It is also important to recognize that in areas where there are shortages of primary care physicians and in poverty areas, nurse practitioners and physician assistants may deliver the bulk of care.

Recommendations

- Develop improved training and 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 including: new indications for marketed products, adverse drug reactions, inappropriate or ineffective uses for established products, new approved products, and products withdrawn.

PATIENT CARE

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? Even in a climate of cost-containment, physicians in managed care, specialists, and primary care physicians must be held to certain standards of care. Improvements in the education of health care practitioners and in changes in clinical care practices are essential. In addition, the insurance industry and the Health Care Financing Administration should be included in the education process that addresses new and emerging applications of biotechnology. The issues are (a) to pay for care that demonstrates effectiveness or (b) not to pay for care when effectiveness is not demonstrated or the impact on clinical outcomes is negligible.

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 better measures of quality of care. To illustrate, a manufacturer of a hip replacement device refused to make a device that would be compatible with the female anatomy despite problems that women were experiencing with the hip replacement device because of its large size. The issue is not just developing new technologies, but also refining technologies and practices from a gender perspective, particularly in managed care settings.

The NIH Consensus Development Program is a significant health technology assessment and transfer program. A consensus statement evaluates state-of-the-art scientific information on a given biomedical technology with the purpose of resolving a particular controversial issue in clinical practice. Statements answer a series of questions concerning efficacy, risk, and clinical applications and recommend future use. However, the effect of the Consensus Development Program on clinical practice is unclear, since there are various non-medical factors involved. The program has, however, had measured success in influencing reimbursement policy and specialty organization policy, thereby indirectly affecting physician behavior. The Consensus Development Program offers one avenue for implementing the following 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

Upon diagnosis of cardiovascular disease, women, particularly black women, have a worse prognosis than do men.[14,15] One of the factors predisposing women to adverse outcomes is older age of onset. Although many of the traditional risk reduction therapies are equally successful in men and women,[16,17] other nonphysiological factors such as compliance with therapeutic regimens and access to care may play a role in prognosis for women.

For HIV, where adherence to prescribed therapies is particularly important, the available literature suggests that gender does not predict adherence. Factors that predict access to therapy may differ considerably from factors that predict adherence, and both may vary by disease. Research is needed into factors that may be barriers to appropriate care among women, including physician-prescribing behaviors, ability to pay, education, age, medical condition, functional limitations, and social support.

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 ability to pay for medications, educational level, health literacy, age, concomitant medications and conditions, functional limitations, and social support.

REFERENCES

1 Szarfman M, Chen MD, Blum C, et al. More on fluoroquinolone antibiotics and tendon rupture. *N Engl J Med* 1995;332:193. (Correspondence)

2 Peck CC, Temple R, Collins JM. Understanding consequences of concurrent therapies. (editorial, comment) *JAMA* 1993;269;1550-2.

3 Honig PK, Wortham DC, Zamani K, et al. Terfenadine-ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences. *JAMA* 1993;269:1513-8.

4 Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA* 1993;269:1532-6.

5 O'Neill R. Assessment of safety. In: Peace KE, ed. *Biopharmaceutical statistics for drug development.* New York, Basel: Marcel Dekker, 1998.

6 Szarfman A. Improving the system needed to handle clinical trial data. *Reg Aff Focus* 1996;1(5):12.

7 Levine JG, Szarfman A. Standardized data structures and visualization tools: a way to accelerate the regulatory review of the integrated summary of safety of new drug applications. *Biopharm Rep* 1996;4(3):12-7.

8 Szarfman A, Talarico L, Levine JG. Analysis and risk assessment of hematological data from clinical trials. Toxicology of the hematopoietic system. In: Sipes IG, McQueen CA, Gandolfi AJ, eds. *Comprehensive Toxicology* 4. Elsevier Science, Inc., 1997, p. 363-79.

9 Report on the IAI workshop on ENSO and interannual climate variability (July 12-15, 1994; Lima, Peru). IAI Newsletter. August 8, 1995.

10 Report of the IAI workshop on the study of the impacts of climate change on biodiversity (Aug. 9-12, 1994; Guadalajara, Mexico). IAI Newsletter. August 8, 1995.

11 Bennet ST, Adams JA. Measuring the clinical development process. *Appl Clin Trials* 1995;4:44.

12 17th French Pharmacovigilance Meeting. *Prescrire International* 1996;5:86.

13 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. *JAMA* 1998;279:1200-05.

14 Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease advantage. *Arch Intern Med* 1995;155:57-61.

15 Tofler GH, Stone PH, Muller JE, et al., and the MILIS Study Group. Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. *J Am Coll Cardiol* 1987;9:473-82.

16 Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. 2. Short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet* 1990;335:827-38.

17 Gueyffier F, Boutitie F, Boissel JP, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. *Ann Intern Med* 1997;126:761-7.

PRESENTATIONS AT BETHESDA NATIONAL MEETING

REMARKS

Barbara A. Mikulski, M.S.W., Senator, U.S. Senate

My heart is filled with joy because of knowing how all of this got started. On that dramatic day, September 10, 1990, Congresswomen Connie Morella, Pat Schroeder, and I showed up on the steps at NIH to launch what we hoped was going to be a women's health initiative. We then went to the conference at Hunt Valley, and we now are at this convocation to decide what is the future research agenda for moving ahead in the women's health initiative.

When I was in the U.S. House of Representatives, the Congresswomen embarked upon a women's health equity act, and we wanted to increase funding at NIH and make sure that the gender-specific diseases were taken seriously. We had a variety of GAO reports that showed that women had been systematically excluded from protocols, but no matter what our exhortations were, we could not bring about the change that we wanted. So I, then as the U.S. Senator, with Senator Kassebaum, called our colleagues in the House and said I think it is time we do something. We have to get all the directors of NIH institutes around the table and ask them what are their goals and timetables for including women in research.

When Bernadine Healy was appointed as the Director of NIH, we considered that an enormous breakthrough. However, a new director, without a firm, clear policy and a legislative initiative could be a hollow opportunity. We went in and had our conference, and we talked with all of the institutes because in addition to breast cancer, ovarian cancer, issues related to pregnancy, reproduction, things specific to being a woman, we also knew that every illness has a gender impact, whether it is heart disease, lung disease, lung cancer, Alzheimer disease, alcoholism, or other substance abuse. They all had gender differences or gender distinctions. We wanted to be sure that these issues were included in the research plan of the National Institutes of Health.

We came back to Congress and introduced legislation. I took the lead in the Senate to establish the Office of Research on Women's Health and then also moved forward with adequate funding. Dr. Healy was sworn in through a very prompt appointment process. She appointed Dr. Vivian Pinn the Director of the Office of Research on Women's Health, and we convened the agenda. I believe the momentum has been growing ever since. All of you are in this room because you want to show that sound science should be able to save lives.

I want to congratulate you. Whatever your fields of endeavor, whether you come from clinical practice, whether you come from a basic research area, whether it might be applied research in medical devices or better diagnostic tools, whether you are in epidemiology, whether you are looking for the genes, or you are looking for another answer, I want to say thank you because what we did was to create a framework to unleash the creative capacity of the scientific community to focus on the women of this country and, therefore, on the families of this country. I just want to say thank you for taking the dream to a reality and having that reality based on sound science.

Let me say that one of my proudest moments, in addition to helping establish the Office of Research on Women's Health, was to be a leader in the United States Congress to keep the women's health agenda a non-partisan agenda item so that we would never, ever play politics with it. When the new women came to the Congress and the Senate in 1992, I organized the Democratic women and worked with Senator Kassebaum. Then, shortly after we were joined by Senators Kay Bailey Hutchinson, Olympia Snowe, and Sue Collins. We hope by the year 2000, we will be nine and beyond, so we have a league of our own and not be a little league in the U.S. Senate.

We meet once a month, and we talk about our lives and our times, and we strategize. We vowed that we would not make the women's health agenda a Democratic or a Republican issue. We would make it an American issue, and that is what we have done.

I was so proud when we worked to move the reauthorization of the mammogram quality standards. We wanted to make sure that mammograms were safe for the women who got them, safe for the people who gave them, and people were trained on adequate equipment. We, the women of the Senate, sent out a historic letter that said, "We, all of the women of this Senate, invite all of the men of the Senate to join with us in the reauthorization of the mammogram quality standards."

Within 72 hours, we had 53 cosponsors on both sides of the aisle, and that law has now been reauthorized on a voice vote. That is what being non-partisan is all about. So whether it is working on the women's health agenda, whether it is working on FDA reform to streamline the regulatory process to make it safe and effective, and also to be sure that NIH and its extramural programs have adequate funding, we are there working and fighting.

In conclusion, let me give you some reminders. One is do your research. I want us to be sure that we look at new ideas and new opportunities. The women's health initiative was never meant to be a new revenue stream for old ideas. We need you to speak up. I want to see women scientists advance because often, although we have new ideas, old cultures continue to persist in the scientific community. We want to fund those young investigators who also might even be iconoclastic, open to new ideas, new modalities, and, I believe, some new profiles of who does the research in this country.

Second, I would encourage us not to look for silver bullet solutions. I know that Dr. Francis Collins will be speaking about the wonderful work that is now going on in gene research, but let us not only focus on the fact that if we find the right gene at the right time, that is going to be the only solution. Each and every one of you knows we need to look at broad-based research, that there will not be any one answer, not only one cure, and not only one solution.

The third thing that I would encourage is that we also do more research into behavior. We know that some of the greatest causes of those issues affecting women, particularly heart disease and lung cancer, are behavior-based. But there seems to be very skimpy research. Often we hear about diet. Behavior-based research is about nutrition and exercise, and yet, it is very hard to get that type of information. We know that when women have a heart attack it is often treated differently. Men go into acute care, and if they are tycoons even find whole new low-fat products. We women are often in Weight Watchers and many of the other programs, by the way, which might even be more effective than some of the other programs, but we often are not treated the same.

We see our problems as obesity. They see their problems as medical ones. We get all tied up with all kinds of other issues in our mind, in our heart, and in our body. We need to have a look at behavior and how we can enhance our health and well being.

We also need to look at the behavior of doctors and how we can take some of the new ideas and the research and move it to clinical practice. Many physicians do not recommend that their patients get mammograms. Many of them still continue some of the old stereotypes and practices, and when it comes to other issues like heart disease and obesity, we know that the failure of phenfen was not a failure of FDA approval; it was the failure of the right advice being given in the right way to patients.

Last, we need to look at caregiving. Right now people are worn out, and they are worn down because of the whole issue of three shifts, one in the marketplace, one in the family and then one often in the community. Taking care of your children is child care and then taking care of your mom and dad is eldercare. We need to focus on caregiving. What does it take to do that? What does it take to support that and then how we can move ahead to be able to do it. These, I believe, are some of the new frontiers of research and how we need to move ahead.

The other thing that I am going to encourage you to do is come out of your labs and fight. Help join with the women of the Senate, the women of the House, and the galas that support us for more resources, for more resources in research for you to be able to do your outstanding work.

I also ask you to come out of your laboratory to fight against the excesses of managed care. We need to bring health disciplines to our health care system, but managed care was never meant to be manacle care. Managed care is systematically believing that it is moving away from a research agenda so that we could have those new ideas that lead to new improvements in clinical practice. Right now, those of us in Congress know that we need to have a framework of managed care: the solvency of Medicare, the reliability of Medicaid, and the other issues related to access of health care.

What I am concerned about is the lack of quality standards. The fastest growing number of constituent complaints in my office are about not knowing what their health care plans cover and whether they will have the health care that they need. I am not opposed to managed care, but I am certainly opposed to its excess. So I will be part of a coalition in Congress talking about quality standards in managed care and for a consumer bill of rights so that you do have access to what you need.

Olympia Snowe, Connie Morella, Nancy Palowsi, we do not want to be fighting this one organ at a time. We really don't. We want to have an organized systematic way that respects us, respects our lives, and fundamentally makes the decisions about patient care in the consulting room and not in the board room.

It is an honor to be here with all of these dedicated people. You are preparing your health research agenda for the 21st century, which is going to be very critical in the development of our agenda for women's health as we go into the new century.

Women's health issues are a high priority of the Congressional Caucus for Women's Issues and also for a number of male members as well. They very often look to us, as women, for the lead, but then they do follow and become advocates too. We are going to look forward to the report that is going to come out of this conference to help us develop our public policy priorities for the next century.

The Women's Caucus emanated in 1989 from a GAO report, which indicated that not much was happening with regard to women. I recall this vividly whenever I see Bill Raub, because he was the one who announced that there would be an Office of Research on Women's Health. We had legislation on women's health equity that was submitted and codified, and you know that the Revitalization Act of NIH contains the requirement that women be included in all clinical trials and protocols unless there is a good reason not to do it.

Since 1990, we have made great progress in the funding for women's health centers; the concerns of breast, ovarian, and cervical cancer; study of osteoporosis; and establishment of the Women's Health Initiative. For example, breast and ovarian cancer funding at NCI has more than quadrupled since 1990. Funding for osteoporosis has grown from only two osteoporosis-specific grants in the entire country in the early 1980s to $80 million in osteoporosis-specific research grants today.

However, I submit our job is far from over. Despite great strides in women's health research, we still must be vigilant and must address some issues that are not receiving the public attention and research priority that they deserve, and those are some of the issues that I thought I would mention.

For example, HIV/AIDS is the fourth leading cause of death in young women, and the number one cause of death for young African-American women. Sexually transmitted diseases, including HIV, continue to ravage our country. Each year 12 million new STD cases are reported in the United States. Twenty-five percent of that number are in teens, which translates into a rate of one in eight teens who are infected with an STD. And these figures only represent the reported cases. Health experts believe that about one in four sexually active teens becomes infected.

Adolescents and minorities are most severely affected by STDs. The highest rates of chlamydia and gonorrhea among women occur in 15 to 19 year olds. Incredibly, the gonorrhea rates in this country approximate those in the developing world. The consequences of STDs are most severe for young women because there are often few, if any, symptoms. STDs, therefore, may go untreated leading to potentially serious conditions, including ectopic pregnancy, infertility, chronic pain, and poor pregnancy outcomes. In fact, the group most likely to die from ectopic pregnancies are African-American teens.

Infection with the human papilloma virus is the single most important risk factor for invasive cervical cancer. STDs also substantially increase the risk of HIV transmission, boosting the likelihood of infection three- to five-fold. The number of new HIV infections are increasing most rapidly among women, adolescents, and within minority communities.

I also believe it is essential that we develop microbicidal products, products to prevent transmission of STDs with an emphasis on methods that women can afford and control without the knowledge of their partners. I have sponsored legislation since 1990 to increase funding for HIV/AIDS research focused on women.

These are issues that receive less attention in our research and prevention agenda, and yet, they represent very serious women's health concerns. Our challenge is to identify and respond to the many health needs of women over the full span of their lifetimes.

The Women's Caucus continues to ensure that Congress focuses on women's health. Earlier this year I sponsored a bill, cosponsored by Nancy Johnson, Anita Lowe, and Eddie Bernice Johnson, and Olympia Snowe in the Senate, to cover bone density tests for diagnosis and prevention of osteoporosis under Medicare. I am delighted to say that that is now law. It became part of the Balanced Budget Act in Congress. There will now be annual mammography screening under Medicare, a long effort begun by Caucus members years ago.

Bipartisan efforts are currently underway on issues such as preventing "drive through" mastectomies, expanding osteoporosis research and health insurance coverage, ending discrimination against battered women in insurance, and banning discrimination based on genetic testing. Caucus members have introduced legislation to increase funding for a number of women's health concerns, including breast cancer, cardiovascular disease, lupus, and DES, just to mention a few.

The Women's Caucus held a hearing on the need for more and improved contraceptive methods for women to meet their needs throughout their reproductive lives. Female sterilization is the most commonly chosen form of contraception in this country, a fact that I find shocking. Almost one-half of all unintended pregnancies result from ineffective contraception, and 44 percent of unintended pregnancies in this country result in abortions. Incredibly, half of the fee-for-service insurance plans do not cover reversible contraceptive methods. We must work to eliminate the barriers to this research and to expand our research efforts in this area.

These are just a few of the successes and the current efforts that are underway in Congress to address the needs of women's health. Our Caucus just celebrated 20 years as a bipartisan force in Congress, and we will continue to be there for you and look forward to receiving the priorities identified by this critical conference for an agenda for the 21st century.

Those of you gathered here already know what a landmark event this is. Most of you have played important roles in bringing us to this point. Six years ago, a similar gathering convened in Hunt Valley to map out the coming decade of research on women's health. It was an ambitious undertaking, but the agenda set at Hunt Valley has advanced beyond many people's wildest hopes and expectations. This conference is the next generation of that critically important endeavor. I am proud that we have made so much progress in just 6 years that we already need to update the national women's health research agenda.

The original Hunt Valley conference took place in 1991 — a challenging year for women's health. Congress had worked for over a year to craft the NIH Revitalization Act, a seminal piece of legislation that proposed to bring new focus to the NIH's research on women's health, allocate new resources for this purpose, and establish a permanent Office of Research on Women's Health. That bill was vetoed by President George Bush, who called it "unacceptable" and "objectionable," singling out the provisions on women's health for special criticism. President Bush stated that the NIH Revitalization Act was "not necessary to increase support for research targeted at women's health needs." This happened about the same time that then-NIH Director Bernadine Healy was quoted as saying that at NIH "Women's health has always taken a back seat."

At the same time, issues like breast cancer and osteoporosis were finally penetrating the American public's consciousness. I spoke to the Komen Foundation that year and congratulated them on raising $11 million for breast cancer research. The National Osteoporosis Foundation was a youthful organization, working uphill to build membership and educate the public. At speaking engagements, I was pointing out to groups that there were more shelters in our nation for abused animals than for battered women and children.

That was 1992. This is 1997. What a difference 5 short years can make!

Today we have a permanent Office of Women's Health Research at NIH, directed with leadership and flair by the incomparable Dr. Vivian Pinn. Dr. Pinn and her staff have proven time and again how important a central office on women's health is for NIH. The office coordinates the interdisciplinary aspects of critical women's health research into breast cancer, DES, lupus, and AIDS. It has worked to give women's health greater prominence in medical school curriculum and move advances in women's health research from the laboratory to the bedside. It has advanced research and education on women's health through conferences and publications, as well as the sheer persistence of its staff. We all owe Dr. Pinn a debt of gratitude for her unceasing labor and dedication to the health of our nation's women.

Further, we now have offices of women's health at other federal agencies like the FDA, CDC, and AHCPR. The HHS Office on Women's Health has launched major education campaigns like Healthy Women 2000 and Girl-Power! to educate women of all ages about their special health needs. Women are finally beginning to receive their due as half of the nation's population and half of the taxpayers contributing toward federal biomedical research.

The private sector has traveled a long, productive road since 1991 as well. In the advocacy community, the Komen Foundation is expected to raise more than $30 million for breast cancer research in 1997, more than triple the amount it raised in 1991. The National Osteoporosis Foundation is a nationally known organization with a membership of more than 150,000. Dozens of women's health advocacy groups have formed and gained new prominence, while organizations like the American Heart Association have established a new focus on the women's health aspects of their issues.

Health care providers are making progress as well. Today one-third of all hospitals have some kind of women's health center, up from 19 percent in 1991. Increasing amounts of private research dollars are being spent on treatments for disorders particular to women, as well as diseases that afflict women differently from men.

We have come a long way in the past 6 years. The question we are here to examine today is: Where do we go from here?

Part of the answer to that question is simple — we keep traveling along the same course that we have followed since 1991. Despite major advances like the discovery of genes for breast cancer and drugs to treat osteoporosis, we still have not cured these diseases. We do not understand what causes the 90 to 95 percent of all breast cancer cases that are not genetic. We still do not know whether DES has consequences for the children of the women exposed to the drug in utero. We do not know whether it is safe for women with lupus to take estrogen after menopause. Women must still rely on the neolithic technology of the mammogram to detect breast cancer. We must continue our pursuit of new and innovative ways to prevent, diagnose, treat, and cure these disorders.

We must strike out in new directions as well. The last 6 yeas have certainly proven the old adage, "The more we learn, the more we learn how much we have to learn." In my view, the Federal Government should take on the responsibility for educating women and health care providers about diseases that are traditionally considered men's diseases and not women's.

Despite the prevalence of breast cancer, heart disease remains the number one killer of American women, claiming one quarter of a million women's lives annually. A recent study showed that older women feared cancer more than any other disease, although they are at higher risk proportionally for heart attack. Though ovarian cancer will affect more than 25,000 women this year, colorectal cancer will strike almost twice as many.

We must begin educating women about these health risks and the steps they can take to ensure they receive appropriate care. Women who have heart attacks are less likely than men to receive the most aggressive treatments, despite similarities in age and severity of illness. Colon cancer is one of the few cancers we can actually prevent if polyps are detected and treated early. I intend to begin a major effort to educate women about their risk for colorectal cancer and appropriate prevention measures. But NIH should play a central role as well, demonstrating through its research agenda the Federal Government's commitment to these crucial women's health issues.

Another women's health taboo that should be broken once and for all is menopause. Too many American women have suffered needlessly in silence because they did not have access to accurate information about menopause. Too many women still view the symptoms of menopause as a trial they must bear alone and not share with anyone, even their doctor. Today, hormone replacement therapy can offer relief to many women for not only symptoms like hot flashes and mood swings but may also afford future protection against heart disease and osteoporosis. However, hormone therapy is not right for all women and some may need to balance its benefits against a possibly raised risk for breast cancer. We must continue working to transform menopause from a condition somehow unfit for discussion in civil society to a natural progression of the aging process that should be addressed and, if appropriate, treated by a medical professional.

This is just a small sample of the issues women's health research should face as the field passes its infancy and begins to mature in the coming years.

It is too early to celebrate victory. We still have a long road to travel toward equity in women's health. But we have made a very good start, haven't we, my friends? I look forward to working with you all to advance women's health into the 21st century — not as an afterthought to biomedical research, but as a full partner in our nation's quest to improve human health.

Louis Stokes, J.D., Representative, U.S. House of Representatives

Presented by Fredette West

REMARKS

I am very pleased to have this opportunity to speak to you on behalf of Congressman Louis Stokes about an issue of importance for many of us, our families, our communities, and our nation — women's health.

The Congressman has been following the forum and is glad that there is such diversity in the participation represented throughout the workshop. Your presence here today is evidence that you join the Office of Research on Women's Health in its commitment to ensure that our nation's racial and ethnic minority communities are included in this important discussion.

The participation of 55 public witnesses in these talks is also encouraging. It speaks highly of this program and of the efforts of the Office of Research on Women's Health to improve the status of all women across this country.

Congressman Stokes applauds Dr. Vivian Pinn on her outstanding leadership of the office, as she has worked very diligently to guide the development and implementation of the national research agenda on women's health. Women's health is one of the most important issues facing this Congress and our nation.

As a member of the House Appropriations Subcommittee, which funds health programs, Congressman Stokes indicates that we still have a long way to go; however, substantial progress has been made. As a result of the subcommittee's action on the appropriations bills for the Departments of Labor, Health and Human Services, and Education, the recently enacted fiscal year 1998 appropriations measure includes $18.4 million for the Office of Research on Women's Health.

For the Ryan White AIDS Program, the bill provides more than a billion dollars. There is $145 million for breast and cervical cancer screening, $683 million for maternal and child health development block grants, and well over $13 billion for NIH as a whole. These are just a few programs that are funded under that particular appropriations subcommittee.

As chairman of the Congressional Black Caucus Health Brain Trust, Congressman Stokes is particularly proud of the role that the CBC has played and continues to play in women's health. Since its founding in 1971, the Congressional Black Caucus has worked diligently to address the health challenges that impact African-American women, families, and communities across this country. In fact, the Congressman recently convened a special health forum that closely examined issues regarding the health status of African-American women entitled *Saving our Sisters*. If you look at the statistics, you will discover that compared to their white counterparts, African-American women still suffer a much more compromised health status.

For example, African-American women are more likely to die of breast cancer. This is, in spite of the fact that they experience a lower rate of incidence of this disease.

African Americans between the ages of 35 and 47 are 38 percent more likely to die of a heart attack. African-American women, college-age and educated, are three times more likely to have a low-birthweight baby. Infants born to this group of mothers have an 80 percent higher risk of dying during their first year of life.

And during 1996, 59 percent of all AIDS cases in women were reported among African-American women.

Congressman Stokes wants you to know that with your help and with the steadfast efforts of the Office of Research on Women's Health, we can make significant strides in reducing the health status disparity of minority and disadvantaged women.

Again, Congressman Stokes sends you his regrets and looks forward to your sharing with him the recommendations of this conference. Such recommendations would be used to help formulate legislative agendas and amendments to various bills.

Audrey T. Haynes, M.S.W.
Deputy Assistant to President Clinton
Director of the Office for Women's Initiatives and Outreach, The White House

REMARKS

It is a great pleasure to be here, and an honor to be in a room with such a wealth of knowledge and information and enthusiasm about the women's health care field. Obviously, health care in general is of interest to me, having just served as Deputy Secretary for Health in our state. For those of you who deal with State issues, all states, including my own Kentucky, are wrestling with many health care issues today. Nationally, I have been very interested in what all the women's health offices throughout this administration are doing, and we are bringing all the directors of all the women's health offices throughout the Administration to meet on such issues.

The President has a very positive track record on women's health, and he wants to continue that track record to make positive improvements and to put into place some important programs and a research agenda, which I know you are working on. You and the President are looking at not only the short-term but the long-term research needs.

Women's health is not just about the health of one woman, but it is about the health of our families and the health of this country. It is my goal in the Office for Women's Initiatives and Outreach to make sure that women's health continues to be at the top of the White House agenda.

You have a great advocacy community, and many of you are probably advocates as well as researchers on women's health. We have a great relationship with the women's health community. These advocates speak loudly and clearly and often. They always have great things to say, and I always listen. I listen very closely. They always provide great information, and I know that we will continue to work with them.

Again, I wish you the very best and a very positive meeting.

Francis Collins, M.D., Ph.D.
Director
National Human Genome Research Institute

GENETICS, GENOMICS, AND WOMEN'S HEALTH

Genetics is a very important part of the research agenda for women's health because genetics has become the central science of medicine in many ways. We are engaged in a genetic revolution, which is already underway, and women are in the front lines of this revolution. Many of the advances that seem to be occurring in genetics are having an impact on women, perhaps disproportionately due to their numbers from the discovery of the BRCA1 gene to all of the focus on reproductive genetics, where clearly women have more than their share of the dilemmas to wrestle with.

It is going to be the case, no matter how clever we get, that, in fact, gender and biology are inextricably intertwined. We know a lot, but we need to know a lot more about why that is. We certainly have learned to appreciate that inheritance patterns are not so simple as we once thought, and issues such as mitochondrial inheritance and imprinting and non-Mendelian kinds of inheritance are now finally receiving the kind of study that they did not get before because people had not quite appreciated their significance.

For many diseases, gender plays a role. We have to be sure that when we make that statement that we are not immediately jumping to the conclusion that that is because of genotype. Because certainly in some instances that is not true, and it is the different environmental exposures that actually account for the difference in risk.

We will not reach the point of deciding where agenda is irrelevant to risk of disease because, after all, there is a very strong biological basis for many of the predispositions that people are beginning to uncover, which differentially affect the sexes. That is in contrast to race where we are increasingly coming to the rather exciting realization that there is very little reason to define race as a real entity at all and that, in fact, our similarities are so much greater than our differences. Similarities between individuals who we socially designate as being of different racial backgrounds are, in fact, as great as similarities within groups of individuals who self-identify as being of the same race. The whole concept of race is in evolution and will be from the point of view of science moving in the direction of being less and less relevant. The way that our cultures have developed over time, we will be talking less about race, which is going to challenge us socially.

Clearly, when it comes to women's health one of the challenges for researchers will be, as everywhere else, the distinction between what is genotype and what is environment. Now, your working groups (all except the one on careers) are focusing on particular areas of research that have some genetic components. I am not arguing that they are all genetically predetermined, which would be absolutely indefensible, but everyone of these particular areas of medical research clearly involves factors that are written with the DNA double helical sequence. As you plan this agenda for the next century for women's health research, it will be very critical to include a consideration of how genetics is going to push that agenda forward.

The human genome project is going to make a very significant contribution to what is possible. The genome project has the three major goals, which are to get genetic maps, physical maps, and the DNA sequence. The genetic maps are essentially done, the physical maps are 98 percent done at the level that was originally defined as being needed, and the DNA sequence of all three billion base pairs of the human genome is just getting underway. It would be hard to find individuals working in the field who are not pretty confident that we will achieve this goal of the complete sequence of human DNA by the year 2005.

That will be quite a milestone that will profoundly alter the way that research is done. We spend so much time these days cloning and sequencing genes in research laboratories, and we will have at least a reference example of every gene. Great effort is being put into making sure that this information is publicly available. Laboratories are depositing their data in electronic databases in a fairly unassembled form every 24 hours so that people who want access to it can get that.

You might ask, whose sequence are we doing anyway, and is it a man? We had a very interesting discussion about this because we really had to decide what should be the source of the DNA that is going to be used to produce that first sort of reference genome. We decided it was not very sensible to go out and find a perfect specimen because there are not any; we all have flaws. We decided that it would be fairly dangerous for the whole sequence to come from a single person because that person's DNA sequence would sort of be laid out. Instead the proposal was to put out a call for volunteers to come in to have DNA obtained, and then we would have a subset of those individuals have their DNA actually turned into the libraries that are being used for the human genome sequence analysis. Their identities are anonymous.

Obviously, however, it will possible to determine their sex. There are slightly compelling reasons in that sperm makes a particularly good source of DNA because of the absence of somatic rearrangements that might arise in DNA from blood. The human genome project is going to focus on men. So, in fact, the source of the DNA that is being used for this project will be ethnically somewhat diverse, although we do not really know the ethnic origin of the individuals, and will be gender diverse. The point of this first sequence is to get the 99.9 percent that is the same among all of us identified. The part that is responsible for variation will be the next phase to understand.

This is a very exciting development, but the real point of the genome project is to make it possible to understand disease, not just clone genes, but use that information medically to develop better diagnostics and better therapies. As these gene identifications are happening — and they are happening with great profusion these days with as many as about 25 new disease genes being identified this year — we ask what are the pathways that have to be traveled after that identification has occurred. The more immediate ones are often in the diagnostic arena where we are able to make predictions about who is at risk for something or whose children are at risk for something. The longer term ones are to develop this into therapies.

How does all this interrelate, particularly to research on women's health? I will mention four topics. The first one is sort of the traditional one where people consider the interface between genetics and women's health to be most strong. I think in the past a vast quantity of the dialogue that occurred between genetics and women's health was in this arena. This is changing as others come along, but this will continue to be a major area for discussion.

Consider, for instance, a recent NIH consensus development conference on genetic testing for cystic fibrosis. CF is a disease that is quite common in the Caucasian population, where 1 in 25 or 1 in 30 Caucasians are carriers for this recessive disease, and less common for other ethnic groups. The gene was found 8 years ago. We know that there are lots of different mutations in the gene, but if you test for about 30 or 40 of them you can identify roughly 85 percent of the carriers.

Now, two carriers who have a child face a 1 in 4 chance that that child will have cystic fibrosis, and so immediately after the gene was identified, people began to discuss the possibility of offering carrier testing to the general population. NIH funded a variety of pilot projects in various settings to try to find out what was the interest in the possibility of CF carrier testing, outside of those who had a family history.

The discovery was that there was relatively little interest, except in one setting: women who were coming in for their first prenatal visit who were sort of triggered to begin to think about genetic issues by the obstetrician talking to them about neural tube defects and other disorders. Then if offered this possibility of finding out about CF carrier status, many of them did, in fact, turn out to be interested in proceeding down that pathway.

At the conclusion of this consensus conference, which looked at all of the data that had been carried out through those pilot projects, the finding was that there is now sufficient scientific justification to begin to offer CF carrier testing to individuals outside of a family history. In fact, that sort of stirred the community up considerably. Up until then everybody had said that would be premature.

Why is this relevant to women's health? Many of the proposals about how to carry this out suggest that the most efficient way to identify couples who are at risk is to begin by testing the woman for carrier status, and only if she tests positive do you then try to identify the partner and determine his carrier status. It is sort of sequential sampling process, as opposed to testing the couple up front.

There are consequences to that, not yet have fully explored, on the burden of the decisionmaking, the burden of the possible stigmatization of women who are finding out their carrier status, whereas their partners only are offered that opportunity if the woman turns out to be positive. This, I think, is an area of considerable possible utility, as far as research studies because CF is the first example of a DNA-based carrier test that is being offered on a large scale or will be probably in the course of the next 2 or 3 years. We have not yet fully explored what the consequences might be of that kind of leap into the new genetics on such a large scale. I would certainly encourage you in your deliberations to consider what opportunities are there that ought to be followed up on.

One of the issues really is research on pregnant women in the first place. This has not been an easy area. There have been examples, for instance, of the testing of drugs, which have left out, in many cases, women of childbearing age because of fear of possible impact on pregnancy, a well motivated sort of original idea, but obviously one that has been carried to an extreme. Women are excluded, particularly pregnant women, even in circumstances where there is no medical, physical risk to the fetus, just because in a patronizing sort of way researchers say, it is a stressful time and women do not need to be bothered then.

On the other hand, there is the other end of the spectrum where, in something such as CF carrier screening, there seems to be almost a targeting of women. It is easy to find access to them, and they are likely to participate because they are motivated about the health of their unborn child. How do we sort of balance this and figure out what is the appropriate ethical stance to take when it comes to this kind of study? I think there are some interesting questions there as well.

The second topic, and probably the one that gets the most media attention right now, is the area of pre-symptomatic testing. Women really are on the front lines here, in particular because of BRCA1 and BRCA2, and many other examples that will be coming along. Just to remind you, in our rush to be enthusiastic about the research advances that have occurred in breast cancer with the discovery of BRCA1 and 2, let us not forget that 90 percent of breast cancer arises in women who do not have alterations in those particular genes. We need to work much harder to understand what is going on there, because there probably are weaker genetic factors at play in that 90 percent. They are harder to uncover, but in the aggregate, they may involve more women than the relatively uncommon but highly risky BRCA1 and 2 mutations.

We critically need to find better answers of what to say to women who turn out to have mutations in BRCA1 and 2. We have the diagnostic ability now to determine this, and the test is commercially available, but we are woefully ignorant about exactly what options are effective in this circumstance.

A paper from the Cancer Genetic Studies Consortium, an effort which has been funded by NIH and led by the Genome Institute but has had important support from the Office of Research on Women's Health, reviewed the entire world's literature on what we know about the effectiveness of frequent mammograms, of a prophylactic surgery, either breast or ovarian surgery, and other options that might be offered to women in the high risk circumstance of having a BRCA1 and 2 mutation. Basically, the bottom line is we have very little data. There are anecdotal reports of this kind of outcome or that kind of outcome, but the best you can do, as far as making recommendations, is say this is expert opinion. Expert opinion often turns out to be wrong after you have real results.

The National Cancer Genetics Network, which has gotten underway through NCI, will be looking at areas where hopefully we will be able to develop better answers to these questions, which women desperately need to make their own decisions about what options are most appropriate.

Pre-symptomatic testing for cancer for men is going to be interesting. There has been this identification on the basis of at least a linkage analysis that there is a gene for prostate cancer on chromosome one. We are trying to focus in on this and find this gene hopefully in the next not too many months. If that happens, we will then see a situation where it will be possible to make predictions about which males have a very high risk of prostate cancer.

I think there will be some fruitful areas of investigation to compare those two arenas. Will we see proposals for men to undergo prophylactic surgery for prostate cancer risk? I suspect not, and why is that? Does that say something about the difference in the medical circumstances or more about the way in which we view dispensability of organs, if you are talking women versus men. I think there are some very interesting questions there.

An interesting thing to look at, which as far as I can tell has not been considered, is pick a disease where the disease itself is not gender-specific, and there is a strong heredity predisposition. In colon cancer, for instance, we now have several different genes that carry a high risk of colon cancer, for which testing is available. What happens when somebody is identified at high risk, and they are offered the various options of surgery or colonoscopy on a regular basis. Is there a difference between the men and the women, in terms of what choices are made, and, if so, is there a difference because of the way that the risk is presented by the care givers, or does it reflect some other aspect of how decisionmaking is made between men and women. I think this is a very interesting area to look at and would be an important agenda item for the future.

Up until now, most of our genetic analyses have been for things like BRCA1 and 2, where we pick a relatively common disease and then dissect out of it a subset of individuals who have essentially a single gene disease. If we have an altered copy of the BRCA1 gene, we are going to see a pattern in the family which looks Mendelian. The real challenge is to go after the much more complicated situation where many genes are involved, but each one of them has a relatively modest effect. The other 90 percent of breast cancer probably has some polygenic effects, and virtually every disease that has an effect on women's health will have some polygenic contributions.

The exciting aspects of this is we are on the brink of being able to attack those situations with considerable power over the next 5 or 10 years. We will be uncovering those predispositions, which have an effect on very large numbers of people. An example is autoimmune disease. We do not understand why autoimmune diseases tend to be more common in women than men.

An exciting recent observation is to try to see where are the genes that predispose to autoimmunity. We collect families in which more than one individual has the disease. We scan the entire genome with large numbers of these genetic markers, and we try to identify a region that tends to predict who has the disease and who does not. This is a sort of a linkage study often done with affected sib pairs. The results are often at the borderline of statistical significance because the genetic predispositions may be quite weak. This study scanned the results from about 20 different studies on different diseases and looked at them side by side to ask are the genes that predispose to multiple sclerosis, type one diabetes, rheumatoid arthritis, and lupus totally different or are there some similarities here?

The MHC is involved in virtually all of those, and it could be argued that autoimmunity might have some common basis and then specific outcomes based on some modifications of that common basis. The various human chromosomes are areas where there are clustering of disease predispositions for different autoimmune diseases, which happens in a non-random way. This suggests that there are going to be common predisposing genes that are involved in autoimmunity across the board. Finding those would be an extremely high priority.

Linkage studies are terribly difficult. Sometimes more promising efforts are association studies, where you pick a gene that you believe may be involved in a particular disorder and you try to find variation in that gene and then see if that variation associates with a particular disease. An exciting example that has not gotten much attention is osteoporosis, obviously a disease of great interest in women's health because 80 percent of those with severe osteoporosis are women. A study has been done to look at a variation in the gene for type one collagen. There is a regulatory region of that gene that is probably responsible for how well the gene is transcribed and how much protein it makes. There is a singular nucleotide, which varies in the population. In some people, it is a G, and some people, it is a T. They are calling one of those alleles "big S" and the other "little S." They are looking to see what is the association of the genotype with severe osteoporosis demonstrated by a vertebral fracture. In the study, the vertebral fracture group has a larger number of people who are heterozygous for little S or even homozygous for little S, which you do not find at all in the controls, suggesting that this variant, which is the one that would potentially reduce the transcription of this gene, is a significant risk factor for osteoporosis.

Here is a disease that we think we could prevent, if we knew who was at highest risk. Here is an area where I think considerable research opportunities would exist, first to confirm that this result is right, then to try to consider what kinds of interventions would be appropriate for those found to be at risk.

Association studies of this sort, which we could never have found by linkage analysis because the effect is too weak, are very exciting when you get a result. The problem is most of the time we do not know where to look. If you were trying to figure out, for lupus, for instance, what genes are involved, what would you pick? We could make some guesses, but probably the things that are involved would not be on the list.

A new strategy is to go out and try to identify variation in the human gene element in a much more systematic way than we have done before, so we can do these kinds of association studies without having to be able to guess what the right genes are.

We would like to do two things. One would be to directly go out and identify the variations that occur in coding regions of all of the 80,000 genes or as many of them as we can get our hands on as soon as possible. It is not possible to do the whole thing because at the present time we only have full length copies of maybe 5,000 of them, but we could start there. Every one of those genes will have the possibility of a common variant, and those common variants may, in some circumstances be associated with disease because they change the function of the gene. With the catalog, we could do what I explained we did for osteoporosis without having to get lucky by making the right guess.

Even if you cannot do that for all 80,000 genes, there is an indirect way to get the same result. If we had a very, very dense genetic map, as shown by each one of these tic marks, we could identify a region of a chromosome that is predisposing to illness, even if we had not identified the precise base change that was itself the cause and effect contributor. By identifying the neighborhood, we can get to about the same point.

An initiative called SNIP is about to get underway and will probably result in the generation of such a catalog over the course of the next few years. It will make this kind of genetic analysis to identify genes that have weak contributions to common disease much more plausible. Those genes when they are discovered will have an influence on large numbers of people because these will be common variants that maybe 10 or 15 percent of the population have, not like the current situation where you study a relatively rare variant that has a very large effect.

What about therapy? Clearly, genetics will continue to play a role. It is not possible these days to run into a pharmaceutical company that does not have a genomics division, because they are counting on genomics and genetics to be the source of their new drug discoveries. Virtually all of them are planning for the day where gene testing will be used to identify who is a particularly vulnerable subject to the toxicity of a particular drug and who is a particularly good subject for a particular drug. The notion of individualized drug therapy based on the genetics of the host is a very real concept, which will probably come about in the next decade or two.

I would predict that gender will have a large effect on that kind of analysis. After all, that is a particularly powerful set of genetic differences. If we see a pharmaceutical company that is proposing to do this, not taking into account gender of the subjects and not including sufficient numbers of both genders, then you might end up with a result that is not, in general, the one you want.

A common variant in a blood clotting factor, called factor five, produces ranine instead glutamine. We find this in 3 percent of the population, but if we look at patients that have had a significant episode of venous thrombosis, you find it in 21 percent of them. People who have one copy of this, probably have a five- to tenfold increased risk of thrombosis. The homozygote may be as much as 100-fold increase, and there is some sketchy but intriguing evidence that oral contraceptives may unmask this predisposition. At least one editorial has suggested that all women ought to be tested for this particular variation before going on oral contraceptives or other estrogen therapy. Here is the possibility of genetics and pharmacology interacting with each other, and yet I think there are many questions to be asked there about whether this is an appropriate step to take, most particularly in the area of the ethical, legal, and social issues.

This brings us to the fourth and final area. As I said, women are in the front lines of the genetic revolution. I am afraid that also means that they have been particularly vulnerable to misuse of that information when it comes to things like health insurance. I cannot resist the opportunity to make the case that this is a problem we have not yet solved, that women are particularly in a circumstance where this is being used against them. This is in part because BRCA1 and 2 testing is out in front of a lot of other opportunities, and I think also because women are more likely to be in a situation of less than a vigorous health insurance and, therefore, more prone to be discriminated against if some result is discovered about them.

With the Kassebaum-Kennedy bill, we now have protection for individuals who are covered by group plans, but not sufficient protection in an individual plan. I think we collectively just have to fix that. I certainly have enjoyed my experience with the National Action Plan on Breast Cancer working on this problem, but we still have to see it solved. There is lots of enthusiasm for doing it on both sides of the aisle, and both houses of Congress, but we cannot stop until it is done.

Genetics is sort of part and parcel of everything you are talking about today and tomorrow in your workshops. I think it would be inappropriate to try to pick out just one area and say well, this is where genetics really needs attention. It is probably all the way through there.

Women, I think, are going to continue to be on the front lines. I would like to see that happen in a way where the women are the victors and not the casualties. I think collectively we can do that, but we have to roll up our sleeves. We have to keep our eyes open, and we have to be resolved that that is the outcome we are going to settle for, and nothing less.

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SOCIAL, LEGAL, AND ETHICAL ISSUES

I had the honor of working in Dr. Pinn's office for a year, and she had the vision to let me work on genetic issues. That gave me the opportunity to work closely with Francis Collins and Richard Klausner and to take a proactive role in setting the agenda for genetics. I would like to place Dr. Collins' presentation into a broader societal context. These are warnings that may dampen some of our enthusiasm about what might happen in genetics in the next few years.

First, I caution you about "genetic myopia." This is a blindness that occurs when we try to explain everything in terms of a genetic solution, a genetic answer, or a genetic cause. This can be very dangerous because it blinds us to other things that are affecting us. Individuals should not think that their health is so heavily determined by their genetic makeup that changing their behavior will not affect their health. Thinking that we can not change our health status, no matter what we do, does not empower us to improve our health.

Secondly, we all need to be aware that genetic testing is not a "quick fix" in and of itself. It is a means toward an end — better or improved health and reduction of morbidity and mortality. It is not an end, and sometimes the commercial market may lead us to think that is the stopping point.

Third, we want to be careful about not perpetuating a genetic underclass. For example: Those who have access to prenatal care have access to prenatal testing. Those who do not have prenatal care do not have access to prenatal testing. Those who are involved in a research protocol may be able to get testing, but then may not be able to benefit from any of the information. If they do not have insurance for a prophylactic mastectomy, or they do not have funding to get mammograms more often, what good is this information? Will we continue to perpetuate even more divisiveness in our country?

The fourth issue that concerns me, particularly with respect to women, is accountability. If this information is available, do we have a duty, particularly with pregnant women, to get all this genetic information? Over the past 20 years, we have focused mainly on pregnant women. We have had genetic information on pregnant women, and my prediction is this will continue because they are the targeted audience that can be marketed commercially.

Fifth, a social construct is developing that I call "genetic identity." It is the Jewish gene for breast cancer, the African-American gene for sickle cell trait, and the Native-American gene for alcoholism, and so on. The irony is that to conduct good research, particularly in genetics, you may have to focus on certain ethnic groups. Subgroup population analysis is very important to good research, but how are you sure that you do not target and stigmatize a group so much that these people say we have had enough. How do we really do good research that is meaningful to those particular groups and at the same time not injure them?

Within this societal context, the major legal, ethical, and social challenges include: informed consent, discrimination, privacy and confidentiality, and family rights and responsibilities.

Many unanswered questions create challenges for the informed consent process. For example, in predictive genetic testing, the value of the predictive information is unknown. We have very little data on its value in terms of the individual's health. We risk misinterpretation, both from the perspective of the consumer and from the perspective of the provider. We have limited clinical data on the effectiveness of prevention and intervention strategies. The impact of predictive testing on changes in health behavior is also unknown. If, in fact, one has a susceptibility for a particular disease, for example, lung disease, is one more or less likely to smoke?

In addition, it is difficult to quantify and qualify the social risks of genetic testing and research. How much discrimination is there? What are the privacy concerns? How does genetic information change family relationships? Do people experience group stigma? All these social questions are beginning to emerge. We must still face the unforeseeable risks and benefits that are yet to be identified. In the 21st century we must continue to address the complexity of the social, legal, and ethical implications of genetics.

SOCIAL AND ETHICAL PRIORITIES FOR WOMEN'S HEALTH RESEARCH AND HUMAN GENETICS

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I am pleased to respond to Dr. Francis Collins' talk, in which he emphasized that women's health research and research in human genetics are interdependent. I agree with his main points and consider myself a strong supporter of each. My response to him and to the movement to improve women's health research is to offer a framework of seven social and ethical priorities that have claims on advocates of women's health research and genetic research. These claims remind us that we are all part of a larger whole, and when we forget it, our causes can be harmed by lack of foresight and political isolation.

Universal Primary and Preventive Health Care: Incrementalism — The Prevailing Approach

The overriding priority is to remedy a longstanding condition of unfairness of access to adequate primary and preventive health care. America's moral paradox in health care is stunning technical success (symbolized by the Human Genome Project) and the nation's failure to serve all citizens adequately. The connection between the work of this conference and health care reform is that the longer reform is delayed, the less advances in women's health and genetic research will be broadly perceived as benefits. The reason is simple. Many of these advances will be beyond the reach of many uninsured and underinsured American women and children. We are here to renew our nation's efforts in women's health research. Yet, how a nation treats its children is an indelible index of its real moral practices. Today, there are at least 11 million children without health insurance.[1] They comprise one-fourth of the more than 41 million Americans who lack insurance. A sound body of evidence documents the inadequate health care received by uninsured families with children as compared to the insured.[2] Congress' action to remedy the problem has ambiguities and problems of its own.[3]

When one adds the underinsured and enrollees in Medicaid programs, almost 90 million Americans, more than one-third of the population, have inadequate preventive and primary care. It is unrealistic to expect that advances in diagnosis and treatment that are generated by women's health research and genetic research will benefit these persons, because most of them will be unaffordable. So, there is a great gap between the expectations that the health of all Americans will benefit from advances in women's health research and genetics and the reality. Recognition of this gap will cause more bitterness. Great bitterness already exists, because individuals and families can lose their life savings from a single, catastrophic illness or accident. Also, these insecurities are being exacerbated by aggressive competition by large for-profit managed care companies that underbid health insurance contracts with employers and then create allocation policies and financial incentives for physicians to acquiesce toward the least, rather than the best, that can be done for patients.[4]

The basic problems in health care reform are not basically economic. As a nation, we now spend one trillion dollars in the health sector, more than enough to afford adequate primary and preventive care. The problems lie in moral vision, mistrust of government as a partner in reform, and a badly unbalanced health policy. Permit me a few words on each of these causes.

What is the prevailing moral view of health care? Is it, as I and others who want reform see it, an obligation of society towards all its citizens? Or is it mainly understood as a commodity to be bought and sold in a free marketplace whose excesses are regulated by government? The business aspects of health care must be governed by its characteristics as a moral relationship, or else the whole enterprise suffers. Adequate health care is a basic social good necessary to enjoy other social goods — e.g., education, family life, work, etc. However, this is not the prevailing moral vision of health care that underlies U.S. health policy or its practices.

Moments of sobering reality have arrived for leaders in U.S. medicine and the nation's communities.[5] The professional integrity of clinicians has greatly diminished. Race and class divisions are starker in the nation's communities because the majority economic and political forces channel health care into three tiers for the poor, a slowly vanishing middle class, and the affluent.[6] Hopefully, the bitterness about health care inequities can be translated into politically effective action. Only a long-term commitment to reform will moderate and alter public opinion with a vision of adequate preventive and primary health care as social goods and a moral obligation of the state and national communities to which we belong as Americans.

Our nation's health policy is heavily one-sided. There is not enough money to afford both the array of intensive technological services whose imperatives so strongly drive the present system and a vastly improved preventive and primary care system. To remedy the structural imbalance of a wrong health policy requires correction of national priorities. Jacobs[7] diagnosed the major obstacle to health care reform as a national health care policy for a "supply state" that continually expands the supply of technically sophisticated health care to the detriment of attention to access to good preventive and primary care. Increasing genetic services (a good thing) will further add to the costs of technology. However, the policy results in deep political obstacles and fractured interest groups that provoke leadership elites to refuse to make access the priority and supply responsive to access. Compared with other advanced nations, the United States has both failed to create an adequate system of preventive and primary care or to provide access to adequate care within the existing system of health care. The structural incentives that promote the welfare of the "supply state" need to be radically altered to promote better access and supply of preventive and primary care services. This will require reengineering and downsizing a vast area of the health care sector heavily invested in acute care and intensive services. Long-term structural reforms guided by an access-guided health policy are needed.

Iglehart,[8] an astute observer of health care, described a "new era" of incrementalism after the failure of the Clinton health plan, i.e., modest reform efforts and managed care. Blendon, Brodie, and Benson[9] gleaned lessons from public opinion surveys about the failure of 1994. Although Americans wanted health care reform in 1993, they feared that the Clinton plan would limit choice of physicians and hurt them personally. Furthermore, Americans were deeply cynical about national government as an agent of change. Clearly, this trust must be rewon over the years, because there cannot be a national resolution without government as a partner and the ultimate arbiter of what constitutes adequate primary and preventive care.

In the interim, an incrementalist approach may be more cost effective and generate more public trust when done experimentally at the state and regional levels, where the word "community" has more meaning than in the context of one sweeping national strategy.

Inclusion of Women in Clinical Trials

The second priority is the one that originally brought us together. Progress has clearly been made in inclusion of women in clinical trials, but there are still great distances to travel. Congress and NIH guidelines now require evidence of such inclusion in NIH-funded trials.[10] ORWH's report on inclusion in extramural trials (April 11-12, 1996) does indeed reflect real progress in that 92 percent of grant applications satisfied the inclusion guidelines. However, an institute by institute comparison would help. FDA reports indicate progress in pharmaceutical trials on inclusion of women, but their data gathering is not coordinated with NIH. The two agencies pooling and analyzing data together would yield a much more informative picture.

Enhancing Biomedical Research Funding in an Era of Managed Health Care

None of this research can occur without financial support. Managed health care systems are not currently doing their part to support the costs of biomedical research. They are making profits but not reinvesting in the research sector. Academic medical centers are also suffering significant losses in research dollars due to this condition. Congress may want to remedy this deficit for tax measures on managed care systems to benefit research. Also, the national trust fund for medical research is an idea whose time is coming.

Reshaping a National Agenda for Women's Health Research — The Role of Gender-based Biology

The fourth priority is the development of the science base for women's health research. This means advancing the scientific study of gender differences in the pathophysiology, diagnosis, treatment, and prevention of human diseases, i.e., gender-based biology. Such studies focus on the biologically based differences between males and females over the whole range of issues that matter to scientific medicine. This concept is revolutionary in its impact on clinical medicine. Gender differences of significant clinical relevance have already been discovered in the immune system, susceptibility to lung cancer, use of pain-killing drugs, and treatment of angina. NIH and other federal science agencies should lead the way in creating this new knowledge base.

The last three priorities directly respond to Dr. Collins' talk.

Integrating Genetic Knowledge and Services into Mainstream Medicine

Prior to recent developments, genetics has been seen by most physicians as dealing with rare diseases addressed by clinical genetics and reproductive medicine. Now that the Genome Project is deciphering the genetics of common diseases like cancer, cardiovascular disease, diabetes, and neurodegenerative disorders, it has the attention of mainstream medicine. At my university in the past two years, new genetic clinics have opened in cancer, neurology, and cardiology. Vast changes will be needed to integrate this new knowledge and services into medicine, and it is impressive to see the National Cancer Institute moving rapidly in this direction. The task of educating U.S. physicians about the new genetics is formidable and exciting.

Removing Obstacles of "Genecity" (Fear of Genetic Information) and Fear of Discrimination (Insurance and Employment)

Many years ago, Alexander Capron coined "genecity" as a word to describe the reaction in many quarters of the public to advances in human genetics: fear, images of mad scientists and Nazi eugenics, and a sense (actually there since Darwin) that there were no longer any secrets or mystery about human beings. I am concerned that "genecity" also prevails among persons who need genetic services and among counselors who serve them, and in the warnings given by counselors that genetic information could be misused and be dangerous to a person's employment or insurance status. It is widely believed that individuals at higher genetic risk are also at high risk for denial of health or life insurance. The empirical evidence for genetic discrimination is sketchy at best. Two studies have been published that found some cases of self-reported genetic discrimination in insurance and employment. The respondents answered advertisements[11] or were members of genetic support groups.[12] Questions about bias and self-selection can be raised about these well-intentioned but limited samples.

Other data, collected by Dorothy Wertz in 1997,[13] indicate that the problem is not widespread if geneticists and physicians can be trusted as good observers. Questions on the incidence of genetic discrimination were included in a survey with 1,084 U.S. geneticist respondents. They had a median of 9 years experience and saw a median of six patients a week. They reported a total of about 550 individuals who were refused employment, let go from a job, or were refused life insurance on the basis of being a carrier or having a genetic predisposition. Further, a sample of 499 U.S. primary care physicians in the United States who see 100 to 150 patients per week and are likely to see their patients on an ongoing basis reported only a few instances of refusals of employment or health or life insurance. Wertz's data, also a form of self-reporting, leaves the impression that there are some cases but not many.

Looking at the data, my impression is that fear of genetic discrimination is more a function of the insecurity and uncertainty of one's health insurance status in a nation that permits the inequalities discussed above under the first priority than it is of great statistical significance. Nonetheless, the President and the Congress are determined to use the law to prevent genetic discrimination, no matter the incidence. The Kennedy-Kassebaum bill in 1996 denied health insurers from discrimination based on genetic reasons when enrollees are moving from one group plan to another. New legislation will be aimed to prevent such discrimination against those with individual insurance.[14] Predictably, each state and the Federal Government will legislate against such uses of genetic information. Perhaps impetus will be brought by such actions to universal health coverage, since the public will be more aware that each person's genes are different but that all persons are more or less susceptible to common diseases due to their inheritance.

The last priority may be one of the hardest to embrace because of its controversial nature, but it is necessary to close the largest gap of all in genetics, i.e., the one between diagnosis and treatment.

Confronting Controversial but Vital Research (e.g., human embryo (stem cells) and fetal research) for Understanding the Pathophysiology of Genetic Diseases and Bridging the Gap between Diagnosis and Treatment of Genetic Disorders by Gene Therapy and Other Treatments

My introductory point is one I know that Dr. Collins will affirm. Collectively, there should be more fear of and action about the growing gap between diagnosis and treatment than about genetic discrimination. However, Congress and the President are going in the opposite direction, in my view, on controversial research policy vital to closing this gap. I am speaking about embryo research and the tortured history of U.S. policy on fetal research.

Congress has banned any federal support of investigative human embryo research, even if the embryos are "spares" that are not transferred after IVF procedures. Federal funds cannot be used for research in which a human embryo may be "destroyed, discarded, or knowingly subjected to risk of injury or death." The ban overrides a majority view in the final report of an expert NIH Human Embryo Research Panel of 1994,[15] which approved fertilizing ova for research purposes under certain conditions. The report was endorsed unanimously by the Advisory Committee to the Director of NIH, Dr. Harold Varmus. A few hours later, President Clinton issued a statement announcing that he did "not believe that federal funds should be used to support the creation of human embryos for research purposes,"[16] and that he had directed NIH not to support such research. It is likely that Mr. Clinton, not unlike many thoughtful persons, opposed creation of embryos for research on the basis of a moral intuition that it is simply wrong to do so. Such a position was taken in an editorial in the *Washington Post*[17] in early October of that year. It alerted the Administration to embryo research prior to the 1994 elections. It criticized the recommendation of the Panel to permit fertilizing ova for research only. The writer was "deeply alarmed by . . . scientists purposely causing conceptions entirely divorced from the purpose of reproduction." The writer, like President Clinton in his statement, gave no attention whatsoever to the scientific and clinical losses in forgoing this option. Possibly, the Post editorialist and President Clinton would respond differently if there was more evidence assembled as to the benefits. The NIH Human Embryo Research Panel report lists thirteen areas of knowledge with clinical benefits ranging from immediate to long range. Each one directly affects women's health.

Providing Basic Knowledge about Normal Early Human Development

A serious collision has occurred between progress in the federally funded Human Genome Project, the hope of treating genetic disorders, and the barriers to federal support of embryo and fetal research. The basic social problem with the Human Genome Project is that the power to diagnose is disproportionate to the power to treat genetic diseases. The power to diagnose virtually every genetic disorder in utero and after birth is vastly eclipsing the power to treat. Abortion or voluntary sterilization are the two major ways to prevent genetic disease. Blocking embryo research prevents several alternatives to selective abortion as a means of prevention. It is essentially cruel and unfair to parents at higher genetic risk for Congress to block progress in embryo research and reduce the chances of using two options to avoid genetic risks: 1) preimplantation genetic diagnosis and 2) early embryo or fetal therapy. How can in utero gene therapy succeed without embryo research?

Basic studies of pathophysiology and gene expression in embryos are clearly needed for human gene therapy, whether attempted in utero or in the living child or adult. The present effect of the stalemate in the United States on embryo research is to infringe on scientific freedom even to study the pathogenesis of genetic diseases in the human embryo. NIH's role in embryo research ought to flow from this imperativeness. There are sound internal reasons for doing so. Stuart Orkin and Arno Motulsky were commissioned by the Director, NIH, to report on NIH's investment in human gene therapy. Their 1995 report[18] strongly recommended basic studies of pathogenesis and pathophysiology of genetic disorders. Such studies must eventually be done in the embryos of couples at higher risk for genetic disorders, in order to understand the molecular onset of such disorders. It is important that the public and Congress understand why "spare" embryos will not provide answers to these questions. President Clinton, unlike Congress, favors research with unused "spare" embryos if donated voluntarily for research by a couple in treatment for infertility by IVF. However, "spare" embryos will not answer questions about genomic imprinting or gene expression for specific diseases. Specific embryos from couples at higher genetic risk must be recruited for such research. NIH has funded no embryo research in light of the Congressional ban.

This public policy and the search for sounder scientific foundations for human gene therapy have already collided, but it is doubtful that the American public or Congress is truly aware of the consequences. This situation also defeats the sound science already required as NIH funds experiments in human gene therapy and anticipates funding of in utero stem cell transplants or fetal gene therapy. Do we know the natural history of any genetic disease if we are ignorant of how it begins or if it begins in the embryo? If our scientific knowledge is incomplete, our ability to do therapy is thereby limited, as long as we do not violate significant ethical principles or norms in carrying out scientific studies. I appeal to Dr. Collins and to other NIH leaders to make the need for embryo research known to Congress and to take the lead in educating the nation on the issues.

REFERENCES

1 Bureau of the Census, Bennefield R. Health insurance coverage 1996. Current population reports. Series P-60. No. 199. Washington, D.C.: Government Printing Office, 1997.

2 Newacheck PW, et al. Health insurance and access to primary care for children. *N Engl J Med* 1998;338:513-9.

3 Budetti PP. Health insurance for children — a model for incremental health reform. *N Engl J Med* 1998;338:541-2.

4 Clancy CM, Brody H. Managed care: Jekyll or Hyde? *J Am Med Asso* 1995;273:338-9.

5 Kassirer JP. Managed care and the morality of the marketplace, *N Engl J Med* 1995;333:50-52.

6 Reinhardt U. Wanted: a clearly articulated social ethic for American health care. *JAMA* 1997;278:1446-7.

7 Jacobs LR. Politics of America's supply state. *Health Affairs* 1995;14:143-57.

8 Iglehart JK. From the editor. *Health Affairs* 1995; 14:5-6.

9 Blendon RJ, Brodie M, Benson J. What happened to support for the Clinton plan? *Health Affairs* 1995;14:7-23.

10 National Institutes of Health Revitalization Act of 1993 (Public Law 103-43), June 10, 1993.

11 Billings PR, et al. *Am J Hum Gen* 1992;50:47679.

12 Lapham EV, et al. Genetic discrimination: perspectives of consumers. *Science* 1996;274:621-3.

13 Wertz, D. 1997.

14 Weiss R. Clinton to support legislation guarding against gene-test bias. *Washington Post*, June 14, 1997, A8.

15 National Institutes of Health. Final Report of the Human Embryo Research Panel, September 27, 1994.

16 Marshall E. Human embryo research. Clinton rules out some studies. *Science* 1994;266:1634-1635.

17 *Washington Post*. Embryo research: drawing the line. Editorial, October 2, 1994, A 21.

18 Orkin SH, Motulsky, AG. Report and recommendations of the panel to assess the NIH investment in research on gene therapy. National Institutes of Health, Dec. 7, 1995.

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LEGAL AND ETHICAL ISSUES*

We must make a distinction between screening and testing. The term “testing” in genetics is often used to cover both issues. For ethical reasons, however, we should recognize that testing is done in a clinic, for a family with a reason or, in some cases, an age-related reason for doing the evaluation. The patients are assured of getting either a positive or negative result and receive some information about the importance of the tests. With screening, however, individuals are tested without any prior reason for wanting the testing. Ethically, informed consent becomes an important issue and a critical part of the process.

In 1975, a National Academy of Sciences Committee, and in 1995, an Institute of Medicine Committee, determined four reasons for genetic screening: management of disease, reproductive information, to prevent a disease that has an effective treatment, and to conduct research.

A genetic task force at the Hastings Center developed guidelines for setting up a screening program. When one is considering setting up a screening program, I recommend following these guidelines. Members of the community should play a role in setting up the program, that is, women in general, not just women who are highly educated or especially interested. Representatives of all groups should be involved. Informed consent should be a critical part of any program. The diagnosis of the screened-for disease must be accurate and unambiguous. For example, the diagnosis for cystic fibrosis (CF) is ambiguous because some 15 percent of people will not be certain if they get a negative test result whether they, in fact, have a gene that has not yet been identified. The test is much better than it used to be, but it is still, by some criteria, not acceptable.

Professional genetic counseling is a critical part of any medical or genetic screening program. We have a shortage of genetic counselors. If we were to start nationwide breast cancer screening or CF screening, we would have a problem getting well-trained people to do the proper counseling. Test results should be kept confidential.

I think that the biggest problem in genetic testing of women is stigmatization. When you are labeled as having a mutant gene, whether it is a disease gene, a disease susceptibility gene, or just being a carrier for a gene, you have a mark. People often tend to lie about their genetic status. In screening an entire village to reduce the frequency of sickle cell disease, researchers found that counseling people not to have children with a man or woman who had the same sickle cell gene had no effect whatsoever because the people simply lied about their genetic status. The people understood perfectly well what that meant, but if they fell in love with somebody, the rules changed. Of course, we know human behavior is very unpredictable.

Genetic testing raises the specter of stigmatization. One program, Tay-Sachs testing, followed the guidelines on ethical and legal issues suggested by the Hastings Task Force, and sickle cell testing program did not. The sickle cell test was a disaster. It produced all kinds of problems that took years to remedy. The Tay-Sachs program, however, has been a resounding success, so much so that we are now seeing Tay-Sachs disease predominantly in populations of non-Jewish individuals rather than among Jewish populations.

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* Presentation edited from the meeting transcript.

HEART DISEASE RESEARCH IN WOMEN: A LOOK BACK AND A VIEW TO THE FUTURE

Claude Lenfant, M.D.
Director, National Heart, Lung, and Blood Institute

Whenever the subject of women's health issues comes up, heart disease is one of the first topics. In a way it should be, considering, it is likely that one-third of women will die from heart disease. For nearly a century, heart disease has been the leading cause of death in women.

There is a widespread perception that the research has not done the best it could by women, particularly in the area of heart disease. The National Hearth, Lung, and Blood Institute is celebrating its 50th anniversary, so I hope you will all come up with exciting recommendations for the next half century of our existence.

Two recurring questions have been raised about our historical efforts: Has research on heart disease neglected women? Has research on heart disease benefitted women? With regard to the first question, there are two answers, but I would like to provide some evidence that no should be given greater weight.

The National Heart, Lung, and Blood Institute was founded in 1948 when the most pressing health issue was the soaring death rate from heart disease. There was some increase in cancer and stroke, but certainly not to the extent of what we saw for heart disease. As a consequence, the Framingham Heart Study was launched, which is a project of the National Heart, Lung, and Blood Institute. It was, in effect, the first major population-based study of heart disease in the United States and probably in the whole world. From its inception, the study included even more women than men, and although it is 50 years old, it has contributed enormously to our understanding of the causes of heart disease in both women and men.

In the early years of the study, however, most of the information we gleaned about heart disease and risk were more pertinent to men because women in the middle-age cohort were not developing heart disease at anything near the rate of men. It would be number of years before enough cases occurred in women for us to make a connection between risk factors and disease.

As we came to the end of the second decade of operation, we had enough information to undertake clinical trials of promising interventions to prevent and treat heart disease. I want to spend a bit of time on the subject because concerns about the systemic exclusion of women in all clinical trials have been expressed repeatedly.

The Institute launched its first clinical trial in 1965, and since then reported 59 major clinical trials of cardiovascular disease in adults (major means a population of at least 400). Forty-one of these clinical trials included both men and women, four included only men, and 14 included only women. This looks like a reasonable track record when it comes to interest in women, but the skeptics might argue that the large number of trials conducted exclusively in women represents a recent attempt to play catch-up. In fact, that is true — all 14 trials were started within the past 10 years.

So let us turn to the earlier clinical trials and, specifically, to the four that did not include any women. Our very first clinical trial, the Coronary Drug Project, which was initiated in 1965, was a very interesting trial for two reasons: it attempted to reduce coronary risk in men by administering among other things, estrogen; and it was a failure. This put a very serious damper on clinical trials for the next few years. In fact, it took 6 years for the next clinical trial to be initiated. The very successful Hypertension Detention and Follow-up Program was launched and included 11,000 subjects, of whom more than 5,000 were women. Since then we have conducted an additional

11 major clinical trials on the treatment and prevention of hypertension, all of which have included a substantial number of women. The latest in this long series of clinical trials is the Antihypertension and Lipid-lowering Treatments to Prevent Heart Attack trials, which is recruiting 18,000 women from a total of 40,000 patients.

Following the HDFP, three major trials focused exclusively on men: the Multiple Risk Factor Intervention Trial (MRFIT), the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT), and then the Physician Health Study. How and why does that happen? Why were women excluded?

There are two reasons for focusing research on one population group to the exclusion of another. The first one is public health concerns and the other one is pragmatic considerations. Both MRFIT and CPPT fall in the first category. At the time of their inception, the heart disease epidemic was at its peak (1972-1973), and the segment of the population most affected by this epidemic were men. Overall, heart disease death rates in men and women were not too dissimilar during the first two decades of the century, but from the 1920s onward rates in men soared.

In particular, the devastating effect of coronary heart disease on men in their prime working years was viewed as a national emergency. In 1973, about four out of five deaths that occurred in people under age 55, and three out of four deaths in people age 55 to 64, were in men. Basically, at that time the major burden of premature deaths from chronic heart disease was really in men, and this burden is still borne by men. The *Reader's Digest* article from 1967 described the problems of a 45-year-old Joe but never mentioned that Josephine had a heart too. The message for middle-aged men was clear. Coronary heart disease is going to kill you. The message to women at that time was that coronary heart disease can make you a widow, and health-related counseling was focused on how to avoid that fate. Our initial attempts to reduce risk of premature coronary heart disease focused on the population most at risk, middle-aged men.

Another reason for focusing trials on a particular group are pragmatic considerations with respect to the feasibility, cost, and timing of the trial. A case in point is the Physicians' Health Study that began in 1981, and it enrolled more than 22,000 healthy physicians age 40 to 84 years. The study population was chosen because it was thought that physicians would be cooperative, compliant, reliable subjects, capable of providing accurate information about health studies. Because of the insufficient number of women physicians in the United States at that time, and the lower incidence of coronary events in women, the study was designed to include only men. It should be noted that to provide a study population with a sufficient number, 261,248 men had to be screened. Had it been performed in women, the number of screenings would have had to have been much larger, probably four times as large.

In fact, if you look at the Women's Health Study that we began in 1991, the number of women screened was 1.7 million women health professionals and 39,876 enrolled. The same pragmatic considerations about the feasibility, cost, and timing of clinical trials still apply today and are reflected in the many studies of hormone replacement therapy to prevent health disease in postmenopausal women. Such considerations have a particular influence on the choice of endpoints to be measured.

For example, the PEPI trial, initiated in 1987, sought to determine the influence of hormone replacement therapy on coronary heart disease risk factors, rather than on clinical coronary events. Given this choice of endpoints, it was possible to do the study in a cohort of only 875 women and also to answer this question in a short period of time (followup was only 3 years). The results, published in 1995, have provided very valuable information to women and their physicians who must make decisions today about whether or not to use hormone replacement therapy. However, they cannot tell us whether demonstrated improvements in risk factors will actually translate into an improvement in risk of a coronary event.

At the opposite side of the spectrum is the Women's Health Initiative, begun in 1991 and recently transferred to the National Heart, Lung, and Blood Institute. Its trials are designed to look at clinical coronary endpoints — for example, heart attack, death — and provide a definitive answer on whether hormone replacement therapy does, in fact, make for a healthier heart. Unfortunately, such an answer comes at a very high price. The Women's Health Initiative will have to recruit 64,500 women and follow them for as much as 12 years, with no results really coming through until a few years into the next century.

However, let me assure you that we are not just sitting by waiting for the Women's Health Initiative to come up with its results. We have a number of clinical trials under way using angiographic measurements of the coronary arteries to determine the effect of hormone replacement therapy on coronary disease, sometimes in combination with other approaches such as antioxidant vitamins or lipid-lowering drugs. With this approach, it is unnecessary to include a large number of women for an extended period of time.

I hope that the foregoing information has shed light on our history of including women in studies of heart disease. In the past we have taken advantage of many opportunities to do so, but we have also missed some opportunities for reasons that made sense at the time but admittedly may not seem persuasive to you. But today I believe we are moving forward with commitment, purpose, and speed to address these issues.

Against this backdrop, let me turn briefly to our second question: Has our research on heart disease research benefited women? Once again I will give two answers — a big yes and a cautionary no. The decline that we have witnessed in heart disease has been spectacular both in men and in women, but what the rate today is in men is the same that it was at the beginning of the century. In contrast, the rate for women is much lower, actually 37 percent lower than it was in 1900.

The longevity for both men and women increased quite remarkably in this country. In fact, between the years 1965 and 1993, we can attribute the increase in life expectancy to a 44 percent decline in coronary heart disease in both men and women; 16 percent of this increasing longevity is due to the decrease in death rate from stroke. In looking at this, we can demonstrate that about 60 percent of the increasing longevity that we have seen in this country during the last 30 years is due to a decline in the death rate from cardiovascular disease. With regard to change in coronary heart disease death rates, when we began many of the clinical trials we mentioned above, you can see that these rates have declined remarkably, particularly in the younger age groups and that men and women have benefited from this trend to approximately the same extent.

My cautionary note stems from the observation that while calling for an ever increasing share of research attention, women are not taking full advantage of heart-saving information that we already posses. Risk factors for heart disease in women have been known for years, and we made an effort to educate the public about them. However, the current prevalence is higher actually in some cases than in men, such as for women with obesity and a lack of physical activities.

Our enormously popular *Healthy Heart Handbook for Women* has appeared in three different versions over the last 10 years, but its message that heart disease is every women's concern has not yet captured the attention of women. Indeed regarding perception and reactions of women in the face of heart disease, the results of a survey published in *USA Today* revealed quite clearly that women's perception of heart disease as a health risk far underestimates the true risk. My point is that we can put millions of dollars into research, but the yield will be low if women and their physicians fail to use the knowledge to improve their health.

In the area of hypertension our record of including women in critical trials has been impeccable, and we continue to generate new evidence of the benefits of hypertension control, especially in the elderly. Data from the Systolic Hypertension in the Elderly Trial, which included 1,359 women and analyzed its findings for women and men separately, clearly illustrate that treatment of isolated systolic hypertension greatly reduces the risk of heart failure. We are focusing particular attention on women because they constitute 61 percent of the 24 million Americans over the age of 70.

To this end we have joined forces with the Alliance on Aging in a campaign that is called "Controlling High Blood Pressure in Older Women, You Have What it Takes." Indeed, that is exclusively under the control of women. We know what to do; the physician knows what to do. The issue is whether women are going to take advantage of what we know. In individuals who have a relatively normal blood cholesterol, there is a decrease in the risk of clinical events of 54 percent in women as compared to 34 percent in men.

Our 50th anniversary logo represents people doing science to improve the health of people. By that we mean all people, and I can assure you that we will carry this philosophy with us into the future. My last thought is this: "There is more future ahead of us than past behind us."

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Harvard Medical School

RESEARCH ON WOMEN: AN INVESTIGATOR'S VIEW

We all know that the need for a continued and expanded commitment to a broad range of research issues in women is ever more important and timely. However, as investigators, I think it is important for us to also remember that we are increasingly coming to know very deeply that the need for more research in women on an ever expanding agenda of issues is urgent. Regardless of the specific issues that we are interested in and that we are doing research on, the planning and the conduct of such studies must always be driven by the commitment of providing to women the fruits of the best high quality science that can be done to answer the question.

Research on women's health requires well-designed studies of sufficient sample size to answer important and timely questions in women definitively. These investigations in women without question are likely to have unique and important scientific and logistic problems that are different from doing trials or studies in men. These simply have got to be recognized and addressed by whatever means it is possible for us to develop. The real bottom line is that what we want to do, the goal of all of the studies that we do or that we think are important, is to provide either a definitive, positive result on which individual clinical decisions and public health recommendations can be reliably based or provide us with a reliable, definitive no result, which will allow resources to be safely redirected into other promising areas of research. We owe not just research to women, but the clarity of an answer to women as well as to the community.

The fact is that the underlying goal of all of our research has to be to provide an answer. In many situations, it has been suggested or it is logistically easier to simply add a few women into a study. The numbers have not been calculated to be sufficient to add important information to the totality of evidence on the scientific question in women, but rather to just include women. The intent may be good, but this unfortunately can and has led to misleading conclusions on scientific questions in women and could set us back in terms of our knowledge.

Some of my research has related to evaluating the role of low dose aspirin in the primary prevention of cardiovascular disease and cancer in healthy women as well as men. In cardiovascular disease, our clinical trial was to answer the question in healthy women, which represented the last step in a process where the role of aspirin has been appropriately evaluated first in women who have a history of cardiovascular disease. In the early 1980s, if you looked at the Food and Drug Administration's prescription labeling or professional labeling of aspirin, it approved labeling indications for aspirin for patients, men and women, with a prior heart attack; patients, men and women, who have unstable angina or chest pain; and men with a history of transient ischemic attacks (TIAs), which are the pre-strokes of short duration. The problem is that if you look at a recent *Physician's Desk Reference*, it will say that aspirin works to prevent TIAs in men, but it does not work to prevent TIAs in women.

When you actually went and you looked at the data, you saw something very different. In fact, this was the study on which it was based, the Canadian study of TIAs. In men there was quite a clear benefit of 47 percent, which was statistically significant, but there were 406 men and 179 women in the trial. We had a relative risk that was not indicative of benefit and was not statistically significant, but the thing that we all look at first is the confidence interval, which clearly showed that these data were compatible with the benefit, but could not demonstrate a benefit due to the small size.

Over the last few years we have formed an aspirin strategy group, which has worked with the investigators in Oxford, England, to look at the entire world literature on this question. Seventeen years after FDA first made their ruling, it has been changed. In 1997, the advisory committees to FDA have voted to approve expansion of the professional labeling for aspirin to include women as well as men with prior TIAs. For 17 years, we were under the belief that it did not work in women, whereas the true interpretation of the data was that there had not been sufficient numbers of women for us to answer that question definitively.

In 1982, the Physician's Health Study wanted to answer a very simple question. If we take an aspirin tablet every other day, will it reduce our risk of having our first heart attack? We wanted to do it in a very cost-effective way because we knew the sample size would be very large. We wanted to do this study entirely by mail, and we would, in fact, never see the participants in the trial. Thus, we wanted to do it in health professionals, and in particular, we chose to do it in physicians because they would be aware of possible side effects and be able to give us their health history with a high degree of confidence.

When we went to design the study, we had no intention of doing it in men, but we wanted to do it in physicians. However, only 1 out of every 10 physicians over the age of 40 in the United States was a women in 1982. Women have lower risks of heart disease than men at the same age. Therefore, we calculated they would have one-third the number of coronary events by the age of 60, as the same size sample of men. When we looked at what participants were available to us, we would have been able to randomize 22,000 men and 2,200 women, whose event rate would have only been a fraction of that in men. If we did not have enough women in the study, we would never be able to test the hypothesis that aspirin was effective in the primary prevention of cardiovascular disease in women. We would never be able to evaluate the question, is the effect of aspirin on cardiovascular disease different for men and for women?

We put the grant into NIH, and the Review Committee said to put the 2,200 women in the study. What we did was actually go back to NIH and say we really wanted to talk to them about this because we really envisioned a very important thing happening. In particular, at the end of the study, if we did see a benefit in men, then we would know what to recommend, but if we saw no statistical benefit in women, nobody was going to know whether it was not there because we did not have the power to do it or because it does not work the same in women. We wanted to do two trials, one in a sufficient number of women and one in a sufficient number of men.

Dr. Claude Lenfant, the National Cancer Institute, and NIH supported us in this and, in particular, funded us to do the Women's Health Study (on which I am a principal investigator), which is looking at the benefits and risks of low dose aspirin and vitamin E for the primary prevention of cardiovascular disease and cancer among 40,000 U.S. female health professionals. This is a trial done by academics, funded by NIH, and supported by the drug companies that are providing the drugs to us.

We sent letters to 1.7 million U.S. female health professionals throughout the United States, and 453,000 of them returned a questionnaire to us. We have 39,876 randomized into the trial with 79 percent of them with at least 3 years of followup and with 70 percent of them having provided, by mail again, a blood specimen so that we have the opportunity to bank it as a future resource. This is a wide variety of female health professionals from dentists to dieticians to nurses, physical therapists, physicians, veterinarians; a whole host of people who allow us to have a very diverse group in the study.

It was important to note that the study in men required a sample size of 20,000 men over the age of 40 and the analogous study in women required 40,000 over the age of 45 because women have a lower risk of heart disease. The cost was the same, $80 per participant per year, but the total cost of the Women's Health Study was much more because of the increased the sample size.

It may be that lower numbers of events for women for many outcomes of interest, such as cardiovascular disease, require that the trials will have a bigger sample size and thus a bigger cost. Some trials will have more logistical difficulties to overcome. However, if they are well designed and conducted, they will allow us to get direct inferences in women, rather than generalizing from research in men. We will be able to make clinical recommendations for women from women.

Richard Klausner, M.D.
Director, National Cancer Institute

THE CANCER PROGRAM AT THE END OF THE 20th CENTURY*

I wanted to give you a brief slice into our vision of where we are in our struggle against cancer as we end this century, a century of remarkable discovery. Some real progress has been made, but we continue to have great frustration with the enormous burden of these diseases. A remarkable thing has happened in the science of studying cancer, and that is as we end the 20th century, many years, decades, centuries of wondering and arguing about the nature of cancer is reaching some critical level of resolution. We know what cancer is. Cancer is a genetic disease generally, not an inherited disease, but a genetic disease.

We know that all cancers arise extremely gradually. The moment of diagnosis is an extraordinary event in an individual's life, but it is in some ways a random moment interposed upon an extremely long process. It is a process whereby one of the hundreds of trillions of cells within the human body that we have throughout our lifetime has accumulated a set of changes or instructions that determines the behavior of the genes. That is why it is, we know it to be, a genetic disease.

It results in the misbehavior of cells, which we clinically call cancer. It is a result of an accumulation over years to decades of probably small — although we still do not know the exact number — critical changes in the instructions that guide the behavior of cells. That is why they misbehave. Now, that simple statement is important and defines our central hunt in cancer biology. It will define profound alterations in our approaches to preventing, to detecting, to finally correctly diagnosing these diseases and determining treatment.

Why is that? If we knew how to read and interpret the altered instructions and the altered machinery that those instructions direct, we believe we would be able to move from a period of extraordinarily and remarkably successful, highly practiced therapeutic empiricism to a new period of design and predictability. This is very much the way we looked into the blueprint of HIV, saw a machine, and pretty rapidly were able to design something directed not towards the phenomenology of a viral infection but to its precise machinery. It is not the answer, but it is a real step in the right direction.

Knowing that there are a set of genetic changes that define the behavior and the development of any cancer and with the ability to read and interpret all of those changes opens up the possibility of removing an enormous amount of the mystery of these diseases and to finally think about designing interventions that will define cancer therapies in the future. The gradual accumulation of changes tells us something about the problematic definition of these diseases.

When does cancer begin? When do we call it a disease? When do we treat it? We know that these diseases emerge from decades of changes, of states that are precancer. Pathologists have been looking at some of these changes. These precancerous changes represent cells that have accumulated some but not all of the altered instructions that ultimately result in a clinically diagnosed disease. The ability to read again and to detect those earlier changes provide a new way to think about prevention, to think about cancer as a process and not an event, to recognize that if cancer emerges over decades with partial changes, those alterations ought to be the diseases we learn or the pre-diseases that we learn to intervene.

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* Presentation edited from the meeting transcript.

There is, in fact, a continuum of treating the initial change to intermediate changes we need to learn and to direct our attention more and more on not treating cancer but precancer. The line between prevention and treatment will get dramatically blurred over the next few years. We need to make sure that artificial distinctions defined by where you get funded or how you identify yourself do not drive our view of the world. What drives our view of the world is the disease and the individuals who are susceptible and who have these diseases.

Our ability to identify cancer allows us new opportunities in early detection. Most of our early detection is based upon waiting until there are enormous numbers of cancer cells so that we can see a physical mass or that we can see the effect eroding into a blood vessel. There really is the possibility that we now know how to systematically search for all possible molecular markers and to ask the question once and for all, are there valid markers for the development, progression, and existence of cancer.

This begins with the cancer cell and our knowledge about the cancer cell. We want to understand, of course, what causes cancer. We can begin to see the progression of changes in a cell, the multiple inputs that determine the likeliness that there are changes in our DNA, and the likeliness that we allow those changes to survive in the population of cells. This is where we begin to get a sense for external and modifiable inputs in effectors of cancer.

We know that the vast majority of cancers are due to potentially modifiable external factors; we know that from epidemiology, from migration studies, etc. However, identifying those factors is quite difficult. The causes of these changes in our genetic instructions that accumulate in the life of a cell and will become cancer include in a small percentage of cases an inherited defect, an inherited alteration. What those alterations are represent the fact that some fraction of individuals are born with one of those changes that are going to have to be accumulated in anyone that gets cancer. So the need to probablistically accumulate 5, 10, or 15 changes is altered because an individual already starts with one of those changes, giving them a predisposition.

I emphasize that there is no such thing as a cancer gene. Our language is all wrong, and it is dangerous. We talk about ethnic genes, which is a disaster. We talk about cancer genes when what we are talking about is identifying a gene whose normal function is to protect us from cancer. We need to be careful as we move into this genetic age that we understand genetics and use language carefully that communicates correctly the issue of risks and not predeterminism. We have the opportunity with genetics once and for all to end the misconceptions about the genetic bases of race and ethnicity that drive so much that has been misused throughout history, if we use our language carefully and our concepts correctly.

Cancer genetics is inherited differences between people that alter their risk of cancer. It does not mean people are predetermined to get cancer, and it does not mean that those with altered risk are not, in themselves, profoundly modifiable. There are other causes of cancer, infectious causes. Only in the last 10 years have we identified a virus, a group of viruses, that cause one of the most common cancers in women in the world and that is cervical cancer. Human papilloma virus and a series of subtypes we now know are the cause of at least 90 percent of cervical cancer. Knowing that is incredibly important. It allows us to modify our approach to what may be overarching detection, that is the Pap smear, where we recognize abnormalities, but we do not know which of those abnormalities are going to lead to cancer. This is a problem with mammography. It is a problem with PSA. We need to be able to not only have sensitive detection but detections that we can interpret what we are detecting, that they are predictive.

Knowing that certain subtypes of human papilloma virus cause cervical cancer will help us make decisions about how to treat women with abnormalities on Pap smears. Perhaps more importantly, we are moving quickly to try to create a vaccine against a collection of these subtypes, and we hope that within 6 years, we will move through NCI-sponsored phase 3 trials of polyvalent vaccines, the first vaccine specifically developed to prevent cancer. Actually, the hepatitis vaccine also prevents cancer, but it was not developed for that. This is an extremely important program, especially for the developing world.

We assume carcinogens cause many of the changes. What are carcinogens? They range anywhere from oxygen to iron that we all need, to contaminants from the environment, to tobacco smoke. They work through the crucible of these genes. They work because they alter genes and for the likeliness that genetic alterations are corrected. We must remember that every time a cell divides, it has to copy three billion different bases of DNA in several hours; that copying machine, which is spectacular, makes a few hundred mistakes every time. So, it is 99.9999 percent good, which is incredibly good, but it is not perfect. The fundamental aspects of life itself predispose us to cancer, but it is dramatically changed by exposure to environmental factors that damage DNA, directly or indirectly.

Modifying whether an altered cell becomes a cancer is an extremely important part of understanding cancer risks. Diet, which may include carcinogens and anti-carcinogens, may modify whether an altered cell grows and is able to develop into a cancer. There is no question that hormones play a central role in the risk for and development of important cancers, especially breast and reproductive cancers. This is going to be an area of extraordinary complexity and challenge. Estrogens present powerful modulators that beckon us to the possibility of effective interventions and preventions but raise issues that are fought with enormous complexity.

Estrogens represent complex collections of compounds, and they work through at least two receptors, each of which are modulated by a collection of genes that only now are being identified. We know that suddenly altering the estrogen molecule can produce dramatic changes in the effects of the estrogen. This complexity of estrogen biology raises the possibility of the ability to design extremely specific estrogen response modifiers, but what if we find that specific anti-estrogens reduce, possibly dramatically, the risk for example of breast cancer? How are we going to deal with that? Who in our society perceives themselves to be at increased risk of breast cancer? What level of increased risk results in recommendations or decisions by healthy women to intervene in hormonal pathways? What is an acceptable risk? How should a woman go about determining and evaluating that?

Clearly the benefits of an intervention must be weighed versus the risk. It is clear that with this new understanding of estrogen biology, the ability to at least modulate risks by more precise design of these interventions is possible. However, the challenge of hormonal manipulation of healthy individuals to reduce the probability of disease is something we are going to be struggling with over the next several years.

Other areas such as exercise, I do not have time to comment on. All of the factors that I have talked to you about, carcinogens, genetic susceptibilities, viruses, hormones, diet, are themselves filtered through other genes that determine individual variation, how they metabolize hormones, metabolize carcinogens, repair DNA, and on and on. We are only beginning to get a glimpse at how we are going to rethink the area of genetics, not by thinking about these rare and Mendelian inherited or high penetrance predisposition genes, but, in fact, it is the enormous variability of each one carrying about three million variations.

There is overwhelmingly more variation between individuals, other than identical twins, within any historically, culturally, sociologically, or superficially defined ethnic or racial group than there are between any groups in the entire human population. It is these subtle variations that will be the nature of cancer genetics.

It is important because we struggle and will continue to struggle to identify causes of disease, causes of cancer. We use epidemiology, but epidemiology gives us associations, often misleading associations, often interesting surrogates for real associations. It does not give us cause and effect. It is knowing cause and effect that allows us to predictably go back and alter risks. We hope that the marriage of classic epidemiology with understanding variations among individuals in terms of their interaction with their environment at large, behavior, etc., and the ability to use, especially in cancer, these genetic changes as a type of environmental dosimetry will hopefully clarify some of the elusive environmental, hormonal, behavioral causes of cancer.

How we are going to go about capturing all of this information is an enormous challenge. Cancer is an enormous puzzle. We are trying to put together a jigsaw puzzle, not knowing how many pieces are missing, not knowing how important the pieces are that we have, not knowing how important the pieces are that we are missing. In terms of the biologic pieces of cancer, we now know we ought to be able to get all of them, once and for all, to make sure we are playing with a full deck.

We have established an infrastructure called the Cancer Genome Anatomy Project, which is a web-based discovery structure, whose goal it is within the next few years to attempt to discover all genes that are expressed and altered between normal cells, premalignant cells, and malignant cells. We have finished moving through prostate cancer. We are now doing breast cancer, and for the first time, we are getting a complete description of all of the genes expressed in breast epithelial cells, in ductal epithelial cells, premalignant lesions, and malignancies. Our goal is to do one to two million sequences. It immediately goes onto a public database and provides a means of discovery.

As we do this, we begin to get hints at identifying the molecular tags that actually characterize tumors. From prostate, where we have been sequencing through normal prostate epithelium, something that had never been done before, we can then ask the question do we see any genes that are only expressed in malignancy. It turns out the answer is yes, and we see that the first line that is expressed in normal premalignant and less so in malignant is prostate-specific antigen. That is what is used as a screening test for prostate cancer, and it is not specific for prostate cancer at all. However, in this genome anatomy project, we are beginning to discover genes that appear to be only expressed as a function of the abnormal behavior of cells.

We know that we have been incorrectly diagnosing cancer. Children with neuroblastoma, when you treat these children the same, about 60 percent of them survive and actually are cured. Sixty percent — we accept that in oncology. We accept the stochastic nature of the roll of the dice of life, but it is not true because we are treating different diseases. These are distinct molecular diseases. They look the same under the microscope, but we should no more expect cancer to be defined by what it looks like under the microscope.

In early breast cancer, we know that some fraction of women with early breast cancer will recur regardless of the treatment, but who? We will have to see if it holds up when we look at some molecular markers, and we see in these molecular markers that women by all other criteria we predicted the same outcome. We can see a dramatically different outcome for women with a certain molecular type of breast cancer versus the other. Modern medicine is based upon correct diagnosis. If we cannot correctly diagnose a disease, we are not going to correctly choose treatments.

Cancer, in terms of its relative toll on the population, has grown. In 1973, about 17 percent of deaths were due to cancer. In 1994, it was up to about 23 or 24 percent.

How are we doing? Are we making any progress? Mortality rates do appear to finally be falling. Sometime around 1990, when we look at overall age-adjusted mortality, a figure that had been climbing throughout this century since the early 1930s when we started following these numbers finally appeared to peak and now is falling. It is falling at what appears to be a significant rate.

Of course, this is lumping all cancers together, and they are different diseases. In fact, to understand where we are going with cancer, we need to look at different diseases and in different individual populations. This overwhelmingly is the epidemic of cancer. For lung and bronchial cancer, we see the ravage of the epidemic of smoking, first taken up by men and then by women. The increase in the mortality rate was enormous in a disease that was rare in 1940. We have done not very well at treating lung cancer, a disease that we know as much about preventing it as any other disease.

If we look at all other cancers through this time, we see about a 15 percent drop in the mortality rate. For all cancers in all people below the age of 65, there has been about a 25 percent drop in mortality rate over this time, and the drop in the mortality rates are accelerating over the last 5 years.

If we look at the burden of cancer in women, approximately 20 percent, somewhat less, of women right now will die of cancer. In all studies, women dramatically over estimate their risk of getting breast cancer and of dying of breast cancer. This is not to minimize the importance of breast cancer, but it is very important because our perception of risk determines what we do. For women ages 35 to 55, cancer is the number one cause of death. About 3 percent of women will eventually die with the current numbers of breast cancer. About 4 percent, current numbers, will eventually die of lung cancer.

We predict about 270,000 women will die of cancer in 1997. Fifty percent of those deaths will be due to colon/rectal and lung cancer, 16 percent of those deaths from breast cancer, and 10 percent from other reproductive cancers. Right now the average 5-year survival of women diagnosed with cancer is between 60 and 65 percent and significantly higher than for men. In men, there is a much larger differential between the survival of white and African-American men than there is for the survival of women.

With all of the incremental interventions made over the past several decades, we are seeing an effect. The change in the mortality rate among groups, and this is all people, men, women, white men, white women, black men, black women, in every case mortality rates were growing between 1973 and 1990, and since then, for all of these groups mortality rates are dropping.

One overwhelming trend is a dramatic increase in the deaths of women, especially older women, from lung cancer. Breast cancer mortality rates are dropping, and they are dropping significantly. Overall, about 9 percent in the last several years. For women below 50, a 12.5 percent decrease; women below 45, it is almost 15 percent; and the latest numbers from 1995 show those trends continue. Finally, in 1994 and 1995, we see a drop of mortality rates, not just among white women but also among African-American women. However, this epidemic of deaths from lung cancer, especially in older women, is extremely dramatic.

There is some good news: we are making progress against many cancers, but it is incremental. We are only going to capitalize on all the things, if we can do two things. If we can move our biomedical approach to this disease from empiricism to a much more specific knowledge. At the same time, we must do a much better job at incorporating our approach to modifying the risks for cancer in our approaches not just through understanding the genes and our biomedical models but also our public health and especially behavioral models. NCI has created a new division that Barbara Reimer will be heading up to really try to create an extremely strong behavioral and public health approach to dealing with risk, with risk perception, with health communications.

Embedding our knowledge about the disease within our knowledge about people, behavior, our society, and the multiple cultures within them is the real challenge in making sure that the drop in mortality not only continues but accelerates.

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WOMEN AND RESEARCH: QUO VADIS?

More than anything I wanted to talk to you because you are a little bit like me, small enough to be personal but large enough to be powerful. Now, it has been said that there are five messages a woman has to hear as she grows up: she is loved and special; she can do anything that she wants; she can dream of greatness; she is able to take risks; and she is able to use creative aggression and still remain feminine. The problem is that the world has only told us that we are loved and special. The message that I want you to get today is that we are here to tell the world that even if they forgot to tell me I can do anything I want, I can dream of greatness, I can take risks, I am able to be assertive and still be feminine, because I happen to be a woman, and I happen to be very, very good.

I can also tell you I believe that the measure of a leader is not always found on what he or she has done but on the measure of his or her character; basically, the kind of character that becomes apparent when the spotlight has been turned off, the applause has died down, and no one is there to give you credit. Friends, is that what we women to do day in and day out? Let's tell the world that we absolutely have a lot of character.

We know that character and leadership are complicated words; however, they mean many things to many people. For us women, I hope that leadership is not merely a goal and character is not merely a word but a reality of life. I can tell you that you would not be here today if you did not feel that your life and mind are worth celebrating, that our careers and societal standings are worth preserving, and that we have to work for a better tomorrow.

In all of us I believe is the capacity of nurturing and of healing that so often conflicts with the harsher requirements posed by our professional ambitions. Today, like men, we are supposed to be married to the job, while expected, as women, to be traditional wives and mothers and, in the interim, be accused by some of being bad wives, bad mothers, while they are trying to be like men. How can we set the record straight to show that there are equally effective alternative feminine styles that need to be emulated?

As I look into this audience I am extremely impressed. I see strength, accumulated experience, and intelligence that, despite whatever the world thinks are obstacles for us, we will have no problem in the year 2000 getting what we need. We women are not petitioning for charity. We are just insisting on our given rights, by our own merit and not just by political quotas. We can do it without being counted. We can do it on our own merit.

I do not subscribe to the narrow concept about biology being destiny. It has been in the news all the time, but women and men are totally different. Men tend to think only in terms of work-related goals, while women tend to set goals having to do with others to the exclusion of their own needs. I believe in the process of restructuring our lives, of becoming an authentic person. We women must cease to think of ourselves as a collection of habits, jobs, and roles, and instead think of ourselves as perfectly imperfect.

I do not mean, of course, that one sex is better than another one. We need both. I do not know if our differences come from nature or nurture or a combination of both, but we need new ways of working and living together that really take care of our respective strengths. For us, it means recognizing that women are very good on intuitiveness, empathy, attention to details, tendency to solve problems through work, and, more than anything, team work, listening, and providing strength in the face of adversity. Of course, I know that you know many men who have these qualities, but I also know that you know many women who lack them as well.

Experience tells me that women, most women from all cultures and from all social classes, have those characteristics in abundance, and life has no way by which to recognize them. I can tell you that happens very frequently at the workplace. On top of that, when we finally make it, the world tells us that we have been lucky.

For me, lucky means when preparation meets opportunity. Our luck is be based solely on our merit and reflect our true worth. It will go without saying that the harder you work, the luckier that you become.

I can tell you that today all the women are moving up the corporate ladder and are reaching positions of senior responsibility in the academic world and in the corporate world. There are still only two women executives in the Fortune 500 and only seven women in the top 1,000 firms. After winning seat after seat in the 1990s, I can tell you that women's progress is trickling down as shown by the fact that although 84 percent of the Fortune 500s have a woman that is exactly what they have, a woman. For that, I can tell you that women make up just under 11 percent of the Fortune 500's 6,081 seats. I can also tell you that despite our greater number in this country — 137 million, 2 million more than men — professional women are still a minority group.

Women in biomedical research have, in a sense, been immigrants in the men's world. In 1994, medical schools graduated 15,555 doctors, of which 5,919, or 38 percent, were woman. In 1993 there were 15,108 people graduated with doctoral degrees; 38 percent were women.

Sadly, as you can see, academic medicine has a glass ceiling as well. For one, men achieve the rank of full professor in 12 years. Women achieve it in 20. Even worse, women are four times less likely to ever make full professor during their careers. In 1993, women in medical schools were 23 percent of the faculty while only 13 percent were tenured in science faculty and 10 percent tenured in the clinical faculty. Likewise, today we find 51 percent of women at the assistant professor level, 20 percent at the associate, and 10 percent at the full professor level. If that is not bad enough, only 1 percent of women are deans, 14 percent associate deans, and 4 percent department chairs, not to mention only two executive vice presidents.

At NIH during the last decade, women have been 29 percent of the post-doctorals, but only 18 percent of tenured scientists. When I look at the 1997 data on the NIH research grants data report, although they say it is incomplete because 3 to 10 percent of people do not put their gender when they submit their grants, I can tell you that from a total of 32,109 research grants in of all types, the number of female PIs ranged from 85 percent in the National Institute of Nursing Research to 13.5 percent in the National Center for Research Resources, representing an average of 21 percent female investigators submitting research grants to NIH and succeeding in getting awarded.

The 1993 data in the NIH extramural government program show that 16.4 percent of research grant dollars went to women, compared to 10.2 percent in 1984. In dollar terms, that is exciting because it means that funding for women tripled and for the men doubled it. The success rates for women were a few points higher than for men in first awards (28 vs. 26 percent), K awards (42 vs. 38 percent), area grants (29 vs. 23 percent), and small research grants (25 vs. 21 percent).

In 1997, the percentage of women trainee appointments was 47.5 percent compared to 1992 when it was 45.5 percent, accounting for only an increase of 2 percent in the past few years. I ask you, is 2 percent enough for 52 percent of the population of the United States? I say no, and I think we are tired of the status quo, and this needs to be changed. This is why meetings like this are extremely important.

Those of us who have gotten to the top have done so by sacrificing family relationships, personal time in favor of faxes, meetings, and, more than anything, difficult assignments. I know that despite the fact that we still make only 74 cents to the dollar, we are close to 50 percent of the American work force. Our success throughout our life has been based on consistently exceeding performance expectations, while making it look easy, not to mention adjusting our personal style so as not to threaten our male colleagues.

The reality is that we are not supposed to be attractive, smart, assertive, or even sexy. We must pretend we are not mothers, we are not married or worse, we pretend we are not having marital problems. Instead, right smack in the middle of the year 2000, we must continue to retain our pride without lingering at the altar of personal ambition. We must transform without transgression, share without imposing, and integrate with interrupting. Basically, we are not supposed to rock the boat.

I think it is time for a little rage, a rage that is called PMS when it comes from women, but it is called assertiveness and initiative when it comes from men. I think it is time for a more enlightened equality. When our male colleagues have been asked why is it that we have not excelled as much as they have, they attribute the lack of progress of women in research to a lack of general management or line experience or not having proceeded far enough through the institutional pipeline. That is the man's response. However, when women have been asked the same question, they have suggested that it is the exclusion from informal network, added to the lack of opportunities, and the lack of support services that were the major barriers to progress. The sad truth is that even though, at the dawn of the millennium, we are living longer as women — we are not living better.

I would like to challenge you today. I believe that the time has come to bring to the table the discussion of women's issues and our research agenda, and then address them accordingly. After all, it has been said that justice will return to Athens when those who are not injured are as indignant as those who are. The time has come to close the gap of what we say and what we do. After all, most people enjoy the comfort of opinion without the discomfort of thought.

So what are we going to do? I tell you that in the year 2000 we will have 137 million women, 47,000 of us alive past the age of 100 years; we will make up 48 percent of the labor force of this country; 70 percent of us have children under the age of 18 and we work; 18 percent of all firms in the United States are headed by women; and women older than age 65 will outnumber men of the same age two to one. So if we are going to be the largest numbers, and hopefully, not only in nursing homes, I can tell you that the time has come to find out why is it that the greatest deterrent for women not achieving their potential is gender bias. For that, I tell you I am not all together encouraged.

In my view, the greatest hope for women of today is recruiting, training, and retaining and then demanding that women are treated as equals: encouraged by schools, propelling to academic excellence by the universities, recognized by their male counterparts, and appointed to positions of distinction by their merit equal to men. The problems the world faces are too large to solve with only half of the brains of the world at work. I can tell you that ignoring the talent of half of the human race assures mediocrity.

In my mind, many of women's problems reflect a lack of empowerment in the planning process and lack of accounting for the societal problems that affect us throughout our lives. Again, what do we do? I would say the first thing we have to do is follow like a hound dog the development of our research agenda, something that goes hand in hand with better data. You don't know how depressing it was for me to find that the only data I found about our research was from the early 1990s.

When we look at our data we must try to get current data, because how can our research institutes and the agencies begin to shift funding in the direction of women's research when so little is known about the numbers, the severity, and prevalence of the very areas that warrant the greatest research funds? How can our researchers focus on the diseases that are killing women — HIV/AIDS, cancer, tuberculosis, diabetes, and heart disease — when epidemiologic data are sparse at best and nonexistent at worst.

The data on Hispanics in this country only became available in 1989 when we had the first Hispanic notation on the death certificate and on the birth certificate. We are 64 percent Mexican, 11 percent Puerto Rican, 5 percent Cuban, and 7 percent who still do not know where they came from. Out of 266 million Americans, 15 percent are African Americans, 9 percent Latinos, 3 percent Asian Pacific Islanders, and 1 percent Native American. We still have only data that say African Americans, whites, and others. How can you plan for me if you still do not think I exist? May I remind you that by 2014, the largest emerging majority of these United States are going to be these minorities, and you better shape your act together because we are going to be here to stay.

I think the time has also come to address the difficulties regarding women's research and try to take away the perception of researchers and help them really do what is necessary. For example, most women's health has historically meant gynecological health. There is a perception, however, that linking the health research needs of women and children inevitably equates the value of women with bearing and caring for children only. Similarly, as well in some bureaucratic minds, it is assumed that when you link maternal and child health concerns, the linkage implies a tacit ranking of child concerns above maternal needs. I think the time has come to tell people that I love children, but as women we need our position in this country, and more than anything, we need it in a more broader case than gynecological. We have many more diseases that are killing us.

Equally important, researchers desire homogeneous study populations with perceived assumptions that women's cyclical hormonal changes would confound research results. Don't these researchers know that the potential for gender differences in research is exactly what we are looking for?

Scientists believe, as well, that it is more costly to recruit women because they need help with child care and transportation. Ladies, these problems are not different and not necessarily more expensive. If you pay attention to issues like these, the best thing you are going to get is better protocol compliance.

Likewise, researchers believe that studies are more expensive when they must test gender-specific hypotheses or complete subgroup analysis by gender. The truth is that if women had been included when they did the 20-year aspirin study and the 20-year aging study, they would not have had to duplicate the studies, which cost them even more money. Surely, it would have been cheaper to include both genders initially. The time has come for researchers to understand that 52 percent of the taxpayers of this country are demanding that research funds paid by them are used in their research as well.

In the recent past, the fear of harming pregnant women and their fetuses led researchers and policymakers to adopt protectionist policies that excluded not only pregnant women but also fertile, non-pregnant women who wanted to participate. Researchers must realize that there are women who are unlikely to become pregnant or may delay pregnancy altogether and therefore would be wonderful research subjects. Again, researchers must realize that a virtual ban on research participation for all women of childbearing age is an excessive response to unfounded fears.

I believe that perhaps women's health has been neglected because of an unconscious sense in the mostly male research community that issues pertaining to women are of secondary importance, especially if the issue has already been studied in men. The truth might be that in this publish or perish world, many researchers avoid repeat studies, particularly if the studies show no significant differences and, thus, not publish it. In the future, we must be able to promote research more as a life-saving tool rather than just an extension of your bibliography.

Now, what do we do next? We have heard enough rhetoric, enough double talk, regarding the women's agenda, and have seen very few changes in response to our requests. I believe that the time has come for action, and we need it today. Stalling women's agendas for perceptions rather than realities is not only bad politics, it is bad economic policy, and it is bad public health policy. I have to tell you it is time to reap the benefits of our work and see where are we going from here. It is time to fold the barriers and put them outside the door. We need clear thinking; absolute ends to self-limiting attitudes; a real appreciation of intellect, training, and accomplishment of women in all fields; and an insistent, even aggressive, self-appreciation of our worth.

We might be more complex, but the time has come to stop all the things that have kept us behind and get us back on track. If we have done one thing in life, it is to believe that the degree of caring in America is ultimately a function of our leadership, but no amount of leadership can save us if we do not want to or we do not know how to save ourselves. Remember, if we are to succeed and promote our research agenda, we, the promoters and the policymakers alike, must step in the shoes of the unfamiliar before we develop programs that are responsive to the needs of those people entrusted in our care. As the Indian proverb says: Don't tell me what to do unless you have walked a mile in my moccasins.

In that sense, to succeed we must learn to develop partnerships, not only among ourselves but among local research groups and universities and among the communities that we serve. If we do that, I can tell you that we can combine skills, specialties, and ensure more comprehensive services as a result.

Again, where do we go beyond Hunt Valley? Allow me add my counsel to what I am sure you have already discussed and will be discussing in the future. First and foremost, when you get to your work please don't forget to keep up the momentum of our meaningful interchange and do not allow the pace to slacken in the face of other pressing commitments that await our return to daily life. Above all, let's search for creative solutions, and some come to mind.

There are three things that I think we should avoid: first, throwing out what is good; two, smugness and complacency; and three, looking back too much and forward not enough. First, don't throw away what is good. You must wonder why I ever suggest such a thing when we may be in danger of abandoning the principles and the mechanisms that have been responsible for the premier research system. If we think about it, there are pressures that are edging toward just that. Difficult financial times, for one, may force us to abandon the integration of teaching, publishing, and research. I believe that instead, these activities need to become even better integrated and mutually reenforced. We must be teaching, publishing, and research communities in the deepest sense, and we must do all that we can to protect that endeavor.

Above all, I say that we must ensure that the velocity of the political debate that happens in Washington today does not make women and their research agenda a political football used by liberals, conservatives, or whatever they want to call themselves, as a mere rhetorical tool to press some ideological agenda. Politics is rough. I know from experience, but there is never any excuse for turning the human needs and claims of women into the hollow utility of rhetorical or political gamesmanship. We should know better than that.

Second, don't fall prey to complacency or smugness. The excellence that we have attained in our agenda does not mean that we should not incorporate or accommodate change. Our own worst enemy can become smug and complacent, and we could be guilty of both. We must honestly and continually assess what we are doing and how well we are doing it. The instability in health care financing and delivery has placed enormous pressures on research and on different professional groups, including our own. But, it is important that we do not fool ourselves that what is best for health institutions is what is best for women's research. This is an important distinction, one that we keep in mind as we push for research and then target the monies for research, even when we work in an institution.

Finally, stop looking to the past instead of the future. We cannot justify the investment of federal monies just because we want to benefit the future generation. Send me the money and shut up is no longer an acceptable modus operandi. Instead, we need to look to the future, conceive improvements of our role in the national agenda, utilize the very technologies we have helped develop, improve communications both inside and outside our departments, and then learn to sell our ideas more effectively to Congress, to review committees, and to the scientific review boards.

At this point we need to work more aggressively to prepare ourselves for the international, globally integrated, environmentally challenged world that we are entering. We need to tailor our agenda to encompass the demands of the new marketplace. But in doing all that, we must not forget to humanize the research environment. We need to think carefully about the issues that concern the everyday woman researcher, issues like laboratory availability, economic security, and tenure ship in the long run. We need to work effectively to include more women in research and retain departmental excellence.

The time has come to hold top management accountable for women's lives and women's promotions. More than anything women have worked very hard and deserve a chance to move into the ladder of opportunity. Institutions in the future will have to sponsor daycare, support programs for the elderly parents, job sharing, and flex time. Women today are spread unbearably thin for all they have to do, and, as a consequence, we feel terrible, destructive guilt about slighting children at home or having to work and leave your family. Maybe it is time to recognize that the superwoman notion, although a great concept in today's world, might not be totally realistic. In the long run, a woman's life is all about choices. But more than anything women must continue to take risks and offer challenging assignments where they can show their true worth.

Having said all that, we must acknowledge that women have been slighted at work, whether it is consciously or unconsciously. Therefore, women do not deliver the sermon of equality but live by it. By that, I mean do not preach in the dark and continue to practice the abuses of power that we so much criticize. I mean things like withholding information, leap frogging through hierarchy, lack of clear expectations for employees, displacement of deserving professionals at work, and in publications, unfilled promises and inequity of salaries. None of these are to be tolerated. They are called abuses of power. We have tolerated them enough. The time has come never to do that, even more so when the boss is one of us.

Finally, I will suggest another arena where we should be more active, and that is advocating our cause. Though we must not blindly advocate our cause, we absolutely must advocate it. That means go to the editorial pages, in the television news, in public lectures, in the most popular magazines, and in local political gatherings.

The future has no political constituency. We must become that constituency. We must raise the level of debate. We must show the relevance of research to society and especially how the average life of every American will be safe because of the research that we conduct. More than anything, we do not need to engage in hyperbole, because we have a wonderful, strong defensible cause.

To be realistic, this new advocacy must not be done in the abstract. It can only work if it reflects the wisdom and the suggestions of those of you who are being touched day by day by their research experience. It must embody your desires as well as your needs, and it must become an extension of your courage. If this is not accomplished, then the system only serves itself, but not the people for whom it was intended.

I can tell you that there is an infinity of important things to discover, understand, and apply. We, as a group, cannot lose our will if we are to continue our great adventure. But, as we listen to each other here, let's remember that when solutions come our way we can no longer sit there and expect things to happen without us participating. We absolutely must watch over the process and participate in the outcome. Those of us who have the power of speaking for those who cannot communicate must absolutely do so loudly, clearly, and constantly.

So as it was said in Kismet: "Why be content with an olive when you could have a tree? Why be content to be nothing when there is nothing you couldn't be? Why be content with a grove when you could have the world?"

Colleagues, Yehuda Bauer said it best: "thou shall not be a victim; thou shall not be a perpetrator; and thou shall not be a bystander." In the lives of women, their future, and their research, let none of us ever be bystanders.

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BEYOND HUNT VALLEY: PERSPECTIVES

I was able to participate in the Hunt Valley workshop 6 years ago, and I took the time to review the proceedings of that workshop and the research that I knew and could learn about. I thought about the picture as a whole and tried to think about the overall development of this program.

As a result, I will make three suggestions. The first suggestion is to focus on research priorities. The last 6 years of active development of this program seemed to highlight issues more than research goals. We talked about agendas more than priorities; strategic plans more than systematic studies; and short-, rather than long-term results. Looking at the picture as a whole, the trend seemed to have been towards applied, rather than basic research; therapeutic, more than causal and prevention research; and one disease or categories of disease at a time, without attention to cross-cutting and underpinning mechanisms and towards current, rather than new hypotheses.

The cross-cutting mechanisms include immunocompetence, the foundation of healthy reproduction, healthy growth and development, and healthy old age. We do not really know its determinants and what maintains it. Another is the regulation of mood and emotion, which influences not only the depression that threatened those of us that are in my age group but also cancer, heart disease, and obesity. Others are the regulation of body mass, which influences heart disease, cancer, and diabetes, and the new cardiovascular risk factors and mechanisms. There is much less smoking, even though we know it is a problem in women. There is less uncontrolled high blood pressure, fewer homebound mothers. In those settings, what are today's most common predictors of coronary heart disease in women and how do they work? Finally is the mechanism of long-term, low-dose exposures, and I do not mean just exposures to environmental chemicals and toxicants. We have to think about natural products like vitamins and beta-carotene. We have got to think about common treatments, drugs used to lower high blood pressure, hormones, mood-controlling drugs, and obesity drugs.

My first suggestion, therefore, is to begin work on the integration and prioritization of the research agenda and move towards rebalancing priorities to include more basic science and more of the risky cutting edge of science.

My second recommendation is to do what I would call process research, a part of health services research. I want to emphasize a feature that I believe has really been nurtured by women's health research and that is community and science partnerships for targeted research. The goals and responsibilities of these leadership planning and management partnerships are varied and include one, some, or all of these tasks at different times.

The membership of these groups also varies enormously in background, types of commitment, and personal agendas. The success of these groups, from time to time, can be studied scientifically, and we can learn for the future the best composition of groups for different sets of responsibilities. We must be able to plan much more successfully to appoint groups to share in these partnerships and be as successful in deciding upon and monitoring our research as we would like them to be. At the same time, we need to clearly differentiate this innovation from specific sociological and public health intervention strategies such as participatory research, community level interventions, community organization, and population-based research. I am continually bothered by the lack of communication among people who are using these words and who are not clearly communicating what we had in mind when we used them. I believe there are appropriate social scientists who analyze the interactions of these groups who are working so well in these fields and begin to give us some rigorous description of the process and the success.

My third suggestion, which may sound retrogressed, comes from my time in medical school, in the late 1940s and early 1950s. I went to a medical school in England that had a very active department of pediatrics that engaged in community-based pediatric teaching and research. We all were out in the community learning about children, and they did a cohort study of a random sample of families in Newcastle, where the medical school was based, to look at what they could do, the pediatricians and the family practitioners, about improving the health of children, which they knew was not good in that city at that time.

The book they published went into descriptions and analysis of the health of the children and what could be done about them, and the authors came out with a recommendation that did have an impact on British health care. At that time with the tools available, the authors believed that the mothers and grandmothers could do more to promote the health of the children than the pediatricians and family physicians. They recommended that there be an organized effort to educate the mothers and the grandmothers to provide them with the knowledge and tools and the backup of the public health agencies. They, of course, pointed out that we still should do research, biomedical research to find new ways and new tools that the physicians could use. At this time, in terms of the health-related behavior of adolescents and such things like cigarette smoking and teenage pregnancies, an approach like this could be considered for dealing with some of the very important problems in young women.

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IMPLICATIONS FOR EDUCATION AND PUBLIC POLICY*

I always felt that the first years of my education as an ethnic minority were a challenge, until I entered medical school. Then I realized that I had two major challenges, and the second related to my gender. In the world of medicine and medical education, particularly in administration, I wear a couple of minority hats: I am black, and I am female.

Another challenge is that I am also an osteopathic family physician, which means that I wear another hat — a minority hat. When you wear that many hats you either have to stand tall and be proud, or you curl up and die. So I am probably one of the most arrogant, black, female, osteopathic family physician deans that you will ever want to meet.

My very first lecture in medical school was delivered by a pathologist who ended his lecture to this brand new class and this brand new school of osteopathic medicine with words of advice. His words were: “Remember students, you are what you communicate.” I thought that was really profound, that if I acted like a professional, I would be treated like a professional. Then I realized that therein lay the basic difference in medicine and in health and in the medical profession. My fellow students, certainly, could take those words at face value, but I learned the hard way that it was not so much what I was communicating, it was how I was being perceived. To a large extent, as a woman and as a minority, in all avenues of health care, whether as a patient, a professional, or a physician, I ultimately was treated based upon the stereotypic perceptions of the population or the person I was dealing with.

It came as a rude awakening because it is hard enough being black and interacting and also having to carry the mantle of my gender. I learned the hard way, in many instances, that it was more difficult being female than it was being black in a health profession.

Little girls don’t grow up wanting to be the President of the United States because this option is not presented to them. Certainly in medical education, females are not presented with the possibility of becoming dean of a medical school. After being in medical practice for 10 years, I knew there had to be a better way for patients, particularly vulnerable populations of women, children, and minorities, who made up my practice, to be treated by the health care system. I chose to go into medical administration to make things change, and I am still trying to do that.

First, I found that the medical education system, both its structure and its internal organization, colludes with the absence of cultural and gender issues in the curriculum and with the ascendancy of women and minorities into the medical professions. Actually, medical education has a significant proclivity towards the status quo. Much of the change that has occurred in medical education has come about by the change in the student body and the increased representation of women, and, hopefully at some time in the future, minorities. In fact, medical education for decades has cloned itself, and need I tell you what that clone looks like.

The evolution of medical education has focused heavily on research, and has been preoccupied with disease research with an organ focus and an absence of population focus or life span issues. The issues in research that are most appropriate and extremely important for women were essentially reproductive health.

* Presentation edited from meeting transcript.

We have come a long way, and we have made some significant changes. This is not to imply that we are close to where we need to be, but we have come a long way. We have a more diverse workforce. There are female health professionals in medicine, nursing, and other related fields in much greater numbers than ever before. We have a women's health curriculum. We have opportunities to facilitate research on women's health issues through policy changes and funding strategies. We are beginning to see a broader population focus in the area of research. We are starting to see outcome studies and research studies that can impact the way in which care is delivered or at least give us some information about it. We are seeing a greater emphasis on primary care versus the organ system specialties. We are seeing a major emphasis on prevention and health promotion.

We are now seeing managed care, which ideally will promote prevention and health promotion strategies in the delivery of health care. Furthermore, managed care is important because more and more medical education has to partner with managed care to create a product that will meet the changing needs and the changing health demographics of the society.

Historically, our service delivery system has depended specifically on the product of medical education and, for the first time in history, medical education must now respond to the service delivery system. This is a very significant power shift, which, from a policy perspective, we can now start to take advantage of. That will be difficult because one of the things we do not recognize is the fragmentation in medical education — first, in the way medical education is structured, but also from a policy perspective — what are the policy institutions that can have an impact on medical education and where will that impact be.

At the federal level, we have the Medicare and Medicaid programs that impact health and health care and, in fact, Medicare and Medicaid impact graduate medical education through funding strategies. We have research funding at the federal level that can provide incentives to improve research on women's health issues, and we have educational grants at the federal level that can provide incentives. Finally, we have the Department of Education that focuses on standards and accreditation issues and makes sure that those things occur.

The states also have policy agencies and institutions. Licensure occurs at the state level. Standards and expectations for the practitioners are set at the state level. Undergraduate and predoctoral education are funded at the state level, particularly through the public schools. You also have subsidizing of private medical education on the state level. The states are in charge of Medicaid. Medicaid funds, in some states, go to graduate medical education, and, interestingly and becoming more important to us, is that the insurance commissioners are at the state level. The states are in charge of insurance, and the managed care organizations, of course, have to respond to the states from a public policy perspective.

Professional policy seems to be an area where we have not been able to focus as effectively, but it has been focused on the positioning of women in the health professions. The professional institutions and policies are set based upon accreditation and certification. This is an important place to bring about an impact on women's health and women's health issues in the curriculum.

Even as we talk about the fragmentation of policies and policy arenas, medical education is fragmented and overlaps through different authorities. For instance, the colleges are responsible for pre-doctoral education. The academic teaching hospitals are responsible for residency training, and the professions are responsible for continuing medical education and certifications. To impact medical education, those levels must be impacted through all of the various policy agencies to facilitate change. At best, redressing the fragmentation is going to be incremental.

It is important that we look at education as a continuum so that our strategies, although incremental, can occur over the full gambit of medical education. At the colleges, we are looking not only at the curriculum content, but also the methodology. At the colleges, we certainly need to make changes to a more enlightened leadership. That is not always easy. Much change can occur from the top if the appropriate tone is set, and we are becoming more successful as women emerge through the system, but we still have a long way to go.

Teaching hospitals need to be a part of a consortium to facilitate this continuum. From policy perspectives and changes in medical education consortia, emerge opportunities for partnering and therefore facilitating many curricula changes around the country, which can then address some of the issues of women's health and minority health.

The osteopathic profession has established this continuum of education through the consortium approach as part of its accreditation process. We know now that we have an infrastructure. We can start to facilitate changes in curricula not just at the undergraduate level but also at the graduate level, and hopefully, at the continuing education level.

Whenever we mention continuing medical education, we focus on medical schools and residency training programming. More than 90 percent of practitioners who provide health care to women are not in medical school or in residency training programs. We also know through funded research at NIH or at the federal level that changing physician behaviors and attitudes and knowledge base once they are in practice is a challenge that we have been unable to change significantly. If 90 percent of the practitioners can only be approached through continuing medical education for licensure or for certification, then the policy arenas that we should be focusing on are the states and the professions. If we want to incorporate much of the research into actual practice, which is a challenge, then we need to focus on other areas of policy and public policy than just at the federal level.

I leave you with my suggestions for research. Number one, focus on the life-long learning portion of medical education, on the continuing medical education requirements, particularly at the state level and in the professional organizations. Second, we need further studies on how to change practice behaviors because that will be the next challenge if we are going to make any significant change in how health care is delivered on a daily basis in the many practices across this country. Third, with the changing environment, we need to understand or study the impact of managed care on medical education curricula, particularly as it relates to women and women's health issues.

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WOMEN IN BIOMEDICAL CAREERS*

I would like to begin this morning with a parable that I discovered about a year ago. I think that this parable contains many elements that all of us must feel as we progress through our careers in any field. This is from a novel called *Side Show* by Sherry Tepper.

Once upon a time, there was a turtle who lived in a pond with grey reeds, grey mud, and grey moonlight falling, which is what a turtle sees because she does not see color. Not for her, the glory of the sunset or the wonder of the dawn; not for her, the flash of a hummingbird's throat or a butterfly's wings. For her, the liquid sounds of water moving, the slosh and murmur of the stream, the wind in the trees. For her, the difference between shadow and darkness.

She was content, as turtles are content, to be deliberate in her habits and slow in her pace, to eat leaves and the ends of worms like fodder, and to think long, slow thoughts on the log with her fellows, where she knew the sunlight was warm, though she did not know it was yellow.

But a time came, on an autumn evening, grey leaf and grey thorn and grey mist rising, where she sat over long on the log after the sun was well down and the swallows came to drink and hunt on the surface of the pond, dipping and dancing upon the ripples, swerving and swooping with consummate grace so that the turtles saw them as silver and black and beautiful. And all at once, with an urgency she had never known before, she longed for wings.

"Oh, I wish I could see them more clearly," she murmured to the bullfrog on the bank; "that I might learn to fly."

"If you would see them clearly, you must go to the secret sanctuary of the birds," said the bullfrog, in the careless voice, as if he did not take the matter seriously. And when the turtle asked where that was, the bullfrog pointed westward to the towering mountains and told the turtle the sanctuary was there, among the crags and the abysses where the birds held their secret convocations and granted wings to certain petitioners.

The turtle thought how wonderful it would be to go there and come back and tell the bullfrog all about it. On the next night, she asked again where the birds went when they left the pond, and the owl pointed westward with its talon, telling her of towering peaks and breakback chasms, in a calm and dismissive voice. And again she thought of making the journey, and the wonder the bullfrog would feel, and the owl, to hear of it when she came back.

On the third night she asked yet again, and this time it was the bat who answered, squeaking as it darted hither and yon, telling of immeasurable heights and bottomless canyons. "No one dares go there," the bat squeaked, but the turtle herself, if she dared, even if no one else would.

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* Presentation edited from meeting transcript.

So for three nights the turtle watched, each night her longing growing. And at midnight on the third night, when the bat had spoken and the swallows had departed, the turtle went after them without telling anybody goodbye, slowly dragging herself towards the great mountain structure towards the west. She went by long ways and rough ways and hard ways, always. First across the desert, where she would have died of thirst, had not a desert tortoise showed her how to get moisture from the fruits of a cactus; and then across the stone, where she would have died of hunger, had a wandering rabbit not given her green leaves to eat; and then into the mountains themselves, where she would have given up and died many times, except for her vision of herself going back to the pond to tell all of the creatures there of this marvelous and quite surpassing quest.

They didn't know, the turtle told herself, they had no idea what it would be like. They made it sound easy, but when I go back and tell them what it was really like . . . . She dreamed of the cold nights away, visualizing herself telling her story to her kindred turtles on the sunlit log and to the bullfrog among the weeds and to the owl and the bat, all of whom would be admiring and astonished at her bravery and perseverance.

And so, sustained by this ambition, she went higher and higher yet. Grey stone and grey cliff and grey rain falling year after year, until she came at last to the place where the swallows danced in the air above the bottomless void. When they saw her, they stopped dancing to perch beside her on the stone. And when she saw them there, silver and black, beautiful as the night lit with stars, she was possessed once again of a great longing and told them of her desire for wings.

"Perhaps you may have wings, but you must give up your shell," they cried. And even as they told her she might have wings, she seemed to hear in their voices some of the carelessness she had heard in the voice of the owl and the bat and the bullfrog, who had told her to go without telling her of the dangers of the way.

She heard rightly, for the winged gods have a divine indifference towards those who would seek flight. They will not entice, and they will not promise, and they will not make the way easy. For those who wish to soar must do so out of their heart's desire and their mind's consent and not for any other reason.

And the turtle struggled with herself, wanting wings, but not wanting wings. For if she had wings, they told her, she would no longer be interested in going back to the pond to tell the creatures there of her journey, that comfortable telling, the anticipation of which had been perhaps more important to her than the wings themselves. And so she struggled, wanting and not wanting.

I think, for those of us in biomedical science, that we find the path that we each must take as we seek our own place within our field and in our own lives. I think too often we have told the young ladies and we ourselves have been told that we can have everything, and we can do everything, and we can do what we wish. And we can. The problem is that, all too often, we forget that we cannot do everything all the time. We cannot be everyone, everything, to everybody all of the time. There are choices that we must make.

The other thing that I think this parable tells us is the importance of the people around us. We are not supposed to make these journeys by ourselves. We must seek strength in each other. We will all need mentors and peers. We are never too young to be a mentor, and we are never too old to need a mentor. We all need mentors at every stage in our career. We need someone with whom we can explore the job that we are doing, the manner in which we are approaching things, and to find validation for our own approach as we move into positions of leadership in this enterprise.

There are clues. I mean, the bat and the owl said that there were deep chasms and mountains that could not be climbed easily. But there are times, I think, in our careers when we are not ready to listen to that, and that is probably good.

I think many of you in this room can certainly think about some of the hard jobs that we do in the laboratory and in the offices and in the administration and in the patient care room, and we know that we don't tell the bright, young students about many of the difficult times, but they will be there.

I'm not sure that that's a favor. I think we should tell them how hard it is, because it is important; that as people go forward into this career, that they have their eyes wide open, because we are certainly needed in the halls of power, at the universities, and the hospitals. The points of view that women and individuals of different backgrounds bring to those kind of endeavors are critically important as the nation changes, and we will have done ourselves no favors if we either elect ourselves out or go into institutions where we are not allowed.

But you do have to know that it is a battle. I think many young women today believe that they will not run into problems as they progress because in school, in medical school, and in at least most graduate fields, women do not have trouble as they enter as students. However, all of us know that as you get higher and higher, then it can become ever more difficult, and there have been many times where it is apparent that the pathway to the very top is one which is open only to a very few, and those very few must be those willing to make enormous sacrifices to get there.

The specifics of how one gets to any particular place are not very important. When I was a graduate student, the only thing I wanted to do was run a laboratory. It never occurred to me that I would become a bureaucrat. However, a time came in my career when it was apparent that the contributions that I could make in the office were perhaps greater than those that I could make at the bench. And so, after a great deal of soul searching, I closed the lab and moved into a position that now involves me in science at a very broad level; so that my broad interests now become a strength rather than the non-focused kind of critique that one gets in a grant.

So often, despite what the world says, you must know your own strengths and weaknesses, and you must be able to move with them when those opportunities arise. Very frequently, it feels like jumping off a cliff, but that can be invigorating and freeing and can allow you to maximize your own potential.

WOMEN AND HEALTH:
TIME FOR A NEW PARADIGM

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There has been an increased focus on women and health in the last decade. This is evident by the number of conferences, such as this one, devoted to the topic. Journals, monographs, and books are proliferating and striving to define the field. Although the term "women's health" is widely used, it lacks a clear definition and has been the target of debate. Efforts to arrive at a definitive conceptual model are likely to fail because the field is dynamic and any model would inevitably become dated. As an alternative, a framework has been proposed for the field by Chesney and Ozer as the first article in the inaugural issue of the journal, *Women's Health: Research on Gender, Behavior and Policy.*[1] This framework is illustrated as a multilevel circular figure that characterizes the evolving quality of the field of women's health. At the top of the multilevel framework are the key content areas of women's health. Included are topics that have traditionally been considered, such as reproductive health, which addresses the key issues of hormone replacement and infertility; diseases more common in women than in men, such as breast cancer, depression and eating disorders; and the leading causes of death among women, most notably coronary heart disease, lung cancer. More recently studied topics in women's health also highlighted in the top of this multilevel framework are gender influences on health risk behaviors such as smoking, alcohol, and physical inactivity; societal influences on women's health, encompassing social norms and roles, as well as poverty; violence against women, and women and health care policy.

A feature that often sets research on women's health apart involves the processes and methods that are used in conducting research. Thus, the second tier in the multilevel framework, beneath the content areas, are processes and methods. These approaches span each of the content areas and include, for example, increased attention to diversity of populations of women in health-related studies. Thus, this tier suggests that each of the content areas in the top tier would be investigated in diverse populations of women. Similarly, other methodological issues that span the topic areas of women's health include careful examination of the appropriateness of research questions, variables of study and research tools to research on women. For example, variables such as "number of children," "work," and "social class" need to be very carefully defined so that they capture the important domains that are necessary for understanding and addressing problems important to women's health. Specifically, variables that might work well in studies with men should not be automatically transferred to research on women.

Finally, another tier that is most important in a framework for women's health is represented by the various conceptual models that characterize the work of the numerous disciplines involved. These disciplines include but are not limited to anthropology, sociology, nursing, psychology, epidemiology, and medicine. Each of these disciplines brings expertise that is important to the field of study. Indeed, women's health is best studied and advanced by a multidisciplinary perspective. It is apparent that traditional models, particularly those that are competitive and "reductionistic," are not adequate to address the needs in the area of women's health. The proposed framework is designed to be an alternative to more traditional models in that it is collaborative, dynamic, and respects multidisciplinary and interdisciplinary perspectives. This framework implies that the field of women's health will expand best if those engaged in the research work together and join forces.

REFERENCE

1 Chesney MA, Ozer EM. Women and health: In search of a paradigm. *Women's Health: Res Gender Behav Policy* 1995;1(1);3-26.

PUTTING IT ALL TOGETHER*

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First, I want to pay honor to the women's health movement. I never speak before a group without recognizing the women's health movement, which is the reason for our being here. It is especially significant today to be in the room with sisters who helped to start this movement some 20-plus years ago; my hat is off to you. I also say it because I want every one of you to know how you got here.

No one opened the door and said, don't you women want to come and talk about health? It didn't happen that way. It happened because women took risks, put themselves on the line, and were called everything just to get our health care system to be more humanistic, to share information with us, and to give us the service that we deserve. It is a model for everyone.

Someone spoke this morning for the men's health movement. We need the men and women to work together; this is not just about women's health. What is important is the perspective that we as women bring to the situation. So, when my black brothers ask, why didn't you start a black men's movement, I say, I don't know. I don't know how you feel about your health, and you deserve to have your own perspective brought out. Women's health can only go a certain distance without the men. I say to you men, you better get on it, because you have 20-plus years to catch up. But I know you can do it.

I do not want to forget that racism and classism still plays a large role in the lives of many of us. It cannot be taken lightly. Yes, we are talking about race again. We have not done very much work around it, and we need to continue. Race is a difficult subject, but it's worth it. It has penetrated the fabric of our society, and we carry out racists acts, whether we know it or not. We unconsciously carry them out, and we have to work hard so that we do not continue to internalize all of the negative messages that have been brought to us.

As you start to do your research, I want you to remember several things. First, there is power in telling stories. So, when you work with women, one of the most profitable, beneficial things that you can do is take the time to listen.

Now, I know you are going to say I'm busy, I don't have all that time, but do you want to be successful? Everybody has a story. When you learn to listen actively, you will get the answers you need. Give your full attention; do not say, this woman doesn't know what she's talking about. Not that kind of listening. Do the kind of listening where you bathe her entire presence with your attention. That attention becomes healing for her and for you. You will find out what you never get from questionnaires or telephone polls; you will get what you need if you are able to give yourself up. You will also have a story to share, because just as you are looking at me, I am looking at you, and I want to know about you. In this exchange, you build a relationship that will enhance all of your work.

It is really important that the affected population be part of all phases of research, and there are enough people who are affected who think the way you think, who have the information you need, who are living with the diseases or the conditions, and who can be involved.

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* Presentation edited from the meeting transcript.

We are all health consumers. If you don't think so, let something go wrong with you, and you have to turn yourself over. Then you will understand what it is like to be a consumer. We only need to look at the AIDS and the breast cancer movement to see the power and the change, the energy, and the insights brought about by having the affected population be a part of designing and implementing whatever program you are thinking about. Whatever questions you have, input from the affected population is absolutely necessary.

There's a lot of talk about recruitment and retention [in clinical trials], especially for people of color, because you can't get enough from studies, because we don't trust you. We don't trust you. We have Tuskegee, we've got every other 'skegee and everything else that comes up. We get these contradictory messages that tell us to do one thing today and something else tomorrow — all that is confusing. So, the lack of trust has got to be worked on. I am not going to tell you how, that's something we have to figure out.

The second point is that when you are want to get people of color and people of low income levels to participate, you have to support their participation. I have several friends who participate in studies. Although they are middle class working women committed to health, it is still quite difficult for them to participate. You need to design something less complicated that can still get you the information. I'm not so sure having something very complicated is going to get you what you want, because you have to remember that you are working with people. This is for people, and people need to feel involved and be part of the planning.

I want to raise another issue: Often, when people talk about working with special populations and low income people, they always think about us black folks or about other people of color. But, poor white people out there need to be thought about too. If you work with poor white people, you would understand what poor people need, then you might be more apt to make sure they get what they need, because when you look at a person, you see a reflection of yourself, and then you understand what's going on in a different way. So, please, include poor white people in your work. There are plenty of them around that need to be included.

We, in the National Black Women's Health Project, also advocate a holistic approach to health. We can't afford to be involved in the disease of the month. We can't afford to be taken in by marketing, because it's easy to market and get involved in one specific disease or the other. We are working on a special program with the American Heart Association — Walking for Wellness — because we are very concerned about cardiovascular diseases in black women. We are concerned about our weight, we are concerned about our not exercising and doing the other stuff you're supposed to do. We all wish we could be like Oprah and hire a cook and a trainer. But since most of us can't, we've got to figure out a better way.

When we told the folks at Heart that we would enter into a partnership around Walking for Wellness — last year we tested out our program in two cities, and this year we are moving to six markets — we said it is crucial that we talk not only about the heart. We wanted to talk about our whole bodies, because the first thing sisters will say is my heart is in my body next to my lungs, next to my liver, next to my breasts . . . .

So, once we get the attention, we cannot afford to talk just about one thing. We need the holistic approach. It's absolutely necessary. If you don't do it, you'll be blown out of the water because people will confront you with their own thinking in our communities.

Last, I want to talk to you as a healer, as a person who is participating in helping us be all who we are through health. I think health is the most important thing that we can organize and work around. Health cuts across all classes and all races; it is a unifying field to work in.

You also have a lot of power. You have a lot of personal power in your daily dealings with both your colleagues and with the people who come to see you. Take that personal power seriously. Be careful what you say to people. If you are in a rush and you don't have time, don't bother with folks on that day because you undo more than you build. Be careful about what you say.

You also need to take care of yourselves. We have become a nation of tired people. You are worn out. You're glad to be here at this meeting because last night you didn't have to do anything for anybody. You could go up in your room and do whatever you want to do. You didn't have to drop the kids off at school; you didn't have to deal with daycare. We have all these labor saving devices, you have cell phones, you have beepers, you've got snail mail, you've got e-mail, you've got faxes, you've got voice mail. We are supposed to be working less with all these things, but we are working more with all of them. No wonder we are tired.

I want to give you my prescription for wellness. It is perfectly all right for you to take one hour every single day of your life to do absolutely nothing. You need to be replenished, clear out the cobwebs of your mind, get rejuvenated. Let me just tell you how I want you to design this hour. When you go home, have a meeting with your family. Let them know that from now on you're going to be taking an hour every single day. And give your children the telephone number to the police department, the emergency room, anything they might need while you're taking your hour. When you go home from work in the afternoon, go for a walk by yourself. Don't take the dog with you because, if you take the dog, the dog is going to be chasing cats and cars, and you're going to have to take care of him.

Or, do what I like to do. Get in the bathtub and take a bubble bath for one solid hour. Don't do anything. Or go in your bedroom, close your door and lock it. Get in the bed. Let me tell you, you'll feel much better about it. When I don't do it, I find that I am angry, and I don't know why. It's because I had no time for me.

Go to bed at night. Your body might not be tired, but your brain needs to rest. Go to sleep at night. We need to get enough sleep on a good mattress. But we get all carried away and think that we're being productive and whatever, when, in fact, you're just on a treadmill.

I'm just saying slow down and start to live. Relax. Enjoy your life. You'll find out that your work will be more rewarding, and you will feel so much better about yourself.

PUBLIC TESTIMONY

INTRODUCTION TO THE PUBLIC TESTIMONY

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

BEYOND HUNT VALLEY: RESEARCH ON WOMEN'S HEALTH FOR THE 21ST CENTURY

These public hearings, sponsored by the Office of Research on Women's Health (ORWH), were held in conjunction with a series of landmark scientific workshops designed to provide recommendations for the National Institutes of Health (NIH) agenda for research on women's health for the 21st century.

The Office of Research on Women's Health was established within the Office of the Director of NIH in September 1990, by Dr. William Raub, then Acting Director of NIH. ORWH was charged with the important role of providing a central focus for NIH-supported biomedical and behavioral research related to women's health issues, and 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 major mission of ORWH is:

1. To strengthen, develop and increase research into diseases, disorders, and conditions that affect women, determining gaps in knowledge about such conditions and diseases, and then establish a national research agenda for NIH for future directions in women's health research;
2. To ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially clinical trials, that are supported by NIH; and,
3. To direct initiatives to increase the numbers of women who are participants in biomedical research careers.

ORWH does not function in isolation. We look to the broader community of scientists, health care providers, and women's health advocates across the United States, and beyond, to ensure that the research we foster and support and our priorities for research reflect the needs and concerns of the women's health community. We rely upon members of the women's health community to provide direction for us in addressing their needs and concerns through research and in pursuing the scientific knowledge that may permit the medical community to diagnose, treat, and prevent the adverse health conditions and diseases that affect women across the life span. One of the most effective ways for us to accomplish this is through public hearings such as this one.

From the time of the establishment of ORWH and the structuring of our first NIH research agenda on women's health, we have utilized public hearings to receive testimony from public representatives, and to build upon that testimony through scientific meetings and workshops to construct priorities for women's health research.

The report of that first undertaking, Opportunities for Research on Women's Health, is based upon public testimony and a scientific meeting held in Hunt Valley, Maryland, in 1991.

Recognizing that there has been progress in addressing women's health through research, but also recognizing that the extensive focus on women's health has brought forward new concepts and scientific questions upon which we need to focus, we began this process to reevaluate the foundation for our research agenda and to reformulate priorities as we go forward into the next century. Therefore, we began a process of revisiting our original agenda, based on the report, Opportunities for Research on Women's Health, often referred to as the "Hunt Valley Report," through a series of public hearings and scientific meetings, of which this is the final, and which we have called "Beyond Hunt Valley: Research on Women's Health for the 21st Century."

We began by establishing a Task Force on the NIH Women's Health Research Agenda for the 21st Century to assist and guide us, and our Congressionally mandated Advisory Committee on Research on Women's Health, through this process.

At our first regional meeting, held in Philadelphia in September 1996, we began the process of reexamining our research agenda to ensure that it is relevant as we move toward the next century. We held the first public hearing at that time. During the New Orleans public hearing and scientific workshop, in June 1997, we invited discussion on aspects of the research agenda based upon sex and gender issues, e.g., physiological, psychosocial, and pharmacologic differences between women and men.

The third regional meeting, in Santa Fe, New Mexico, was designed to focus on factors that contribute to differences in health status and health outcomes among different populations of women, and career issues for special populations of women in science.

Finally, during the national meeting in Bethesda, we held our concluding public hearing of this series and brought together the results of all three regional meetings in this workshop. During the Bethesda public hearing, we specifically requested testimony addressing:

- State of knowledge and continuing or emerging gaps in knowledge about women's health across the life span;
- Sex and gender differences in health and disease;
- Factors that influence differences in health status and health outcomes between different populations of women;
- New priorities for research on women's health;
- Career issues for women scientists: overcoming barriers and achieving success in biomedical careers.

NIH is the primary agency within the Department of Health and Human Services that performs, promotes, and supports biomedical and behavioral research. Therefore, the focus of the public hearings was on research that should be initiated, expanded, or enhanced to add to our existing knowledge about women's health, as well as to consider innovative programmatic and collaborative efforts appropriate for NIH to promote career opportunities for research on women's health, and especially that of women in biomedical careers.

The testimony from all the meetings was received and reviewed by our Task Force. The resulting information was used to guide the Task Force in developing recommendations for the NIH research agenda for the beginning of the 21st century. We are fortunate to have members of the NIH scientific community, as well as women's health advocates, scientists, and health professionals from across the country serving as members of this important Task Force.

On behalf of NIH, and specifically ORWH, we thank all the participants who presented public testimony for their role in reassessing our research agenda so that we can continue to make progress in women's health status as we enter the next century. We are very appreciative of your efforts to share your wisdom and concerns during our consideration of issues of importance for the NIH research agenda on women's health for the 21st century.

SUMMARIES OF PUBLIC TESTIMONY PHILADELPHIA, PENNSYLVANIA SEPTEMBER 25, 1996

Mary J. Berg, Pharm.D.
College of Pharmacy, University of Iowa

Mary G. Bonk, R.N.
Complications of Gynecologic Surgery (COGS)
Women's Support Group

Mary Ann Burg, M.S.W., Ph.D.
Florida Institute for Women: The Health Gatekeepers
University of Florida

Bente E. Cooney, M.S.W.
National Osteoporosis Foundation

Michael J. Gast, M.D., Ph.D.
Wyeth-Ayerst Research

Barbara S. Giesser, M.D.
Arizona Health Science Center

Phyllis Greenberger, M.S.W.
Society for the Advancement of Women's
Health Research

Mary Hammond, M.D.
American Society for Reproductive Medicine

Hazel J. Harper, D.D.S., M.P.H., F.A.C.D.
National Dental Association

Laura L. Hayman, Ph.D., R.N.
American Heart Association

Penelope J. Hitchcock, D.V.M.
National Institute of Allergy and Infectious Diseases
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Lisa Kaeser, J.D.
Alan Guttmacher Institute

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

Dorothy Mann
Family Planning Council

Rita M. May
Sjögren's Syndrome Foundation, Inc.

Margaret K. McLaughlin, Ph.D.
Magee-Women's Research Institute

Powers Peterson, M.D.
American Society of Clinical Pathologists

Marj Plumb, M.N.A.
National Center for Lesbian Rights

Linda Quander, Ph.D.
Clark Atlanta University

James M. Roberts, M.D.
Society for Gynecological Investigation

Roxanne A. Rodney, M.D.
Association of Black Cardiologists

Sheryl Burt Ruzek, Ph.D., M.P.H.
Temple University, Department of Health Education

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

Martha Torres-Montoya, M.S.P.H.
Hispanic Women's Health Association

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

Jacqueline Lee Wolf, M.D.
Gastroenterology Women's Coalition

Elizabeth Yoffe, M.A.
Self

Mary J. Berg, Pharm.D. *Professor, University of Iowa*

The University of Iowa is a research-based university composed of ten colleges, with a student body of approximately 28,000.

Dr. Mary Sue Coleman became the first woman president of The University of Iowa in December 1995. The presence of a female leader in this institution, founded in 1847, gives great hope to women in academia who are forwarding their credentials for promotion with the expectation that fairness will prevail.

The promotion and tenure list at The University of Iowa doubled from 1995 to 1996. This remarkable achievement was noted at the annual ceremony of the "Celebration of Excellence and Achievement Among Women" in May 1996.

Mary G. Bonk, R.N. *Complications of Gynecologic Surgery (COGS) Women's Support Group*

Current U.S. public health policy, statutes, and state health laws adversely affect women who have experienced complications of gynecologic surgery. Occult obstetrical injuries to the pelvic floor and complications of gynecologic surgery not made known to women may lead to progressive digestive and urinary dysfunction and disease. Diagnosis, information, and prognosis have been strictly suppressed by medical politics. Examples include permanent ostomies surgically accomplished in the absence of fully informed consent; cancer, autoimmune diseases, and other disorders that may result from surgically implanted foreign material/devices; critical complications of gynecologic surgery such as post-hysterectomy pulsion enterocele and vaginal/rectal prolapse; and secret surgical research. Patients with postoperative pain and persistent dysfunction are often relegated to psychiatry.

Information and health records of these conditions and injuries have been withheld from patients and family/representatives under Georgia health law §31-33-2(c). Because all research in Georgia is tightly protected from legal discovery by Georgia health laws, the family/representative is also excluded from documentive research information. Furthermore, we believe that health care data systems comprising patient information with diagnostic codes, personal identifiers, and other categorical divisions are coded with psychiatric diagnoses, which blacklist surgically injured persons and/or subjects of secret surgical research from all information and diagnostic health care except in a life-threatening event. Through mental health laws, interstate compacts, and committees there is reinforcement beyond state boundaries by codes with personal identifiers which blacklist the patient throughout the United States and Canada.

Investigative and documented procedures have been obtained on a patient from world experts outside of the United States and their assessments have been sent to the patient's established physician in Georgia. Under Georgia health laws and regulations, this physician cannot provide the information to the patient or representative, and third party release of records cannot be obtained by process of Georgia law. In January 1996, a formal, written complaint with request for investigation of this specific case was submitted by COGS to the Office for Civil Rights, HHS Region IV, in Atlanta.

COGS requests the interest of this workshop's cochairs, leaders, and participants and asks for inquiries through the Freedom of Information Act to the Office for Civil Rights, HHS Region IV in Atlanta, Georgia.

Mary Ann Burg, M.S.W., Ph.D. *Professor in Academic Medicine, University of Florida*

Our country needs major support to establish a National Network of Centers of Excellence in Women's Health. Without it, women's health services will remain fragmented and insufficient. Although some of the lessons from the women's health movement of the 1970s were absorbed by mainstream medicine, an oppressive climate still persists. Too many women have adverse experiences with the health care industry. Too many physicians disregard their symptoms and "talk down to them." It is clear that women's health care needs are different from men's, yet they are not given the same attention and respect. This deficiency is reflected in morbidity and mortality statistics.

I believe that coordinating women's health must be a top priority for those of us who provide health education, research, and services to women. A network of Centers of Excellence in Women's Health is the most efficient and effective remedy for today's disjointed service delivery system.

The Health Gatekeepers at the University of Florida offers a model for establishing a Center for Excellence in Women's Health. We have built partnerships with other academic health centers and women's research institutes across the country to foster collaboration and linkage on the national level, which is essential to make a significant impact on women's health. In fact, we intend to construct a first-class National Center for Excellence in Women's Health to foster cooperative efforts to build upon existing efforts to improve the sharing of data, the mentoring of researchers in women's health, and the development of models for delivering women's health services.

A long-term strategy is critical to the success of a project like a national network of Centers for Excellence. It will require a concerted effort from foundations, philanthropies, and other private funding groups, as well as volunteer organizations. It also needs formal sanction by a host academic health center in order to have the influence necessary to survive in today's political environment. The Brain Institute of the University of Florida, which was founded 5 years ago by a coalition of educational and research interests, provides an exciting model for establishing a unique, dedicated facility.

One of the lessons learned from the 1970s self-help movement — the foundation for the very notion that women's health is a unique field deserving distinct services — is that in order for a cause to flourish, it must be firmly institutionalized. The recent RFP from the Department of Health and Human Services to develop a Model Center of Excellence in Women's Health is an exciting start to institutionalizing women's health. Now is the time to capture this strategic opportunity.

Bente E. Cooney, M.S.W. *Director of Public Policy, National Osteoporosis Foundation*

A comprehensive national strategy to address osteoporosis including a coordinated program of basic, clinical, and behavioral research is urgently needed before the baby-boom generation reaches the age of osteoporotic fractures. Although progress has been made during the last 5 years towards preventing, diagnosing, and treating this disease, there are still unanswered questions that need to be addressed.

The National Osteoporosis Foundation is the only national nonprofit organization solely devoted to reducing the widespread incidence of osteoporosis. The major goals of our research are to uncover the molecular and cell biology of bone and the factors that regulate bone cell activity; to identify the genetic and environmental risk factors that contribute to bone loss; and to develop methods of prevention, diagnosis, and treatment. Because women are four times as likely to develop the disease, and based on data provided by the National Health and Nutrition Examination Survey, NOF estimates that by the year 2000, a total of 25.5 million women either will have osteoporosis or be at risk for osteoporosis due to low bone mass. Therefore, we encourage and appreciate the continued research efforts on osteoporosis, especially as it relates to women. It is our hope that research will address those unanswered questions women need to learn about osteoporosis.

In basic research, questions concerning restoring and reversing skeletal functions need to addressed. Moreover, investigation surrounding predetermining factors such as menopause, hereditary factors, and the role of genes, must be explored.

Relevant to clinical research, we need to know the most efficient and cost effective way to diagnose and treat patients with osteoporosis. While progress has been made to isolate certain risk factors such as race, smoking, weight, family history of fractures, and previous fractures, further research is necessary to refine and clarify risk factors. In addition, more clinical studies on treatment measures, including exercise, must be conducted in order to better understand, prevent, diagnosis, and ultimately treat this complex disorder.

In behavior research, perhaps the most important progress we can make is in the behavior of children, adolescents, and young adults. We must learn to foster lifestyle behaviors that are conducive to healthy living, thereby reducing bone loss. Adequate calcium intake, exercise, and healthy, smoke-free lifestyles must be fostered. Also, as women approach menopause, they should discuss the potential benefits and risks of estrogen replacement with their health care providers.

The current biomedical and behavioral research for osteoporosis deserves much attention. If not provided, this disease will not only bankrupt our health care system, but the lives of million of women and men.

Vice President for Women's Healthcare
Clinical Research and Development
Wyeth-Ayerst Research

Michael J. Gast, M.D., Ph.D.

Oral contraceptive and hormone replacement programs address a wide range of women's health care issues. With lower doses and changes in regimen, oral contraceptives have become safer over the years without a loss of efficacy. Noncontraceptive health benefits, including the prevention of sexually transmitted diseases, the lowering of the incidences of several of the reproductive cancers, and the prevention of a variety of medical conditions requiring hospitalization of women have been additional benefits. Hormone replacement therapies (HRT) are being recognized in recent medical literature as providing superb global benefits for women's health.

Unmet health needs of women include infertility, endometriosis, uterine fibroids, reproductive cancers, depression, and collagen vascular disease. Wyeth-Ayerst has elected to refocus its own women's health care research and development activities with a capital investment of almost $35 million and the establishment of a Women's Health Research Institute devoted to the medical and social issues critical to female health. The Institute is devoted to the development of women's health care medications. By removing the boundaries and integrating women's health research with the company's other discovery efforts in areas such as heart disease, stroke, breast cancer, and Alzheimer's disease, the company is able to leverage all of its resources to find solutions that benefit women's health.

With a primary focus on the definition of steroids, non-steroidal molecules and non-hormonal targets for the treatment and prevention of women's health disorders, Wyeth-Ayerst also supports other biomedical and behavioral research issues in women. Improved screening techniques, important developments in chemical synthesis and molecular biology, and genetic techniques are helping to accelerate advances. Genomic technology in particular holds the potential for uncovering the mechanisms of disease that underlie many women's health disorders.

Wyeth-Ayerst recently funded a $16 million ancillary study to the Women's Health Initiative (WHI) to evaluate the role of HRT in the prevention and treatment of Alzheimer's disease, and is also providing Premarin and Prempro to the 6-year "WHI Memory Study," which involves 8,000 postmenopausal women age 65 and over. Wyeth-Ayerst is also sponsoring the Heart and Estrogen-Progestin Replacement Study, known as HERS, a 5-year, $40-million, multicenter, placebo-controlled, double-blinded trial of the impact of HRT on approximately 2,700 postmenopausal women with heart disease.

In addition to its research program, Wyeth-Ayerst's Women's Health Research Institute will also disseminate information about women's health and support a wide variety of education programs aimed at both patients and physicians. The benefits of HRT for protection against osteoporosis in women after menopause is one such area of education.

Associate Professor of Clinical Neurology
Arizona Health Science Center
National Multiple Sclerosis Society

Barbara S. Giesser, M.D.

Sexual dimorphism in immune function is well documented. Female immune function is more vigorous than that of men. Much of this distinction appears to be related to the most fundamental difference between the sexes: the ability to conceive and bear children. A connection between the reproductive and immune systems has been realized since the last century, although the complex network of interactions that are involved are only just now beginning to be understood. Neural control is well established; however, it is becoming apparent that nervous and immune function do not operate in an isolated fashion, but are interdependent as well.

One of the most important connections between the nervous and immune systems is via the hypothalamic pituitary adrenal (HPA) axis. Females of several species, including humans, have more HPA responsiveness than do males, and have higher cortisol levels in response to stress. Even at a basic level, there appear to be differences between the sexes. HPA axis also demonstrates communication between the neural, endocrine, and immune systems, for example by regulating the immune cell number, activity, and production of cytokines. Cytokines, in addition to their principle activities of immunoregulation, can act directly on the hypothalamus to influence release of hormone stimulating factors. Estrogen, progesterone, prolactin, and testosterone also have been shown to affect immune function. A third way in which the immune and neural systems communicate is via neurally active substances that are produced by immune cells.

In contrast to relatively steady state immune function in men, marked fluctuations in immune status during a woman's lifetime have been demonstrated. The most dramatic changes in female immunity occur during pregnancy, which is generally associated with suppression of cell mediated immunity, and normal or increased activity of humoral (antibody) immune responses. Clinical changes during pregnancy and postpartum are likely to be mediated, at least in part, by the different concentrations of sex hormones. Premenopausal women undergo monthly metabolic and hormonal fluctuations, with immune function suppressed or enhanced coincident with different phases of the menstrual cycle. Many autoimmune diseases, neurologic autoimmune diseases, and non-immune neurologic diseases are recognized to have symptom fluctuation coincident with menstrual cycle phases. Changes in clinical status of women with autoimmune rheumatologic and endocrine diseases have been extensively documented, although less is known about autoimmune neurologic diseases, such as myasthenia gravis and multiple sclerosis, as a function of hormonal climate.

While it is clear that autoimmune disease predominates in women, the precise mechanisms by which this happens is unclear. Future research is recommended to fill the large gaps that exist in the understanding of autoimmunity, not only at a cellular and molecular level, but also as clinical phenomena, both in healthy persons and in persons with autoimmune disease.

Phyllis Greenberger, M.S.W.

Executive Director
Society for the Advancement of Women's Health Research

Gender-based biology — the examination of basic biological and physiological differences between men and women — is the next frontier for women's health research. This protocol has implications for disease research, clinical practice, disease prevention, medical education, and public health policy.

It is a testament to those of us here that there is recognition of gender differences in disease manifestation. While we may continue to encounter skepticism on this, none of us doubt the reality and importance of gender differences.

There is increasing evidence to support the study of gender-based biology. Scientists have observed basic biological differences between the genders in areas of research as diverse as genetics, endocrinology and metabolism, cancer, and pharmacokinetics. These differences can significantly impact disease development and treatment. An organized and methodological approach to gender-based biology could promote better understanding of why gender differences exist and their implications.

Until recently, these discoveries were a by-product of other research. We need to create a system where such observations are recorded and disseminated along with findings from more specific gender-based research studies.

We believe that the potential implications of gender-based biology are dramatic — for research, clinical practice, disease prevention and manifestation, medical education, and public health policy. Issues associated with women's health represent the cutting edge of today's knowledge and have the potential to dramatically change the way clinical medicine is conducted.

Mary Hammond, M.D.

President, American Society for Reproductive Medicine

One of the greatest and most unfortunate gaps in the public's knowledge about women's health is a lack of understanding about human reproduction. Ignorance about human reproduction, whether willful or unintentional, is manifested in many ways, including unintended pregnancies, teen pregnancies, sexually transmitted diseases, and infertility. The unfortunate reality is that all these issues involve sex in some way, a public debate about them becomes embroiled in debate about abortion.

Many women's health advocates outside the realm of reproductive medicine are reluctant to support reproductive health research because they wish to avoid the debate about abortion. This is evident in the ongoing ban of federal funding for research using human embryos that remain after in vitro fertilization. Although the American Society for Reproductive Medicine (ASRM) and the Association of American Medical Colleges enlisted an impressive group of supporters of embryo research, many large advocacy groups are reluctant to back such research because of a fear that lending support would politically harm their own individual advocacy efforts. The Human

Embryo Research Panel developed a set of ethically based and humane guidelines for the research. However, the guidelines received limited support from the President and were completely disregarded by the U.S. House of Representatives, which passed a complete funding ban on the research.

As plans are made for women's health research in the next century, goals to fight attempts to politicize research and rally women's health advocates to support all promising basic and applied research rather than singling out research that benefits a particular body part or condition should be included.

ASRM fears that federal support of contraceptive research and development may be the next casualty. Neither public nor private support for this research has been strong. The enormous human and financial tolls of unplanned pregnancy and STDs could be reduced significantly if women had access to a wider variety of contraceptives that meet their family planning needs. The appalling lack of new contraceptive choices is a result of many factors, including lack of contraceptive research support, liability fears of contraceptive manufacturers, and ideological conflicts. The recently released Institute of Medicine study, entitled "Contraceptive Research and Development: Looking to the Future," serves as a useful tool to navigate the issues surrounding contraceptive research and development. ASRM hopes that the Office of Research on Women's Health will offer its strong support of embryo research and contraceptive research and development and will work to de-politicize such important research.

Hazel J. Harper, D.D.S., M.P.H., F.A.C.D. *President-Elect, National Dental Association*

(Written testimony prepared by: Georgetta Manning-Cox, D.D.S., M.P.H., F.A.C.D., Howard University College of Dentistry; Hazel P. Haynes, D.M.D., University of Texas Health Sciences Center at San Antonio; Hazel J. Harper, D.D.S., M.P.H., F.A.C.D.; Sheila S. Price, D.D.S., Ed.D., West Virginia University School of Dentistry; Marilyn Woolfolk, D.D.S., M.P.H., University of Michigan School of Dentistry.)

The special oral health needs of women that set them apart from men are greatly influenced by hormonal fluctuations, age, and stress. Factors that are age-related, gender-linked, or specifically problematic for minority women include menopause, osteoporosis, diabetes, and stress. Oral manifestations during menopause are profoundly different from those during other phases of a woman's life. Increased sex hormone levels correlate with increased gingivitis and altered gingival inflammatory response. Other common complaints are pain, burning, altered taste sensations, and xerostomia or dry mouth. Since women comprise 60 percent of the population age 65 and older, the oral health needs of geriatric patients will most frequently be the needs of women, with women of low socioeconomic status and/or African Americans and other minorities at an even higher risk. Continuing research on the role of estrogen in hormone replacement therapy in the oral health of menopausal and perimenopausal women is needed.

Oral bone loss can result from several systemic diseases and has been linked mainly with periodontitis or residual ridge resorption. Data suggests that older women are at risk for both osteoporosis and oral bone loss.

Decrease of mandibular bone mass has been positively correlated with tooth loss in females. The role of osseointegrated implants to further retard bone loss in osteoporotic patients warrants further study. Preventive measures for osteoporosis include early identification of the risk factors, estrogen replacement therapy, calcium supplementation, and vitamin D. There is ongoing research on the therapeutic options of fluoride and the trace elements such as zinc, copper, and manganese for treatment and prevention of osteoporosis.

Diabetes is the third-leading cause of death of among black Americans, especially among older black women; other minorities have even higher rates. Uncontrolled diabetes can severely compromise oral health; changes include cheilosis, burning sensation, decrease in salivary flow, alterations in the flora of the oral cavity, and increased susceptibility to infection leading to destructive periodontal disease.

Additional research on the effects of specific combinations of vitamins used in conjunction with pharmacotherapeutics is needed.

Stress has been implicated in the etiology of periodontal disease. Oral manifestations of stress include painful and recurring aphthous ulcers, gingivitis and bleeding gums, bruxism (grinding and clenching teeth), and temporomandibular disorders. Involuntary physiologic mechanisms that may induce stress-related periodontal disease include impaired gingival circulation, lowered host resistance, decreased salivary flow, and endocrine imbalance. The effects of stress and the role of vitamins, minerals (and herbs), and other nutritional variables on a woman's health cannot be overemphasized.

Executive Committee Member
Council on Cardiovascular Disease in the Young
Laura L. Hayman, Ph.D., R.N. *Council on Cardiovascular Nursing, American Heart Association*

Cardiovascular diseases (CVD) are a major cause of disability and the number one cause of death in the United States, killing more than 954,000 Americans each year. Recent estimates by the National Center for Health Statistics show that the number of deaths from CVD began to rise in 1993 after years of decline. More than one in four Americans suffer from some form of CVD at an estimated cost of $151 billion in 1996. CVD remains the number one killer of females, and about 45 percent of female deaths in the United States are from CVD. CVD kills almost twice as many American females as all cancers, and five times as many females as breast cancer.

Until recently, heart attack, stroke, and other cardiovascular diseases in women have not been recognized as serious health problems, particularly by women themselves. Despite the increasing attention to women's health issues, continuing and emerging gaps in knowledge about women and CVD must be addressed. Several examples of research studies that are needed to answer some of the most perplexing questions relevant to women and CVD are presented.

These examples of research needs relate to: the interaction of sex hormones and specific risk factors for CVD and atherosclerosis; gender differences in the distribution of risk factors for coronary heart disease and stroke, levels of risk, and risk of disease at similar risk factor levels; the role of obesity and weight gain in CVD; the role of socioeconomic and psychosocial factors, as well as access to and quality of medical care, on CVD risk factors; the use of luteinizing hormone releasing hormone agonists and antagonists in the treatment of uterine fibroids; risk factors for and onset of stroke; the effect of autoimmune disease and inflammatory cytokines on the development of coronary heart disease, atherosclerosis, and heart muscle dysfunction; the relationship of diabetes and CVD status; and the apparent differences in presentation of CVD and response to intervention. Unique scientific and logistical issues related primarily to hormonal differences, psychosocial variables, and possibly anatomical factors peculiar to women must be addressed in any randomized trial of CVD in women.

The ability to combat CVD correlates directly with the level and quality of overall support for basic and clinical research and prevention efforts. Since 1949 the American Heart Association (AHA) has invested almost $1.4 billion in research to increase knowledge about CVD, making AHA second only to the National Institutes of Health in terms of financial commitment to cardiovascular research. The AHA will continue to commit increased funding toward this research. However, a significant increase in funding for federal biomedical research is critical to win the battle against CVD. Chronic underfunding of heart and stroke research has also discouraged young people from entering this field of research.

Penelope J. Hitchcock, D.V.M.
Chief, Sexually Transmitted Diseases Branch
National Institute of Allergy and Infectious Diseases

Adolescent populations are at high risk of sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infection. In the United States it is estimated that 12 million incident cases of STDs occurred in 1994; the majority of cases are in young adults, with an estimated 3 million occurring in teenagers. Cases of gonorrhea are found among populations of low socioeconomic status (SES) in urban and rural areas. Chlamydial infection is highest in 15 to 19 year olds regardless of SES. For the other viral STDs, the situation is similar to that for gonorrhea and chlamydial infection.

Using the framework of a mathematical model that considers how, why, and whether an infection spreads within a population, biological and behavioral risk factors/markers that alter the risk of STDs, particularly for adolescent populations, are reviewed. Within each factor of the equation there are risk factors that have been causally associated with increased risk of transmission/acquisitions.

In terms of infectivity rate, the following factors represent increased risk for adolescents: genetic susceptibility, sexual practices, age, age at first intercourse, contraceptive methods, alcohol use, drug use (intravenous and other), smoking, and co-infections (STDs). For the rate of partner change and partner characteristics marker, the number of partners, type of partner, age, and age at first intercourse are factors that increase risk for adolescents. Host response, health care behaviors, routine screening, early diagnosis and prescription, prescription compliance, partner notification, and vaccine compliance are all increased risk factors associated with the duration of infection marker.

Currently, diseases such as syphilis, trichomoniasis, chancroid, HIV, and gonorrhea are concentrated in high-risk populations. Diseases such as chlamydial infection, genital herpes, and human papillomavirus infection are currently widespread, affecting the general population as well as the high-risk populations. Theoretically, as an incurable viral disease with an estimated 10-year incubation period, HIV infection is likely to "redistribute" over time, given that there is no biological reason for it to be confined to high-risk populations.

The risk factors/markers identified represent a formidable research agenda that includes basic biomedical and behavioral research, applied research, and clinical and operations research. More support for clinical services for adolescents in a variety of settings is implicit in an effective approach to prevention and control.

Lisa Kaeser, J.D.

Senior Public Policy Associate
Alan Guttmacher Institute

The Alan Guttmacher Institute is a not-for-profit public education and public policy organization that focuses on reproductive health. This testimony addresses the needs in one area of reproductive health, that of further research into successful use of contraceptive methods to prevent unintended pregnancy.

An increasingly greater portion of women's lives is spent attempting to control their fertility. During the last century, both puberty and sexual initiation have moved to earlier ages. The interval for women between puberty and marriage has risen and most married women choose to delay or limit the number of children they have. Women today spend three-quarters of their reproductive lives from menarche to menopause trying to avoid becoming pregnant.

Unintended pregnancies, and their outcomes, carry significant health and social consequences for both the woman and, if she carries to term, the child. However, in 1988, more than 3 million unintended pregnancies occurred in the United States. If contraceptives were always used perfectly by everyone who wanted to avoid becoming pregnant, the rates of unintended pregnancy in the United States would be a fraction of where they now stand. Current wisdom, which provides a major rationale for continued research on new contraceptives, points to difficulties women and men have integrating correct and consistent use of current methods into their daily lives. Clearly, a better understanding of the needs of women and their partners who wish to use contraception is needed, both to increase the use of currently available methods and for the development of new ones.

Specifically, a better understanding is needed of what causes people (1) to delay initiating use of a contraceptive method once they become sexually active, (2) to permit gaps between periods of contraception use, or (3) not to use their chosen method as well as possible.

Obstacles that may prevent couples from using contraceptives when they are at risk for unplanned pregnancy include: (1) women not initiating the use of or stopping the use of contraceptives due to a lack of accurate information or fear of side effects, and (2) access to and payment for family planning services. Research is needed on what may contribute to using contraceptives. Such research may focus on: a woman's ambivalence about childbearing, common mistakes in the use of contraceptives, concerns about disease that prevent women from using the most effective contraceptive method(s), and the impact of education and counseling on the successful use of contraception.

Although contraceptives have been used for decades, many questions remain unanswered. While answers to these questions will not necessarily "solve" the dilemma of unintended pregnancy in the United States, if the answers can assist in reducing the rates of unintended pregnancy, a substantive contribution to women's health can be made.

Virginia T. Ladd, R.T.

Executive Director
American Autoimmune Related Diseases Association

Autoimmunity is a debilitating condition in which the immune system attacks the body's own tissues or cells. The condition is the root cause of more than 80 serious and chronic diseases, including connective tissue diseases (lupus); diseases involving the joints (rheumatoid arthritis); skin diseases (scleroderma); neuromuscular diseases (multiple sclerosis); and endocrine diseases (Graves disease). The American Autoimmune Related Diseases Association (AARDA) is the nation's only organization dedicated to raising the awareness of early warning signs of autoimmune diseases and promoting collaborative research efforts to cure autoimmunity.

During its recent Health Women 2000 conference in Washington, the Office of Research on Women's Health recognized that autoimmunity is largely a women's health problem, representing approximately 75 percent of all autoimmune patients. ORWH has a great opportunity to increase the visibility and focus on autoimmunity as a common cause of diseases that disproportionately affect women.

For many women, getting a proper diagnosis for an autoimmune disorder is as difficult as the disease itself. Misdiagnosis and late diagnosis and their associated problems are major concerns of AARDA. Several factors contribute to improper diagnosis, which delays appropriate treatment. For instance, symptoms of autoimmunity vary and they may come and go. Also, symptoms are often difficult for a woman to describe precisely to her physician. The multiplicity of symptoms and affected body systems may cause the patient to undergo a series of unsuccessful tests as specialists attempt to establish a diagnosis. The difficulty in identifying symptoms may result in a physician not taking the patient's complaints seriously. A survey AARDA conducted found that over 65 percent of patients with autoimmune diseases are labeled hypochondriacs in the earliest stages of their illness. The psychological impact of late diagnosis can be devastating.

The problems of timely recognition and diagnosis results from the fragmented way in which the medical community approaches autoimmunity. Unlike cancer, autoimmunity has yet to be embraced by the medical community as a category of disease. Discovering the root cause for all autoimmune diseases depends on basic research. ORWH is well-positioned to take a leading role in organizing a concerted education and research campaign to improve recognition of and early testing for autoimmune diseases and in promoting basic research into autoimmunity. 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.

The AARDA desperately seeks to bring a national focus to autoimmunity. We feel that ORWH, perhaps more than any other office or institution, can substantially improve our country's approach to this critical women's health issue. We strongly urge ORWH to push for collaborative efforts to conduct basic research that would bear fruit for all autoimmune diseases, rather than continuing to focus more narrowly on individual diseases. Through combined research we will be able to diagnosis, treat, and ultimately cure this debilitating disorder.

Dorothy Mann *Executive Director, Family Planning Council*

The Family Planning Council is a private, nonprofit organization which receives all Title X federal family planning funds for Philadelphia and its four surrounding counties. With these and other public funds, the Council subcontracts with 24 local health care organizations. The typical Title X family planning patient seen in any one of our programs is an African-American woman between the ages of 20 and 29. She is poor, and the family planning clinic offers the basic health care she needs to stay in school, keep a job, or pursue vocational training.

Gaps in knowledge about women's health involves reproductive issues. Specifically, the need for knowledge is greatest in the areas of pregnancy and disease prevention. According to the Institute of Medicine, the rate of unintended pregnancy among American women is disgracefully high, with almost 60 percent of all pregnancies unintended. Regardless of a woman's economic level, unintended pregnancy affects every sphere of a woman's life, threatening her physical well being, her emotional stability, and her ability to obtain or keep gainful employment. The high rate of unintended pregnancy among American women should be a clarion call to the health care and medical research establishments and the pharmaceutical companies to devote the resources necessary to significantly reduce this statistic. Contraceptive research is needed to find methods that offer the full range of protection against unplanned, unwanted pregnancy as well as debilitating, highly contagious diseases.

A number of other questions also have important implications for women's health. These questions relate to HIV/AIDS; the reproductive health care needs of premenopausal, perimenopausal, and postmenopausal women; risks for unintended pregnancy, sexually transmitted diseases; cancer; education about the use of hormone replacement therapy; and infant mortality among African Americans.

Unlike with research and medical service delivery for cardiovascular disorders, breast cancer, endocrine disorders, and Alzheimer's disease, Congress dictates the methodology, scope of research, and medical procedures in the area of reproductive medicine. Currently, Congress is considering legislation that will require the written consent of parents for any research that involves adolescents. Although strict consent requirements and protection of human subject regulations exist, Congress wants to curtail research that examines any research related to adolescent sexual health. In this way a political agenda takes precedence over the quest for knowledge and understanding. It is easier to allocate public and private resources to politically palatable research in such areas as breast cancer and osteoporosis than it is to devote the necessary resources to other equally important areas of women's health that are related to sexuality. While adding women to clinical trials and other research efforts is necessary and important, it will not matter if political agendas dictate subject, method, and outcome. In women's health research, it is important to invest in and examine controversial issues of sexuality and reproduction. It will take courage to expose and stand up to powerful political forces that would otherwise impede this research.

Executive Director
Rita M. May *Sjögren's Syndrome Foundation, Inc.*

Autoimmune and rheumatoid diseases are the stepchildren of the women's health initiative. Despite the fact that diseases such as multiple sclerosis, scleroderma, and Sjögren's syndrome profoundly affect women, they are not considered topics of high priority on any of the women's health agendas.

Medicine and science favor the so-called "interesting questions." They attract the greatest scientific intellects, are well funded, and reflect social priorities. For example, AIDS, a comparatively rare disorder, was successfully transformed from an interesting scientific problem into a well-funded institution. During the 14-year period from 1981 to 1995, about a half-million Americans were diagnosed with AIDS compared to more than 37 million Americans who suffered from other autoimmune diseases. The drive to find a cure for AIDS has made NIAID the third most heavily funded NIH institute, while funding for more widespread autoimmune diseases has declined.

Probable reasons for the lack of interest and minimal funding include the following:

- The sheer number of autoimmune diseases and the dearth of clear diagnostic guidelines
- The association of autoimmune diseases with aging but not death, and the subsequent lack of urgency to discover treatments and cures
- The higher prevalence of autoimmune disease among women than men

Sjögren's syndrome presents an excellent example of the ignorance, invisibility, and unpopular nature of autoimmune and rheumatoid diseases in general, and within the scientific and women's health communities in particular. Although it affects 2 to 4 million Americans — 90 percent of whom are women — it is one of the least diagnosed. Moreover, none of the most likely NIH institutes — NIAMS, NIAID, NEI, nor NIDR — has sponsored epidemiological studies directed at Sjögren's syndrome. Indeed, the chances for even highly sophisticated audiences to have heard of Sjögren's (much less be able to spell it!) are low, sadly demonstrating the lack of interest in these diseases and in the women who suffer from them.

I ask that NIH dedicate research monies to autoimmune disease research and conditions affecting the aging as well as diseases affecting reproductive issues and youth.

Margaret K. McLaughlin, Ph.D. *Magee-Women's Research Institute*

At the Magee-Women's Research Institute, we believe that increasing the number of women scientists and facilitating their careers will result in more women's health researchers. This task requires a concentrated effort to increase public awareness about the significance of scientific research. We believe that our outreach work will result in greater awareness of and interest in science and research on women's health. Our efforts target high school and college students — both boys and girls, men and women. We host tours of the Institute, provide hands-on demonstrations of our work, sponsor a summer research volunteer program, and provide stipends for college students studying the sciences. Some programs we target directly at young women. For example, we have a special relationship with a local girls' high school and pay special attention to women's colleges in our geographic area.

At a more advanced level, we recognize that nursing is a severely underutilized source of women in science. The Institute pays part of the salary for the director of nursing research at Magee-Women's Hospital, where she educates nursing staff about research opportunities and recruits participants for Research Institute projects.

Retention, as well as recruitment, is critical to ensuring there are women in science. We feel that it is important to not lose sight of the problems that face men and women embarking on careers in scientific research. It is critical that they understand the gender issues in research and are supported in their efforts to advance in the areas in which they choose to specialize. Our proactive mentoring program is a crucial tool for assisting new researchers in overcoming these challenges and encouraging them to remain in the field.

We are proud of these efforts and hope others can learn from them in their quest to demonstrate and increase public awareness about the joys and excitement of careers in science.

Associate Medical Director and Professor of Pathology and Laboratory Medicine
Allegheny University Hospital
American Society of Clinical Pathologists

Powers Peterson, M.D.

New developments in the area of women's disease research and diagnosis as well as the increased participation of women in biomedical careers have been encouraging. However, more needs to be done if progress in the field of women's health is to continue successfully into the 21st century.

Women currently comprise a large sector of the health care community. In 1994, women represented 18 percent of all physicians in the U.S. In the field of pathology, women comprised 24 percent of all pathologists in the country and 83 percent of the medical technologists certified by ASCP in 1995.

ASCP has been indirectly involved in efforts to recruit, retain and advance women in biomedical careers on a project-to-project basis. ASCP volunteers have been involved with educational projects, funded through the Title VII Allied Health Project Grant Program, designed to enhance recruitment and retention of minority and disadvantaged populations. One model program utilizes the mentor concept and promotes the recruitment and retention of medical technologists through a four phase design that begins with career awareness activities for elementary and middle school students. Similar projects could be established for the recruitment and retention of women in biomedical careers.

Offices of Women in Health Professions on some medical school campuses provide another successful model. These offices serve as excellent resource centers and bring together a variety of health care providers, both physician and non-physician, to address issues related to women in biomedical careers. In addition, ASCP offers print and video materials describing careers in laboratory medicine; maintains a scholarship fund for individuals wishing to pursue such careers; and has a Career Recruitment Network, which provides mentors for those seeking to enter the field of laboratory medicine.

Although progress in addressing women's health issues is being made, a stronger infrastructure needs to be established to identify and respond to new challenges for women's health. Adequate funding is imperative to explore further and better understand the implications for women regarding new advances in disease research in the areas of cancer, heart disease, and HIV and other infectious diseases. In particular, more must be done to research further and investigate various aspects of women's health and coronary heart disease. In addition, women's health care could be served better as a comprehensive discipline that uses a combination of medical perspectives in patient care. The future of women's health research also needs to include a focus on emerging infectious diseases including chlamydia, sexually transmitted human papillomavirus, and Group B Streptococcus. Despite the continued threat of emerging infections, support for applied research and control efforts has declined during the past decade. For this reason, it is critical that women's health research, and the resources to conduct such research, focus on addressing emerging infectious diseases.

Health Policy Consultant
Marj Plumb, M.N.A. *National Center for Lesbian Rights*

The Lesbian Health Project of the National Center for Lesbian Rights supports grassroots organizing and advocates for equitable public policies regarding health care for lesbians. The purpose of this testimony is to begin to articulate a common understanding of what lesbian health issues are, to share the successes of the modern lesbian health movement, and to present a universal list of recommendations that can be enacted by public health departments, health agencies, research institutions, and medical schools. The lesbian community is more interested in health issues than ever before, is more knowledgeable about the health care system and health terminology, and has greater access to the federal health department than under any other administration. Grassroots groups have developed and implemented lesbian and bisexual women's health needs assessments and have begun strategic planning for program development in many communities.

Lesbians and other women who partner with women have unique health concerns which often go unaddressed in a medical setting which generally assumes heterosexuality. Specific issues include cancer screening, sexually transmitted diseases, HIV, depression, substance abuse, relationship issues, aging, pregnancy, and parenting. Among the most significant health issues for lesbian and bisexual women is lack of access to sensitive medical services. This lack of access may result in lesbians avoiding care until forced to do so by the severity of their symptoms; delay in diagnosis and treatment may result in poorer health outcomes for the population.

Researchers face numerous difficulties in studying the lesbian population, thus complicating the ability to present health status information about this population. Among these difficulties is the challenge of obtaining random samples and women's reluctance to disclose their sexual orientation or the gender of current or past sexual partners. Specific points for consideration in developing future research activities are presented.

Numerous national organizations and projects have been formed to address specific health care needs and are potential sources for researchers to gain technical assistance and access to lesbian research subjects. Recent efforts by the U.S. Department of Health and Human Services to include lesbian and bisexual women's health issues in programs, conferences, and written materials are described; these efforts represent significant advancements in lesbian access to the federal public health department. The testimony outlines recommended efforts within the federal, state, and local health systems, as well as within the private sector to ensure the widest access to information, services, and research for lesbians, bisexual women, and all women who partner with other women. Specific recommendations are made in the following areas: conducting research, providing services for the prevention and treatment of disease, educating and informing the public, recruiting and training health care personnel, and designing guidance on lesbian and bisexual women's health initiatives.

Linda Quander, Ph.D. *Associate Professor, Clark Atlanta University*

Strategic management is a process which requires planners and decisionmakers to accomplish eight key tasks:

- Clarify purpose
- Select goals and objectives
- Identify present strengths and weaknesses
- Analyze future opportunities and threats
- Compare strengths and weaknesses to opportunities and threats
- Decide on long-term strategy
- Implement the strategy
- Evaluate the strategy

Women's health researchers must learn to anticipate rapid changes that affect their projects, working groups, organizations, and even their careers. Conferences — such as this one — can facilitate this by basing training, education, and development on projected future needs.

Needs assessment is critical for identifying learning gaps and discovering weaknesses. It is part of the process in which we ascertain future needs relative to overall performance in women's health care. Therefore, effective communication about needs assessment is paramount in designing, implementing, and interpreting research programs. Researchers must be aware of how communication can ultimately enhance or adversely affect women's health.

NIH and the National Institute of Environmental Health Sciences are to be commended for recognizing that scientific knowledge, combined with effective communications, can empower women to better control their personal environments and thus improve their overall health. I am particularly enthusiastic about NIH's Women's Health Initiative, an important study of strategies that can enhance adoption of healthy behaviors by using a multidisciplinary approach in cooperation with various community-based prevention centers.

Researchers need to analyze various types of traditional and nontraditional channels. For example, studies of African-American women have found that churches are a particularly useful route. We now know that it is important to understand how and why community-based prevention centers appear to be effective in reaching minority populations.

Communication channels to women must be future-oriented and proactive. Strategies need to see women as active, adaptive team members, not as passive obstacles to progress. Cooperative partnerships are effective tools for addressing inequality in health care for women and reaching women throughout the community.

James M. Roberts, M.D. *President, Society for Gynecological Investigation*

One of the refreshing aspects of the increased emphasis on women's health research attributable to the Women's Health Initiative is the heightened awareness that women's health is not limited to reproductive health. Research has shown that there are gender differences in many aspects of health and medicine, and recognition of this phenomenon has led to changes in how women are treated for illnesses not directly related to their gender. Indeed, we are now seeing improvements in female morbidity and mortality statistics that reflect this revision in medical approaches and attitudes toward female patients.

It is now generally recognized that many diseases manifest themselves differently in women than in men. Women face different cardiovascular risks than men, which has certain implications for diagnosis. Similarly, women appear to be more susceptible than men to illnesses such as autoimmune disease, and we now know that women metabolize drugs differently than men.

Of course, we should not abandon research on reproductive health. Reproductive health statistics such as premature births remain alarmingly high, particularly in disadvantaged populations. Likewise, death from preeclampsia — a condition recognized for more than 1,000 years — is the highest cause of maternal death in developed countries. Death rates also remain high for infants of preeclamptic women.

Research in these areas has led to many exciting discoveries with important treatment possibilities for genetic ailments. New findings in molecular biology and our ability to handle data more effectively provide us with opportunities to solve major problems that have affected women and infants.

We must also ensure that researchers interested in women's health are nurtured and supported throughout their academic and professional careers. Money for training — both federal and private — is extremely important. Still, our most valuable resource is the cadre of talented individuals embarking on scientific careers, including the generation of future scientists now in grade school.

In this time of restricted resources and academic upheaval, we must resist the urge to complain that things are worse than ever. We must "hang tough" and remember the importance of our goal. We must convey to our young successors the rewards, excitement, and vital importance of research relevant to women's health.

Assistant Professor of Clinical Medicine and
Associate Director of Nuclear Cardiology, Columbia University
Association of Black Cardiologists

Roxanne A. Rodney, M.D.

(Testimony prepared by the Association's Committee on Cardiovascular Diseases in African-American Women: Sheila A. Robinson, M.D.; Hannah A. Valantine, M.D.; Jan D. Webber, M.D.; Roxanne A. Rodney, M.D.)

Coronary heart disease is the number one killer of American women, and African-American women are disproportionately affected. In 1992, the death rate from coronary heart disease was 32.6 percent higher in African-American women than in Caucasian women. It has also been reported that black women's rate of mortality following heart attack is higher than that of white women, black men, and white men.

Black women also have the highest estimated crude prevalence of stroke, and the mortality rate from stroke in black women is 77 percent higher than that in white women. Hypertension is also more prevalent in African-American women ages 30 to 39 and ages 60 to 69, compared to Caucasian women and Mexican-American women in the same age groups. The mortality rate due to hypertension is also higher in women than men (58 percent vs. 42 percent, respectively). African-American women are also more likely to have risk factors for CVD. Risk factors discussed are hypercholesterolemia, diabetes, smoking, physical inactivity, and overweight.

The Association of Black Cardiologists unequivocally supports increased funding of clinical and basic science research in cardiovascular diseases in African-American women. Women in general, and African-American women in particular, have been underrepresented in research studies. However, in order to obtain accurate data on at-risk populations, these groups must be included in research studies. The Association also promotes the provision of educational programs for at-risk populations. Such programs should address primary disease prevention through risk factor modification and should emphasize the importance of seeking early, appropriate care if symptoms are present in order to reduce the incidence of secondary complications. Coupled with this, health care providers must continually be educated about the prevention, timely diagnosis, and appropriate treatment of cardiovascular diseases in black women.

In addition to the immeasurable impact of cardiovascular morbidity and mortality on the lives of African-American women and their families, the societal impact in terms of lost productivity and health care expenditure cannot be understated. Health care dollars are more effectively utilized in the generation of accurate research data, which can then be appropriately implemented via the education of at-risk groups and health care providers. This strategy is medically appropriate and cost effective.

Professor of Health Education and Women's Studies
Sheryl Burt Ruzek, Ph.D., M.P.H. *Temple University*

The national women's health research agenda should be refocused to address: (1) the prerequisites to women's health that are ignored in a narrow biomedical paradigm; (2) pressing issues in social and behavioral paradigms; and (3) ignored or suppressed research questions grounded in mind/body, alternative, and folk healing traditions. This testimony reflects disquietude with the definition of women's health that is used widely in government and medicine. This narrowly biomedical definition, which focuses on diseases or "conditions" in women, institutionalizes expectations and collective demands for biomedical interventions at a time when access to medical care is particularly problematic. It may be preferable to adopt research priorities that reflect the vision of health that the World Health Organization promotes as "a state of complete physical, mental, and social well being and not merely the absence of disease or infirmity." The definition outlines a number of "prerequisites for health," which have important gender dimensions and raise critical issues about social class and culture in the production of health.

A women's health agenda might profitably build on National Center for Health Statistics reports of a clear gradient in mortality both for white women and women of all races by educational attainment. The inclusion of education as a research variable would help interpret findings that are reported by race or ethnic group. More attention needs to be paid to health status differences among women within racial/ethnic groups.

Emerging mind/body models that emphasize psychological and spiritual dimensions of health seem particularly invisible in federal agendas for women's health. More research is needed on how women's health needs are addressed in traditional, non-western healing systems that posit spiritual and psychological dimensions of health. However, mind-body paradigms pose a "double-edged sword" for many women in that psychogenesis, in the past, has been used against women by physicians. Important relational concepts such as caring also deserve more recognition.

Theoretical and conceptual work is needed to link empirical research areas to one another. Integrative models are needed to understand how working and living conditions, individual health behaviors, psychological and emotional processes, and effective biomedical interventions together contribute to health and well being. Women's health research must also explicitly take into account the health of significant others, including men, children, parents, and life partners.

Many questions deserve attention in a broader framework for understanding women's health. These questions relate to: the cultural relevance and appropriateness of services; links between race/ethnicity, socioeconomic status, and the cultural context of health practices and the availability of health services; the ways in which women in different life situations view and make decisions about health, disease, and health-related issues; utilization of traditional healers and other less conventional therapies; social and environmental factors in diverse groups; and research-content decisionmaking.

Eleanor G. Shore, M.D., M.P.H.

Dean for Faculty Affairs
Harvard Medical School

The representation of women at Harvard Medical School (HMS) and Harvard School of Dental Medicine (HSDM) in 1996 range from a high of 49 percent for students to a low of 7 percent for the rank of Professor. At the student, trainee (clinical or research fellow), and instructor levels, representation is consistent with or better than the availability pool; however, at the voting faculty ranks (Assistant Professor and higher), the percentages reflect a critical problem. Even among those women already appointed as Instructors or Assistant Professors, a smaller percentage are promoted over a 10-year period than their male colleagues.

The Office for Faculty Affairs has launched a number of interventions to try to correct this gender gap including the establishment of appointment procedures designed to assure that new faculty positions are accessible to all qualified candidates; the requirement for formal annual career conferences for women and underrepresented minorities to assist in career planning and direction; and career assistance by conferences, workshops, and ad hoc individual counseling for trainees and junior faculty through the Office for Academic Careers, Minority Faculty Development Program, Women in Academic Medicine Program, and the Office for Faculty Affairs.

The most serious problem faced by women in their academic careers is demonstrating independent academic productivity (research, teaching, grant application, and paper writing) because of a lack of sufficient protected time for these activities. Without substantial tangible evidence of academic creativity, promotion comes more slowly, if at all. The 50th Anniversary Program for Scholars in Medicine provides for ten fellowships a year for women or men who can demonstrate both great academic promise and complicating personal responsibilities which might be remedied by a grant of $25,000. In the first competition, more than 210 women and men applied for the ten fellowships.

A similar set of national fellowships could make a large difference in diminishing the gender gap. Given the challenges in the biomedical field for the 21st century and the fact that more than half of the students in science and medicine at HMS are women, there is every incentive to support these women through the hardest time in their professional lives. Men qualify for the great majority of sabbaticals at HMS since they occupy 93 percent of the senior positions that are covered by the University's sabbatical policy. It seems only fair that institutional resources be directed at an earlier point in women's careers when the need is greatest, rather than saving the support for a sabbatical that few women will ever reach without this additional help earlier in their careers.

Founding President
Martha Torres-Montoya, M.S.P.H. *Hispanic Women's Health Association*

Research into the health needs of Hispanic/Latina women is very limited at present. Notably meager are epidemiological data, program evaluation models, effective interventions, and clinical trials. Where such research exists, it generally focuses on issues of access — health insurance, geographic, language, and cultural barriers.

As a result, little is known about Hispanic/Latina women's health issues and status. The inability to describe the problems or document the needs has put these communities in a poor position to obtain government funding. This lack of original research has seriously impeded health service agencies and community-based organizations from addressing gaps in health care for Hispanic/Latina women. Until and unless community-based agencies are able to document health and social problems affecting Hispanic/Latina women, federal funds are unlikely to be forthcoming. The result is poor, ineffective health care policies that, in turn, impact the availability, distribution, and utilization of scarce health care dollars.

The Hispanic Women's Health Association (HWHA) has a strong commitment to developing and implementing successful research projects in the Hispanic community. We recommend that ORWH conduct research into the following areas of importance to Hispanic/Latina women:

- Differences in health perceptions, physical and mental health, and social support systems;
- Impact of welfare reform;
- Impact of acculturation on health status;
- Health beliefs and practices;
- Preconceptional health issues for use in a national campaign;
- Infertility;
- Depression, cultural perceptions, and coping strategies;
- Interventions to reduce teen pregnancy;
- Interventions that encourage men to become involved in family planning;
- Alcohol use/non-use; and
- Patterns of family formation.

The HWHA also urged ORWH to revisit the recommendations made for Hispanic/Latina women in 1991. They requested that ORWH prepare a report that describes how those recommendations were implemented in the past 5 years and/or how they could be integrated into the 1996 agenda.

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

Women are far more prone than men to hip fractures and bone-related diseases such as osteoporosis, and their susceptibility increases with age. The associated loss of life and suffering involved in fracture and disease is enormous, as are the medical bills, which approach $10 billion each year.

As a mender of broken bones, the American Academy of Orthopaedic Surgeons (AAOS) is deeply concerned that nearly 300,000 individuals will suffer hip fractures this year and that women's fractures will outnumber men's by almost 3 to 1. In addition, women over age 65 have a 1-in-5 chance of suffering a hip fracture during their lifetimes.

These statistics demonstrate the importance of early intervention in reducing the prevalence of osteoporosis. Since many orthopaedic injuries are preventable, early intervention provides the greatest potential for reducing the numbers. As such, education and intervention must begin in childhood. Although evidence shows that increasing calcium intake during adolescence is critical in the development of peak bone mass and growth, there is a desperate need for longer, prospective trials. We need data confirming the current actual intake of calcium in our young people. We also need to determine how we can encourage young people to alter their dietary lifestyles.

While the Academy is concerned with osteoporosis and resultant injuries, we are also interested in the incidence of sports injuries in young female athletes. Athletes and their coaches need to be instructed more effectively about the orthopaedic risks associated with playing sports. Investigation into the increased risk of knee injury in young female athletes as opposed to young male athletes in also essential. Strengthening strategies and training techniques must be explored at every level so that injuries can be prevented.

For many years, AAOS has devoted tremendous energy to osteoporosis research and injury prevention such as our campaign called "Live it Safe," which we sponsored with the American Association of Retired Persons. Although we believe these programs are effective, our own goals are to expand these efforts so that we can better understand the needs of young women and design effective educational strategies to improve their health habits.

The Academy commends the Office of Research on Women's Health for its extensive work in encouraging research on solutions to women's health problems, such as osteoporosis. We believe the Office of Research on Women's Health can and should play a leadership role in identifying the key cause and effect relationships of osteoporosis. The cost of education, intervention, prevention, and rehabilitation amounts to several billion dollars a year. Nevertheless, the improved quality of life is incalculable.

Gastroenterology Women's Coalition
(Representing the American Gastroenterological Association
American Society for Gastrointestinal Endoscopy
American Association for the Study of Liver Diseases
and American College of Gastroenterology)

Jacqueline Lee Wolf, M.D.

Colorectal cancer is the second deadliest cancer in the United States and the third leading cause of cancer-related death in women. Women with hereditary colon cancer are at increased risk of ovarian and endometrial cancers. Further study of colon cancer in women may provide important information on the etiology of these associated cancers. Also, further research is needed on how gender and knowledge of genetic status affect screening participation.

Basic and clinical research is needed on the pathogenesis, immunology, and therapeutic approach to primary biliary cirrhosis, a disease nine times more common in women than in men. Among the additional aspects of liver disease in women that merit expanded study are: the impact of sex hormones on elements of the immune system and on the proliferation of liver cells; the factors responsible for differences between men and women in alcohol absorption and metabolism; and the effects of estrogen and progesterone on the development of alcoholic liver disease.

The *Helicobacter pylori* bacterium is a relatively new discovery that has revolutionized and advanced treatment for peptic ulcer disease. Studies show that *H. pylori*-infected women are 15 to 18 times more likely to develop gastric cancer than infected men. Further research is needed on the role of acid secretion in protecting against the development of gastric cancer and on clinical approaches to preventing gastric cancer. Research on the prevention of peptic ulcer disease induced by non-steroidal anti-inflammatory drugs (e.g., aspirin and ibuprofen) is needed.

Gallbladder and biliary tract disease are twice as common in women as men. The role of estrogens and progesterones in the formation of gallstones particularly during and immediately following pregnancy; the basic biology of gallstone formation, and potential preventive measures merit further study.

Irritable bowel syndrome and functional bowel disorders are twice as common in women as men. Additional research is needed on the effect of the menstrual cycle on functional bowel disorders; and the relative impact of genetics, the environment, and social factors on the etiology and perpetuation of symptoms.

Aside from research priority objectives, the Coalition recommends the following mechanisms for enhancing biomedical research career opportunities for women: NIH should expand small grant support for mentoring programs for women; NIH should provide seed money for the initiation of special academic tracks for women interested in research careers; academic institutions should be encouraged to adopt "stop the clock" policies with regard to tenure and promotion of women faculty; NIH should allow institutions to include in their indirect cost calculations, programs to prepare women faculty members for senior administrative positions (departmental chairs or deans) through which they can continue to foster research and influence the research activities of their institutions.

Elizabeth Yoffe, M.A. *Self*

Conventional medicine is a wonderful, lifesaving, and life-enhancing tool. However, its long monopoly in the overall health care picture is beginning to loosen as laypeople, insurance companies, and even parts of the medical establishment recognize that alternative therapies can complement conventional medicine.

My interest in the health care system was sparked after I suffered a crippling stroke at the age of 30. Conventional medicine and rehabilitative therapy literally got me back on my feet, but their value in the recovery process was limited. To improve my physical functioning, I turned to alternative healing methods: meditation, relaxation techniques, and visualization. I became more intrigued by what was then called “unconventional medicine” and set out to learn more about alternative modalities.

Today, more people — especially women like me — are questioning the existing medical system, taking control and responsibility for their health, and exploring alternative treatments for chronic or degenerative illnesses. However, resistance to alternative healing persists, particularly from conventional practitioners.

There are interesting links between the emerging fields of women’s health and alternative medicine. Both are regarded as outside the medical norm. The same can be said about medical practices that originate in China and India, which are far older and more refined than Western medicine. There seems to be an assumption that only medicine developed from a Western cultural perspective is “real.” Other medical traditions are regarded as backward or primitive. Alternative medicine may receive more acceptance from women patients and health practitioners because, historically, women have a deep bond with natural or folk remedies.

It is ridiculous to deny people education about and access to alternative therapies that might help them recover or better manage illness. I recommend the following four steps:

- Increase cooperation between the Office of Research on Women’s Health and the new Office of Alternative Medicine (OAM);
- Integrate findings from OAM into public health education programs;
- Integrate alternative medical modalities in medical schools; and
- Increase communication between conventional and alternative medical professionals.

Neither conventional (i.e., Western) medicine nor alternative medicine can cure all our ills. However, now that we have access to therapeutic modalities from different cultures and philosophies, it is the responsibility of all medical practitioners to work together to improve on what we have today.

SUMMARIES OF PUBLIC TESTIMONY NEW ORLEANS, LOUISIANA JUNE 11, 1997

Gerald S. Berenson, M.D.
Tulane Center for Cardiovascular Health

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Carolyn Evans, M.S.W.
Grace House of New Orleans, Inc.

Wonda L. Fontenot, Ph.D.
Wannamuse Research Institute

Julie E. Goslee, Pharm.D.
Xavier University of Louisiana

Alton E. Hadley
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Marlene Keeling, B.S.B.A.
CANDO (Chemically Associated
Neurological Disorders)

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Medical Professionals with CFIDS/CFS/ME

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Gerald S. Berenson, M.D. *Director, Tulane Center for Cardiovascular Health*

Heart disease is the major cause of morbidity and mortality in women and accounts for an unbearable cost of medical care in middle-aged and older women in the United States today. Between the years 1979-1981 Louisiana ranked seventh in the average annual coronary heart disease (CHD) death rate among white women and sixth among black women ages 35 to 74 years. Although the prevalence of early CHD is greater in men, the amount of CHD in women after the age of 65 increases significantly; overall, women manifest symptoms of cardiovascular disease on the average 10 years later than men. The high morbidity and mortality after menopause, however, indicate the importance of studying heart disease in women. Diabetes mellitus is particularly severe in women and promotes CHD at an early age. It is also known that cigarette smoking and inactive lifestyles, high fat and high sodium diets and the marked prevalence of obesity, as well as hypertension and dyslipidemia, contribute to severe coronary artery disease in relatively young women.

Studies in the Bogalusa Heart Study, a long-term epidemiologic study on children, adolescents, and young adults, show risk factors can be identified early in life and the major etiologies of heart disease, atherosclerosis, hypertension, and adult onset diabetes all begin in childhood. Morbidity in the young adults ages 19 to 32 years shows that some 10 percent of white females and 22 percent of black females have a BMI greater than 32.3kg/m^2, representing morbid obesity. Of black females, 15 percent already demonstrate hypertension. Further, risk factors tend to cluster with obesity, increased insulin resistance, hypertension and dyslipidemia. Of particular interest the clustering of cardiovascular risk factors in young adults, Syndrome X, results in a strong relationship with coronary atherosclerotic lesions found at autopsy. This clustering is associated with an acceleration of the coronary atherosclerotic lesions. On an average atherosclerotic involvement of coronary vessels tends to be less in young women, but the severity of lesions can be quite extensive in some individuals, predictive of CHD at a relatively young age.

Poor lifestyles and behavior in youths include cigarette smoking, sedentary activity, and dietary intake. Some 30 percent of high school students are reporting consistent use of tobacco and alcohol, more in white girls. With regard to diet, some 80 percent are exceeding the American Heart Association recommendations for total fat and saturated fat intake. Decreased physical activity has enhanced a secular trend of increased obesity.

The study of cardiovascular risk factors and lifestyles in children and young adults has serious implications for the development of adult CHD, cancer, and osteoporosis. The studies emphasize the need, not only to study females as adults, but to continue investigations of the early onset of chronic diseases as they begin in childhood. Such observations can help guide more rational methods of prevention.

James E. Dill, M.D., F.A.C.P.

President, Director
Endoscopic Ultrasound of Virginia

Gallbladder disease and Irritable Bowel Syndrome (IBS) are both common conditions which affect women more commonly than men. This presentation will discuss the relationship between these two conditions and present a hypothesis for a possible etiologic link between them; especially for the subgroup of patients who have histories of abuse or trauma.

A new technique for detecting difficult-to-diagnose gallbladder disease will be discussed. This procedure involves the groundbreaking technology of Endoscopic Ultrasound which allows viewing of the gallbladder and its contents with accuracy not previously possible. A positive result with Endoscopic Ultrasound is highly predictive of a good long-term outcome following removal of the gallbladder. Also discussed will be a type of gallbladder disease with an overwhelmingly female predominance.

Finally new research on IBS and its relationship to sexual abuse, plus threat of such abuse, will be considered as well as a collaborative, office-based treatment model. Our results indicate that threat of abuse has a powerful effect on IBS symptoms. Patients with histories of sexual abuse, combined with threat, will benefit from a unique treatment approach and environment. Our collaborative treatment model involving the physician, nurse, and counselor utilizes the findings from our research on IBS, abuse, and threat in a practical and compassionate fashion and has been tested in both specialty and primary care settings.

Carolyn Evans, M.S.W.

Grace House of New Orleans, Inc.

The unique needs of women in substance abuse treatment are not addressed in most traditional substance abuse treatment programs which are based on male norms. Often such treatment programs are not only ineffective for women but can actually result in victimization. A holistic treatment model which addresses the physical, emotional, spiritual and sociological needs of women is indicated for safe and effective treatment for female substance abusers. Negative factors for women in currently used treatment modalities are explored along with a model program for gender-specific substance abuse treatment.

Indications for future research needs in gender-specific substance abuse treatment for women are explored.

Wonda L. Fontenot, Ph.D. *Wannamuse Research Institute*

This testimony is concerned with the need and relevance of applied research in relation to behavioral health issues of rural women, especially rural African-American women. An equally important concern is how these behavioral issues impact access and quality care for women, as well as the adoption of preventive health care measures. In the testimony I will call attention to health concerns affecting the health status of women based on cultural factors, socioeconomic conditions, and issues of race and gender.

Cultural beliefs and practices associated with causes and treatment of illness, and other lifestyle behaviors, are important determinants of health status, and in the prevention of morbidity and mortality. The lack of cultural sensitivity on the part of health care providers toward the rural recipient, remains an issue in rural communities, and continues to threaten the cost of effective health care, and contributes to a higher risk of poor health among women.

Issues of gender in rural society is also relevant, as often times medical diagnosis and treatment for women is based on the status of women in society. Thus, more research is needed to improve the quality of health care for women, and to fully understand the impact these variables have on the well being of women who are rural, poor, and/or African American.

Assistant Professor of Clinical Pharmacy
Julie E. Goslee, Pharm.D. *Xavier University of Louisiana*

Gender Differences in Prescribing Postmenopausal Hormonal Replacement Therapy

A growing number of women are living longer (up to one-third of their lives) after their reproductive years, and physicians and pharmacists find themselves increasingly needing to intelligently discuss the issue of hormone replacement therapy (HRT). Concerns such as “How will HRT help me?” “How will it hurt me?” “Is it right for me?” and “How do I take it?” are often asked of both the physician and the pharmacist.

Our understanding of the benefits of HRT has expanded greatly in the last 5 years. Effects of HRT can be measured in the potential for lives saved or lost, but it also may improve many harder to measure quality-of-life factors. Postmenopausal hormone replacement therapy has been shown to be cost-effective in decreasing morbidity and overall mortality in users, especially with long-term use.

So then, why are only 3 to 15 percent of eligible women receiving HRT?

This may be partially due to uncertainty regarding the risks versus the benefits of HRT. Strong scientific evidence that HRT may decrease the incidence of hot flashes, urogenital atrophy, incontinence, osteoporosis, and cardiovascular disease is tempered by uncertainty regarding its effects on the risks of stroke and breast cancer. While the infrequent usage of HRT may be related to these risks, other factors may also contribute to its pattern of use. Research of physician behavior indicates that practice patterns differ between female and male physicians suggesting that physician-specific factors may influence the decision to perform particular tests or to prescribe certain medications. Patients seen by female physicians are more that five times as likely to begin ERT than those seen by male physicians according to Seto, et al. (*J Gen Intern Med* 1996;11:197-203). These gender differences are also seen with cancer screening rates; female physicians perform more cancer screening tests for female patients than do male physicians.

After reading this study (and to my knowledge, Seto, et al. were the first to report on the impact of physician gender on the prescription of ERT in actual clinical practice), I wondered if these same differences could be seen in the pharmacy profession. Very often, the pharmacist is consulted by the patient for answers to questions about their medications, and could there be differences in the knowledge and attitudes about ERT/HRT between male and female pharmacists?

Further research is required to determine if these differences reflect differences between male and female physicians and pharmacists in knowledge or attitude about ERT/HRT, or gender-specific differences in how physicians and pharmacists discuss ERT/HRT with their patients.

Alton E. Hadley

Assistant Secretary, Office of Alcohol and Drug Abuse
Louisiana Department of Health and Hospitals

The following are a list of recognizable health-related issues reported among our State Operated Women's facilities:

- Gastrointestinal problems
- Respiratory problems
- Dermatological problems
- Eye infections
- Dental problems
- Urinary tract infections
- Insomnia
- Sexually transmitted diseases
- Seizure disorders
- High blood pressure
- Controlled diabetes

Several medical concerns are cited as barriers to women seeking treatment, including very high risk pregnancy, uncontrolled seizure disorders, and any problem that absolutely requires medication with abuse potential such as benodiazepines, sedative-hypnotics, narcotic and opioid analgesics, and some skeletal muscle relaxants (i.e., SOMA).

The single most common medical problem that interferes with clients in treatment (other than antibiotics) is the need for dental care. A history of neglectful dental hygiene is common in substance abusing clients. Once in treatment, toothaches and dental abscesses can be severe and some facilities do not have dental services available. Clients usually have no resources to access private dental care.

In summary, we advocate the following recommendations:

A. Education and outreach services need to be available to more women and their families in order to provide information on risks and the preventive steps that should be taken to avoid or reduce addiction to alcohol and/or drugs.

B. Medical professionals need to be adequately trained in the alcohol and drug abuse field, so that they can recognize and better counsel women on prevention and treatment needs.

C. There is a greater need for expanded research projects with a focus on the needs of women.

Council Woman, 29th District (Nashville, Tennessee)
Meharry Medical College

Saletta A. Holloway

Health care is influenced by several factors, including the medical needs of patients, the environment for research and major socioeconomic trends. Other important parameters are the societal expectations for health care delivery. Besides being familiar with the health care environment, I am a Council woman for the 29th District. In that capacity, I come in contact with people in my community who have different expectations about health care delivery and biomedical research. I can summarize those concerns as follows:

- *Health literacy.* Consumers need to understand the enormous amount of information about technological advances and health care delivery systems.

- *The concept of disease.* Public perception of disease is changing. People now understand that diseases can be caused and aggravated by many factors, including biological as well as socioeconomic factors. Also, there is a shift in focus from acute to chronic disorders.

- *The need for health promotion and disease prevention.*

- *Management of disease.* The public understand the need for a comprehensive delivery of health care, which takes into account their specific disease and individual needs.
- *Health care cost.* Emphasis has been given to the cost of hospitalizations, physician payments, and diagnostic tests, while ignoring the high cost derived from lack of prevention, lack of access to health care, and lack of knowledge about health. Preventive medicine should be introduced as one of the elements which contribute to contain and rationalize health care cost.
- *Research focus.* Few people benefit from technological breakthroughs, while a high number of our citizens lack access to elemental health care. The public is recognizing that the health of our population in general is as important as the health of individuals. While we recognize the value of genetic engineering, we also clamor for a broadening the base of research areas to find answers on the impact that socioeconomic have on the health of our citizens.
- *Inclusion of women and minorities in research.* The public celebrates legislation mandating the inclusion of women and minorities in biomedical research. While the legislative mandate is clear, poor women and minorities are not participating in biomedical research.

I respectfully make the following suggestions to the National Institutes of Health:

- Develop policies for health promotion and disease prevention.
- Promote research which has an emphasis on population-care management and focus on specific groups such as women, minorities, and pediatric and elderly populations.
- Design strategies and policies to promote the development of women scientists.
- Promote research which looks at disease-management approaches based on clinical as well as socioeconomic factors.
- Promote research which finds approaches to manage diseases through early intervention and prevention of exacerbations. Technologies should be used to educate patients, physicians, and health care organizations, rationalize the use of medications and modify the environment.
- Promote research on how to obtain and manipulate health data from specific populations. Develop the resources and the technology to pull data together and apply it.
- Promote research that looks at quality of care and quality of life throughout the life span.
- Sponsor programs to assist research subjects who can not afford to participate in research trials.

- Make the necessary budgetary allocations to increase the visibility and productivity of women's programs at the National Institutes of Health, including those efforts related to the inclusion and retention of women in biomedical research. Special attention should be given to the Office of Research on Women's Health.
- Promote large clinical trials which look at unknown causes of disease, and have clear clinical endpoints, such as the Women's Health Initiative.
- Find innovative and effective ways to facilitate the involvement of the public in defining the research agenda for this nation.

Marlene Keeling, B.S.B.A. *Founding Director, CANDO*

Research on Women's Health for the 21st Century Needs To Include Chemicals Implanted in the Body

When breast implants are removed, they are labeled biohazardous or poisonous. The FDA has never approved a single breast implant. Women have been experimented on for the last thirty years. How many deaths does it take before this public health hazard is removed from the market? Now is the time to stop the experiment and do the research before one more woman's health and that of her children born after implantation is destroyed by the toxic effects of silicone and silica. Secret Scandinavian research in the 1970s revealed that 2,6-cis-D which is very similar to D4 found in breast implants had estrogen-like activity, caused atrophy of male sexual organs, caused abnormal motility and eventual sperm death, caused stimulation of endometrial growth, caused many other harmful effects, and definitely passed the placental barrier in pregnant mice. We know more about the fetal effects of Tylenol than we know about the effects of silicone/silica. Every child deserves to be born free of toxic chemicals. Is it possible that in this advanced technological age, we are poisoning ourselves and our future generations?

I recently coordinated a data gathering of 100 breast implanted women from different support groups around the country which revealed the following: 68 percent had been diagnosed after implantation with peripheral neuropathy, 36 percent demyelinating neuropathy, 70 percent atypical neurological disease, 42 percent organic brain syndrome (loss of cognitive function), 52 percent lupus or lupus like, 87 percent fibromyalgia, 78 percent atypical connective tissue disease, 39 percent mixed connective tissue disease, 12 percent scleroderma, 55 percent esophageal reflux, 63 percent gastrointestinal dismotility, 95 percent chronic fatigue, and 47 percent Sjögren's syndrome. No one seems to be focusing on the neurological part of the toxic effects of silicone/silica. Women with implants are being diagnosed with reduced blood flow to the brain, brain lesions and tumors, and loss of cognitive function (it appears to be an adult form of attention deficit disorder). Is it possible that silicone/silica is a lipid soluble neurotoxin? Many former hard working productive women with implants are now disabled, without insurance, unable to take care of themselves or their families. The Blue Cross/Blue Shield underwriting guidelines now state that the response to a woman with breast implants is to decline her coverage. This health care crisis grows daily, while the manufacturers would try to blame it on anything but the implants.

Over 1,300 peer-reviewed research articles indicate the harmful effects of silicone/silica in the body. Dr. David Kessler's article in the *Annals of Internal Medicine* states: ". . . 71 percent of the women . . . had either frank rupture or severe silicone bleed at explantation" and ". . . because most studies have focused on well-defined connective tissue disease, they cannot rule out the possibility of an elevated risk for one or more distinct, atypical connective tissue disease-like syndromes that do not meet the standardized diagnostic criteria used in most studies."

Clinical studies are now needed to verify what implanted women have known for some time — something has gone disastrously wrong. It is time to spend our research dollars finding possible preventative causes of disease and remove harmful non-life-saving devices from the market.

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

Professor and Chair, Tulane University School of Public Health and Tropical Medicine

The Cause for Enhanced Behavioral Research

As a result of the tremendous focus on biomedical research and dissemination of the findings, Americans and their health care providers have access to vast quantities of health information. These data enable us to prevent, identify, and control disease. Many live longer and better. However, a substantial number of individuals do not act, or act haphazardly, on such life-saving information.

Of particular interest is why women, who compared to men are by far the more dedicated seekers of health care, are so resistant to life-preserving change? Why do young women persist in smoking and engage in unprotected sex? Why do older women resist mammograms and Pap smears? Why are younger female physicians more likely to prescribe preventive services than older male and female physicians? Is the health professional community sending the wrong messages? Are the messages too much the "one-size-fits all" approach? Does the media with its "latest medical news report" confuse?

We need to examine the differences in the sexes in response to health information and action. We need to determine how to reduce barriers and enable women to act in their own best interests. Learning is not a one-way street from health care professional to patient. Learning is a multifaceted collaboration among women and their health care professionals to protect and enhance the health of the individual. This is especially important now when health care is changing and professional time with patients is being reduced. Behavior change requires understanding, time, and commitment by many forces from the individual and her physician to the media.

I urge the following action for NIH and all research institutions dedicated to health promotion and disease:

1. Recognize and accept that differences exist among individuals and between women and men. Recognize that individuals have different ways of learning and adopting behavior change.
2. Allot sufficient funds to support behavioral research and make it a priority across the myriad of diseases, disorders, and conditions that affect women — and men. Without such research we cannot successfully apply and have individuals adopt the health preserving findings.
3. Integrate behavioral research into as many clinical studies as possible.

Indeed, a great deal of the information is often already there. It simply needs to be identified and utilized.

This is not a plea to rob basic or applied sciences of their critical role or funds in biomedical research. This is an urgent request to acknowledge and stimulate the critical role behavioral research has in biomedical research. Behavioral research is important for it enables us to use effectively the continually emerging research knowledge — as individuals and as a nation.

Marva L. Lewis, Ph.D. *Assistant Professor, Tulane University School of Social Work*

There is little research that focuses on the role of culture and ethnicity as normative processes that permeate the mental health and well being of the lives of women and girls. For example, there are some cultural practices and strong ethnic identity may be sources of strength as well as sources of vulnerability for women and girls in view of the current public health crisis of interpersonal violence. We do not understand the mental health needs of women and girls who are the victims, mothers, sisters, girlfriends, and daughters of the epidemic of homicide that have defined urban settings in the nineties. What will psychological legacy be of the next generation of children who will be parented and socialized by mothers with experiences of unresolved grief and loss?

In the current research I am conducting with funding provided by the National Institute of Mental Health, I am investigating how the task of hair combing may serve as a naturalistic paradigm for research to understand the dynamics of African-American mother-daughter relationships. The hair combing task offers an opportunity to compare and contrast the quality of interactions that occur in this observational context with the interactions that occur in traditional contexts of assessment such as free play and teaching tasks. Developmental theories of attachment, self conception formation, and racial socialization provide a conceptual framework for understanding the significance of Hair Combing Interactions (HCI) and basis for the design of the study. Intense emotions are associated with hair. The critical nature of skin to skin human touch has long been established and more recently, the importance of parent to child nurturing touch to enhance the development of secure attachment relationships. During HCI mothers must repeatedly touch, pat and smooth the hair of the child. Consequently, the functional aspects of HCI offer an opportunity for attachment as well as intimacy. The interactions that occur between mothers and their daughters during the task of hair combing may contribute in important ways to the infant girls developing sense of self and reflect stable attributes of the relationship and the mother's general parenting style. HCI as a method of assessment also offers a potential window for understanding the sociocultural domains of African-American girls emerging sense of gender and racial self concept formation. In data from pilot studies I have completed with diverse samples of African-American women and girls in three different cities, I found it was possible to rate a variety of discrete maternal and child behaviors from videotapes of the interaction.

This study is a descriptive and exploratory study of a low-risk, non-clinical sample of African-American mothers, ages 20 and older with daughters ages 20 to 36 months. The specific research questions this study addresses are: Does African-American mother-daughter interaction look the same in three observational contexts (free play, teaching, and hair combing)? Is the mother's ethnicity the best predictor of specific behaviors in hair combing context? The relationship variables of interest are the mother's emotional availability; the child's affect and level of compliance with the mother and the overall connectedness and exchange of affect between the mother and the child. Each of these behaviors will be analyzed from videotaped interactions in each of the three contexts.

There is a conceptual gap in the research about specifics of the role of culture in the mental health of African-American women and girls. The American Psychological Association and ethical standards committee of the Council of Social Work Education have both recommended that race and ethnicity be considered in the construction and methodology of research studies. It is time to move beyond simple inclusion of descriptions of the race and ethnicity of study participants. Cultural heritage and traditions must be the beginning point for conceptualization, design and interpretation of research conducted on women and girls. I have provided a brief example of my research where a cultural conceptualization of the mother-child relationship led to the selection of hair combing task as a valid method of research.

In conclusion, I recommend the following actions:

1. That funding priority be given to the development of an annotated bibliography that brings together the existing research that examines culture and mental health of women and girls.
2. Researchers, clinicians, and students and educators be provided with continuing education in the form of workshops that help them understand the differences between the concept of culture, race, and ethnicity. In our current context of our collective weariness over the battle for affirmative action, our reactivity and fear of discussions of racism and ethnic relations the topic of culture becomes subsumed and typically lost. If culture is going to be substantively explored that there must first be a clear understanding of the construct.

3. There is need for collaboration and interdisciplinary focus in order to substantively address the issue of the role of culture as a source of protection and vulnerability in the lives of African-American women.

4. Basic research on African-American cultural traditions and practices related to women's roles need to be made a priority with funding priorities given to studies that describe the meaning of culture in order to build theory and hypothesis about African-American culture.

Jennifer C. Lovejoy, Ph.D.

Chief, Women's Health Research Program
Pennington Biomedical Research Center

The mission of the Pennington Biomedical Research Center (PBRC) at Louisiana State University is promotion of healthier lives through research in nutrition and preventive medicine. As part of this mission, PBRC is committed to research in women's health issues, many of which have a nutritional component.

At the Public Hearing on Issues in Women's Health Research, women's health issues will be discussed broadly. PBRC brings a unique perspective to this topic in the special area of nutrition and preventive medicine and we will use this perspective to highlight aspects of the broad field of women's health research. We have chosen "Nutrition and Women's Health Across the Lifecycle" as the theme for PBRC's statement because nutritional issues such as obesity and eating disorders have major implications for the nation's health and there are important gender differences in the prevalence of these health problems. Furthermore, as in many other areas of clinical research, women have been under-studied with regard to the relationships between nutrition and chronic disease and there is much to be learned about the physiological responses of women to nutritional changes.

Because of the influence of reproductive hormones as well as a number of psychosocial factors, there are several periods during a woman's life when she may be at greater risk for developing a nutrition-related disorder. These times include adolescence, when eating disorders typically appear, and pregnancy and menopause, when excess weight gain may be a problem. Furthermore, unlike men, women experience fluctuating hormone levels across a monthly cycle. These changing levels of hormones throughout the menstrual cycle in reproductive age women have been associated with altered food preferences and eating behavior which, over time, may contribute to nutrition-related problems such as obesity in certain women. The unique nutrition-related health risks women may experience at different points in their lives include:

1. *Childhood and adolescence.* Childhood obesity, eating disorders (anorexia and bulimia), and teen pregnancy are major public health problems that put adolescent girls at risk.

2. *Pregnancy and lactation.* Pregnancy and lactation impose a significant physiological and nutritional stress on women, while over-nutrition and excess weight gain during pregnancy can lead to permanent obesity.

3. *Mid-life and menopause.* Menopause may be associated with an increase in body fat and a shift in location of body fat from the periphery to the abdomen and may explain in part the increase risk for heart disease that women experience after menopause.

4. *Aging.* Elderly women are at risk for a number of nutrient deficiencies which may impact their health status ranging from inadequate intakes of antioxidants to calcium.

We will describe several of the ongoing research projects at PBRC exemplary of nutritional issues in women's health research which cross the spectrum from the laboratory to the clinic to the field.

Associate Professor of Biostatistics
Department of Biostatistics and Epidemiology
Frances J. Mather, Ph.D. *Tulane University, School of Public Health and Tropical Medicine*

The Importance of Research To Identify Factors Associated with the Reduction of Preterm Births

Preterm birth (less than 37 weeks gestation) is the major pregnancy related problem in the United States. It accounts for nearly 75 percent of the infant deaths in the first month of life and as much as 50 percent of long-term neurological damage in children. It is the major contributor to low birthweight. Annual direct costs attributed to preterm births in the U.S. have been estimated to be at least 4 billion dollars.

Preterm birth among black women occurs in about 12 percent of live births, approximately twice that of white, Hispanic and Asian women. Low birthweight is associated with an increased risk of subsequent hypertension and death due to cardiovascular disease. Weight at birth and social conditions of childhood are found to affect reproductive capacity. Neurological conditions include cerebral palsy and attention deficit disorders. Other conditions include retinopathy of prematurity, SIDS, bronchopulmonary dysplasia, and other chronic pulmonary conditions. Recent declines in infant mortality, largely attributed to the use of surfactant and other neonatal interventions, have resulted in increasing survival of extremely preterm deliveries at risk to these sequelae.

Little or no evidence is available that preterm prevention programs, social support for pregnant women, early prenatal care, education to increase awareness of the signs of preterm labor and the use of tocolytic therapy to suppress uterine contractions have been successful.

Promising new developments to explain preterm birth and low birthweight include the assessment of the role of infections in preterm births, especially bacterial vaginosis. Treatment with metronidazole and erythromycin has reduced rates of premature delivery in women with bacterial vaginosis and at increased risk for preterm delivery.

The burden of preterm birth falls heavily on black women, many of whom are poor. The cost of preterm birth is high and the sequelae long lasting and among the very-low-birthweight, severe and irreversible. Recent innovations in neonatal intensive care make it possible for greater proportions of tiny infants to survive, but not without the sequelae associated with this condition. About 40,000 to 50,000 of these very-low-birthweight infants per year in the U.S. will, in succeeding years, require additional funds to address the physical, mental and educational handicaps subsequent to preterm birth. Cuts in Medicaid and SSI will certainly impact the financing of needs for this growing population. A number of promising studies support the hypothesis that infections may play an important role in the incidence of preterm birth. I urge that research in the identification of preventive factors associated with preterm birth be made a priority.

Danita M. Muse, M.S.W. *Women With A Vision, Inc.*

African-American women, often members of the poorest communities in America, have the highest death rates in America from cancer. In a culture where it is believed that if you do not feel sick, then you are not sick, it is no surprise that we are dying more often from lung, breast, and cervical cancer. The prevention and treatment messages are not getting through. Treatment agencies are amazed at the condition of that eventually appear for services in emergency rooms.

With HIV/AIDS/STDs, it was certain that the poorest communities would be hardest hit, and more devastatingly, by a disease with no clear outward signs. Treatment administered on the tail of research will always cost more than those of my community can afford. Prevention practitioners must constantly play catch up regarding the disease's "trends," with an only recent arrival of culturally appropriate messages and messengers. This is just the tip of the iceberg.

African-American women are living in communities where violence is normal. The physical effect of that violence, in death and abuse, will only be matched by the damage done to our faith and hope! My community is being left with an even larger terminal illness as result of violence.

What has research done, beside telling us what was wrong? Do researchers come to us and ask us? Do researchers look like us? Research should be done to show a connection among all of the illnesses affecting our communities' members. These illnesses collectively have a unified effect upon my community!

Medical Director for Women's Health
Marcy Ouellette, M.D., M.P.H., T.M. *Louisiana Office of Public Health*

The Louisiana Office of Public Health, Division of Health Services, houses the Maternal Child Health and Family Planning Programs, both of which provide preventive services to women and female adolescents of reproductive age and their children. During the fiscal year, 1995-96, approximately 200,000 women and 148,117 children used our medical and nursing services. These women are mainly impoverished, underserved, and disenfranchised. Despite intensive efforts, and assistance at the federal, state, and local levels, improving the health status of the women who entrust themselves to our services remains difficult. Why?

This is a question many of us who are committed to public health services constantly struggle with. Is it poverty and its enormous destructive consequences, institutionalized racism and sexism, social inequalities, or are there other more subtle differences among women who utilize public health services? Although research regarding women's health is improving, there continues to be a lag in reliable information regarding women of color, adolescents, and the disparities that exist between women who utilize public services versus private, women of color and whites, and among women of color themselves. Epidemiological, scientifically tested rates and prevalence among these groups is difficult to document. Yet, without them, funding to address these issues is not forthcoming.

Despite enormous social, economic, racial barriers, and fragmented health services, many women who utilize our public health services have health strengths and coping strategies that enable them to live healthily and productively, and raise healthy children who are safe and constructive. We seldom look at this.

Research historically looks at illness rather than health. To understand how women prosper and protect their and their children's health and well being, despite enormous odds, would in fact enable us to design interventions based on individual and cultural strengths, which may ultimately have a greater impact.

With the expectation that research conducted on women will involve women in the planning and design, implementation, evaluation, and interpretation of results of research studies, and who are from a multicultural and socioeconomic diverse background:

1. How the perception of being a public health recipient (particularly from a young age onward) where choice of provider, appointment days and times are usually not self selected, and services are generally monetarily free, affects women's self identity and self reliance, particularly one's ability to make independent reproductive and other healthy life choices.

2. How gender identity and responsibility are affected and contributed to by reproductive health clinics that primarily focus on the female.

3. How well informed are women regarding informed consent as it pertains to research involving reproductive health, contraception, and STD/HIV. How comfortable women are in actually refusing to be part of a study. Specifically, how women who cannot say no to a study involving their reproductive health can effectively say no to other issues and actions involving their reproductive health.

4. Infant mortality and low birthweight disparities between blacks and whites.

5. Effects of the media on healthy gender identification and sound health practices on female adolescents and adult women.

6. Continued multicultural, sound, contraceptive research and development because 60 percent of all pregnancies continue to be unintended.

These issues mainly focus on reproductive and sexual health care needs of women, primarily because these are the issues our programs address. We continue to need research addressing cardiovascular disorders, endocrine disorders, osteoporosis, and mental health and illness, but, these health concerns are not controversial and do not come under the same political scrutiny as do reproductive and sexual health issues. To maintain and improve the status of women, we must ensure that these issues be addressed.

Director, The Center for Sexual Health
Eileen M. Palace, Ph.D. *Tulane University Medical Center, School of Medicine*

Research and scientific knowledge on the sexual health of women has lagged far behind that of men. Masters and Johnson (1970) estimate that at some point during a relationship, one of every two couples experiences sexual difficulties. For women, the prevalence of orgasm disorders is estimated at 30 percent and the prevalence of sexual desire disorders estimated at 20 percent (*DSM-III-R,*1987). This means that, conservatively, orgasm disorders affect over 23.5 million women and desire disorders affect over 15 million women in this country. The inclusion of other types of sexual dysfunction affecting women (e.g., sexual arousal disorders, sexual pain disorders, vaginismus), and associated psychological disorders (e.g., depression, anxiety) would provide estimates many times greater. Despite the pervasiveness of sexual disorders in women, very little is known about the basic mechanisms that mediate sexual arousal and response in women, only a handful of researchers in the country conduct research on the sexual psychophysiology of women, and as a result, research on women's sexual functioning and knowledge of women's sexual health is lacking.

There is growing awareness of the absence of medical and clinical research on women's sexuality and the detrimental effects of our gender-biased knowledge. Research funding is needed to foster new programs of research to (a) define the construct of sexual arousal, (b) determine valid and reliable assessment instruments, (c) identify an etiological model of sexual dysfunction, and (d) develop effective, empirically based treatment methods for the alleviation of sexual dysfunction in women. This testimony presents recent advances in knowledge on women's sexual functioning and the potential for new research programs to revolutionize current knowledge on women's psychological and physical health. It presents current findings that identify mechanisms in the etiology, treatment, and prevention of sexual health-related problems for women, and provides implications for new health psychology and behavioral medicine approaches for the prevention and alleviation of psychological and medical disorders. This testimony presents suggestions for new research programs, that if fostered, may provide new behavioral medicine approaches to treatment, where instead of surgery or pharmaceutical techniques, changes in behavior and cognition are used to change physical problems. United research efforts are needed to instigate programs to facilitate understanding women's sexual health requirements, to pursue new approaches to improve the quality of health care, and ultimately, to promote mental and physical sexual health for women.

Jayashree Rao, M.D.

Committee on Women's Affairs
Louisiana State University

Career Issues for Women Scientists and How To Overcome Them

Barriers:

1. Women are biologically different and that has an impact on how they view science, and their contribution to the advancement of science.
2. Socialization of women during childhood, adolescence, and young adulthood is different, and that has an impact on the way they perceive a career in science.
3. Women's roles, as governed by the societal norms, make it extremely difficult to participate and benefit from traditional programs that are now in place to foster a career in science.
4. The traditional type of mentoring process does not address the gender differences in fostering the careers of women scientists.
5. The life cycle of women's creativity and productivity are different and there are virtually no programs that address this difference.

Adequate numbers of women are choosing careers in science. Yet, their progress and creativity do not meet their full potential.

Solutions should be aimed at:

- Mentoring that is mindful of the gender differences.
- Time course for career advancement that recognizes the women's needs to balance multiple roles.
- Newer programs that encourage and foster senior women's entry and progress in scientific careers.

Co-coordinator
Meghan-Morgan Shannon, M.S. *Medical Professionals/Persons with CFIDS/CFE/ME*

Anecdotal evidence suggests that the preponderance of those affected by CFIDS/CFS/ME and related immune disorders are health care professionals. Clearly, considerably more epidemiological evidence is required if we are to understand the incidence and prevalence of this emerging entity in the population. Is it largely a "White woman's disease," or does it affect, but remain largely undetected among, other racial and ethnic groups? Which men are affected and why? Is it more common among medical workers (nurses, respiratory therapists, M.D.s, lab techs) than other professions? Is it because the medical profession consists mostly of women who are on the front line with greater exposure to environmental toxins, viruses, bacterias, or mycoplasmas, combinations, or other factors?

Emerging evidence indicates that CFIDS/CFS/ME may trigger a variety of autoimmune diseases — diseases which tend to be more prevalent among women than men. Thus, steroidal sex hormones are likely to play an important and integral role in the development of CFIDS/CFS/ME and other immune disorders. What is clear is that epidemiological data are required to guide hypothesis generation and hypothesis testing. In an area of shrinking research resources, we must know where to focus research action.

Evidence gathered to date has already shown that early detection and intervention can mitigate the course of the disease, e.g., the earlier the intervention, the more complete and rapid the recovery (if there is to be any recovery). Yet we need a clearer and more comprehensive understanding of the genesis and course of CFIDS and related disorders if we are to avert it entirely, or to intervene at the earliest stages when recovery is more easily achieved. Furthermore, data gathered from CFIDS/CFS/ME investigations will undoubtedly lead to discoveries in related diseases and disorders.

Amanda Sherman *President, DES Action USA*

DES Action USA is a national nonprofit organization representing an estimated 10 million mothers, daughters and sons exposed to the drug DES (diethylstilbestrol).

The purpose of DES Action USA is to provide education and support to those exposed to DES, to increase public awareness about DES so that individuals can discover if they are exposed, and to educate medical professionals so they can provide knowledgeable services to DES exposed people. We also seek to keep public attention on the story of DES as a reminder of the need for vigilance in regard to health care practices.

DES Action USA and the DES Cancer Network are the only consumer groups to which DES-exposed Americans can turn for support, information, and education.

- Facts about DES, a synthetic estrogen, and numbers exposed in U.S.
- Health effects for DES daughters resulting from in utero exposure to DES.
- Previous research efforts led by Office of Research on Women's Health, NIH.
- Present and pressing research questions faced by DES daughters.

Denese O. Shervington, M.D., M.P.H. *Institute of Women and Ethnic Studies*
Women of Color Reproductive Health Forum

The Institute of Women and Ethnic Studies (IWES) is a nonprofit 501 (C)(3) organization dedicated to improving the physical, mental, and spiritual health and quality of life for women, adolescents, and people of color, in particular the poor. The overall goal is to develop culturally proficient, multidisciplinary and holistic health intervention programs, activities, and research models. The Institute of Women and Ethnic Studies is recommending a new approach, a restructuring of biomedical research that would include the full representation of ethnic groups in the strategic planning, discovery, development, testing and evaluation, and distribution of new reproductive health drugs and devices.

1. The development of safe and effective contraceptives must be encouraged and supported:
   - Contraception must not be used as a vehicle for coercive social policy.
   - Contraception must not be separated from disease protection (STD/HIV) but instead be integrated into a holistic approach to women's health.

- Contraception research agenda should be expanded to include more contraceptive options for men.

2. New FDA regulations for the study and evaluation of gender and racial differences in the clinical evaluation of drugs must be encouraged and supported:
   - Increase the participation of subgroups (by gender, race, age) in clinical trials, especially when medically important.
   - Increase the analysis of the pharmacodynamics and pharmacokinetics among subgroups.
   - Encourage clinicians of color to participate in clinical trials.
3. FDA must monitor post-marketing surveillance of drug safety and efficacy.
4. A system must be developed for reporting, monitoring, and responding to consumer and/or provider reports of side effects.
5. A system must be established for safeguarding against drug misuse (by misleading marketing to consumers of inappropriate prescribing by providers).

SUMMARIES OF
PUBLIC TESTIMONY
SANTA FE, NEW MEXICO
JULY 21, 1997

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Lois Grey Long, R.N., M.S.N.
Selves

Jean Charles-Azure, M.P.H., R.D.
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Col. Laurie Davis, Ph.D.
U.S. Army Nurse Corps

Jane L. Delgado, Ph.D.
National Coalition of Hispanic Health and Human Services Organizations (COSSMHO)

Sally Esposito, M.S.
The City of New Haven

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Susan M. Shinagawa
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Women in Science and Engineering

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Leah L. Albers, C.N.M., Dr.P.H.
Associate Professor, University of New Mexico College of Nursing

Each year in the United States, some 3.9 million babies are born. The clear majority of these are born to healthy women, that is, women without medical problems which either precede pregnancy or arise during the course of pregnancy. For historical reasons, about 99 percent of all babies are delivered in U.S. hospitals. Thus, normal childbearing accounts for a large portion of the total U.S. health budget. In fact, “normal pregnancy, delivered” is one of the most common discharge diagnoses from U.S. hospitals.

American childbearing women receive more technical procedures during labor, and are more frequently delivered by surgical methods than are women in any other developed country in the world. The excess use of technology and surgery is problematic for two reasons: (1) it is extremely expensive. These financial resources could be better directed elsewhere, to benefit all childbearing women and their infants, and (2) it engenders excess morbidity, in terms of both unnecessary medical complications and adverse psychological outcomes. In the important transition to motherhood, none of these can be considered insignificant.

There are many examples of overtreatment of childbirth in America. One, is the high rate of cesarean delivery in the United States. Although the C-section rate has declined from its all-time high in 1988 of 24.8 percent, it now stands at 21 percent, approximately twice that of countries in western Europe. Some 30 percent of women delivered by cesarean are known to have significant postoperative morbidity, breast-feeding failure is higher in these women as well. Four technical procedures used during labor in the U.S. can be described as excessive: electronic fetal monitoring, labor augmentation with oxytocin, epidural analgesia, and episiotomy. Electronic fetal monitoring has risen from 45 percent of all U.S. births in 1980 to 81 percent of all births in 1995. Augmentation of labor with intravenous oxytocin is becoming mainstream care. Clearly the operational definition of normal labor progress needs reevaluation when 1 in 6 labors are defined as “too slow.” Epidural analgesia has been termed the “twilight sleep of the 1990s.” In 1981 it was used for 16 percent of all U.S. births. Since, then, no national estimates are available, but large institutions report rates of 30 to 60 percent, and higher. Episiotomy remains a common practice; it accompanies 50 percent of vaginal births in the United States. Numerous studies including randomized trials show that no short- or long-term benefits accompany routine episiotomy at birth.

Obstetrical care in the United States has a very big problem: we are doing too much of the wrong things and not enough of the right things. NIH is encouraged to place the proper treatment of normal pregnancy and childbirth (including appropriate technology) on the national research agenda. The following questions are examples of those which need to be addressed:

- How can childbearing women be effectively prepared for labor?
- How should labor be managed to increase the proportion of normal deliveries?
- How should labor be managed to reduce postpartum morbidity?

- How does the style of care during labor relate to long-term health issues: mother-infant interaction, breast feeding, etc.?
- How can clinicians be encouraged to reexamine the science base for their practice?
- How can medical educators redefine teaching priorities around normal childbirth?

Kathleen Blake, M.D. *New Mexico Heart Institute*

I am a cardiologist with the New Mexico Heart Institute and chair of the committee on Women and Heart Health of the New Mexico and Arizona American Heart Association Affiliate. This committee was established in 1990 by the American Heart Association and the Department of Health of the State of New Mexico to promote awareness in the professional and lay communities about the problem of heart disease in women. After meeting our professional educational objectives first, we have shifted our focus to community programs for prevention and early heart disease detection. My comments address the information needs of organizations such as ours as we design programs and educational materials for women.

Cardiovascular disease will kill 450,000 American women this year. Most women do not know this. They will cite breast cancer as their number one health concern, although this disease takes the lives of just over 40,000 women in the U.S. per year. Women are, therefore, unlikely to seek out information about heart health for themselves. They are less motivated to adopt heart healthy behaviors. They are also, unfortunately, slower to seek medical attention at the time of a first heart attack because the disease is not one they expect to have.

We want to see research on successful health education strategies for women. We must learn what motivates women to seek information about heart health. Where and when do women get health information they believe and incorporate into their daily lives? In the managed care era, we suspect that less education is provided by physicians in office visits that are shorter than ever. What are better substitutes? Will it be other health care providers, or the media or volunteer organizations such as the AHA? A special group of women already available to help answer these questions is the women who participate in cardiovascular clinical trials. Acquiring information about what motivated each subject to participate may give us the insight we need to then target subgroups of women with similar characteristics for community programs.

New Mexico and Arizona have large populations of Native American and Hispanic women. Very little is known about the best strategies for heart disease prevention in these women. Ethnic differences exist in dietary habits, diabetes incidence, smoking, and obesity. These differences must be understood if successful prevention efforts are to be implemented.

Specific issues related to childbearing need to be addressed. Limited teratogenicity data are available about cardiac drugs that may be needed for specific situations during pregnancy. Minimal prospective, controlled-trial data are available to guide anticoagulation decisions during pregnancy. A randomized, controlled-trial of heparin, low molecular weight heparin, and coumadin should be designed and funded.

Basic research to elucidate gender differences in vasomotor tone and endothelial function should be supported. Comparison of the effects on endothelium of estrogen, tamoxifen, and extreme cholesterol lowering by HMG CoA reductase inhibitors is needed to enable the clinician to make informed therapy decisions with women who may not be able to take estrogen after menopause.

In summary, we need to know who wants heart health information, how they want to get it, and what format works best to promote behavioral change. The best strategies for prevention in Native American and Hispanic women are unknown. Childbearing needs to become safer for women with heart disease who need drugs, especially anticoagulation. The endothelium will be final common target of what we suggest for women; we need to know how to achieve, if possible, the same benefits seen with hormone replacement therapy in women who cannot or will not take estrogen.

Jeanne Carritt, M.A., M.Ed. and **Lois Grey Long, R.N., M.S.N.** *Selves*

The organization of this conference seems to preclude input from elderly women. Once women leave the workforce, few have access to fax or e-mail. The titles and affiliations requested on the registration form represent serious roadblocks for elderly women. Input about the elderly is, therefore, coming from younger people. Little first-hand observation comes from the population who is coping with specific problems of the elderly. Some concerns of elderly women are as follows:

1. In the agenda for this conference, elderly and frail elderly women were combined. Issues for women who are 65 or 70 and 85 or 90 years of age are enormously different. Since this is the fastest-growing segment of our population, it can only be ignored at the peril of society as well as of the women whose problems we hope to address. This is a woman's health issue because in the over 65 age group, women outnumber men 2 to 1.

2. Considerable research on aging issues has been done, much of it on men. Generally the research has been divided by disciplines (e.g., one group working on housing and another on cardiovascular disorders). The great need is to integrate these data and make information available between disciplines. We must find ways to provide reliable easy-to-understand information based on this knowledge to the general public and to the elderly and their families.

3. In this population, one cannot separate physical health issues from economic problems and from the components that make up psychosocial well being. Some of these are depression, poverty, and loss, including those of mobility, friends, health, and general physical self confidence. Societal attitudes

toward women is a major concern that applies uniquely to women. All of these factors affect physical and mental health along with longevity and quality of life.

An example of a related economic concern is the cost of drugs. The current emphasis on treating osteoporosis in older women with the new medication, Fosamax, costs about $55 per month, putting it beyond the reach of many women without insurance coverage or prescription coverage. The new sleeping medication, Ambien, costs about $2 per tablet.

An example of maladaptive approaches to some of the losses is the increasing use of alcohol and mind-altering prescription drugs to help cope with disturbed self concept and body image and the related stresses unique to women. Elderly women are more likely to be prescribed drugs that affect judgment and safety, leading to yet greater health-related problems.

Many questions relate to the activities of daily living for which guidelines have not been established in the context of prevention for elderly women at any age. Available information is currently not geared to this age group.

In the parameters of "normal aging," for example:

- How should diets be altered to accommodate metabolic changes and meet daily nutrition needs?
- Should older women use the same aerobic parameters currently standard for younger women?
- To what extent are dietary supplements and nutritional additives helpful or relevant?

Peripherally to women's health, the change in living conditions brought about by women working outside the home is creating change in the caretaking role, geographic disruption, and the demise of the extended family, all of which have changed the whole pattern of intergenerational living. These factors have created housing problems of large proportions. Agencies that have attempted to address this issue are divided among city, state, and Federal Governments. How can these services be integrated to best serve all ages and economic levels? As women become much older and energies fail, must they attempt to navigate these various systems to get their needs met?

In addressing these problems, it must be understood that chronological age has little to do with functional status and with the kinds of support systems needed. There is a danger in standardizing services based on age alone. Our current knowledge includes the information that each woman who reaches a certain age plateau can expect to live x-number of years and be reasonably healthy. There is a lack of information about changes in services and support systems needed as these women become more frail.

With regard to the research focus of this conference, and in light of our original comment about obtaining information on perceptions of needs from this most-advanced age group, perhaps the greatest challenge is simply finding ways to elicit accurate information.

Director of the Nutrition and Dietetics Training Program
Indian Health Service

Jean Charles-Azure, M.P.H., R.D.

I am a member of the Lummi Tribe in Washington State. I also have Omaha, Ponca, and Sioux heritage. Accompanying me is Carolyn Lofgren, Coordinator of the HQW Women's Wellness Initiative and member of the National Indian Women's Health Steering Committee. Our discussion focuses on nutritional issues related to Native American women's health.

As a Native American woman, I have long been interested in health care and health promotion for American Indian/Alaska Native (AI/AN) women. Native American women are concerned about their nutritional health throughout the life cycle, especially in the childbearing, perimenopausal, and postmenopausal years. Many tribes are interested in resuming healthy nutrition and food traditions, such as breast feeding, lower fat cooking, becoming more physically active, reducing risk for diabetes and osteoporosis, and achieving and maintaining healthy weights.

Native American women, often the decision makers regarding food selection and preparation, are committed to improving the nutritional health of their families and communities. They can be found leading community efforts to provide healthy meals and physical activity for children and adults. They play a key role improving the nutritional health through their active participation as parents and community members on advisory groups for day care centers, schools, Head Start, and elderly meals programs. Nutrition during recovery from substance abuse is stressed in the concept of a grassroots group, Gathering of Native Americans (GONA), "Indian Women in Action" support efforts. The community concept is making an impact in all areas of women's health, but particularly in EtOH/Substance Abuse. Continued support for "community mobilization" interventions are essential for lifestyle changes and long-term outcomes.

The strategies developed to address the health problems of AI/AN populations need to consider the characteristics of the population. Over the past three decades, the nutritional health of AI/AN has changed dramatically from morbidity and mortality associated with infectious diseases to chronic diseases associated with obesity. An American Indian School Children Height and Weight Survey found that 40 percent of this population were obese. Obesity has long been known as a major risk factor for cardiovascular disease, the number one killer of American Indians and Alaska Natives. Another major consequence of obesity in children is the increasing incidence of Type II Diabetes Mellitus, as early as age 14 years. Native infants who were breast-fed have been found to have lower rates of diabetes than bottlefed infants. Native infants whose mother's were obese during pregnancy have higher rates of diabetes. Some American Indian Tribes have diabetes rates 10 times the rate of the U.S. population, virtually all in Type II diabetes or diabetes in pregnancy.

Throughout the history of the U.S., AI/AN peoples have been an integral part of the American character. Tribal America has provided certain values and ideas as well as many native foods, that have become a part of the general American culture. Today, however, we see the health challenges facing American Indians. The research agenda for American Indians and Alaska Native women should consider these components:

1. Community-directed pilot projects that rely on the public health model and foster partnerships between community members and program staff to develop and implement nutrition and physical activity interventions. For the Indian Health Service (IHS), partnerships could include IHS, Tribal Programs, Urban Indian Programs, Indian Community Colleges and Tribal Schools, Head Start, Food Distribution Programs on Indian Reservations, Women and Children's Supplementary Food Program, Housing Programs, Treatment Programs, Youth Programs, university research programs, and so on.
2. Information to learn the most effective public health strategies for reducing rates of chronic disease (diabetes, obesity, and cardiovascular) among Native women and in their communities. We need to know the key characteristics of the successful strategies for community mobilization, school interventions, worksite interventions, family interventions, multigenerational interventions, and nutritional interventions while respecting traditions, culture, and values.
3. Information dissemination to translate and transfer what is learned about successful interventions to other Native communities is an essential component of research projects.

Col. Laurie Davis, Ph.D.

Project Director for Women's Health Coordination
Nursing Consultant to the Surgeon General on
Advanced Practice Nursing and Women's Health
U.S. Army Nurse Corp

Until 1994, the vast majority of research conducted within the military population has focused solely on military men with little to no research aimed at the female soldier. With the increase in numbers of military women (340,000) and the expanded roles women are assuming within this predominantly male environment, it is vital that increased research emphasis be exerted towards this group. This need for increased research focus on military women resulted in a 1994 Congressional directive which mandated that women be included in all DoD-sponsored research. This directive was backed with a $40 million appropriation bill that enabled the establishment of the Defense Women's Health Research Center (DWHRC) for "multidisciplinary and multiinstitutional research" on military women's health issues (Institute of Medicine, 1995). While this is a substantial initial step, much more remains in addressing the multitude and variety of military women's needs. This brief will present demographics of military women along with current research endeavors, and ongoing issues in need of continued and/or future research.

National Coalition of Hispanic Health and
Human Services Organizations (COSSMHO)

Jane L. Delgado, Ph.D.

I am pleased to provide the perspective of the National Coalition of Hispanic Health and Human Services Organizations (COSSMHO) on the funding priorities for women's health programs. COSSMHO is a private non-profit organization representing the needs and concerns of 1,500 health provider members and the people they serve. COSSMHO is the only national organization with a primary mission in Hispanic health. As a national organization, COSSMHO is unique in three major ways:

- *Diversity is our strength*. Since its founding in 1974 in Los Angeles, by two Mexican-American social workers and one Puerto Rican social worker, COSSMHO's goal was to represent the needs of all Hispanic communities. The COSSMHO symbol represents the Mexican-American, Puerto Rican, Cuban, and Central American and South American communities joining hands to work together.

- *Commitment to funding local programs*. COSSMHO obtains funds for implementing model programs with local determination being the hallmark of our activities. Today 80 percent of COSSMHO's budget is allocated to implementing multisite community programs. Approximately 50 percent of COSSMHO's program dollars are awarded locally in the communities we serve. Our commitment to local determination is reflected in the positions we take as a national voice on Hispanic health policy issues.

- *No funds from tobacco or alcohol companies*. As the only national Hispanic organization with a primary mission to improve the health and well being of Hispanic communities, COSSMHO does not accept any funds from tobacco or alcohol companies or their subsidiaries. COSSMHO is the only national Hispanic organization to have adopted this policy.

Hispanic Women and Research Issues. COSSMHO's President and CEO, Dr. Jane Delgado, in association with the National Hispanic Women's Health Initiative, has authored the first comprehensive compendium on Hispanic women's health. The book, *¡SALUD!: A Latina's Guide to Total Health–Body, Mind, and Spirit,* will be released by Harper Collins Publishers in September 1997. In addition, COSSMHO has sponsored a university-based research consortium on Hispanic women's health issues, in particular issues of chronic illness and access to health services for Hispanic women. COSSMHO also sponsors a number of efforts in the area of breast and cervical cancer early detection and treatment. These efforts include the development of the Salud para Todas Breast and Cervical Cancer Resource Kit and a model outreach program for community educators. In addition, Unidos por la Salud, a research network of comprehensive cancer centers, is completing a landmark study of the treatment experiences of Hispanic women diagnosed with breast cancer. This network is coordinated by COSSMHO with funding from the National Cancer Institute and the NIH Office of Research on Minority Health. Women's health has been a long-standing priority for COSSMHO.

Sally Esposito, M.S.

Director of Department of Services for Persons with Disabilities
City of New Haven

My department, the Human Resources Administration (HRA), is a division of the city of New Haven government. HRA includes Health, Elderly Services, Children and Family Services, the Fighting Back Initiative, and the Welfare Department. The Health Department also includes Healthy Start and the Maternal and Child Health Outreach Program, the Mayor's Task Force on AIDS, and the Ryan White Title II Program. The common denominator among us is that we have a role in the provision or facilitation of services that impact the social and health needs of all New Haven residents.

New Haven is a diverse city best known, perhaps, for its medical and health facilities and services, and for a steadily growing biomedical technology industry. The population of New Haven is declining. In 1995, the population of New Haven was estimated to be 123,770, although the U.S. Census Bureau estimated the 1995 population to be as low as 118,000. Although Connecticut had only 5 percent of its population living below the poverty level in 1989, New Haven's rate is four times higher at 21 percent. The distribution of that poverty is particularly hard on female-headed households. In general, 65 percent of New Haven families are headed by women who live in poverty. They also are the population group with the least access to cars and telephones, without which scheduling and attending medical appointments is tremendously difficult in New Haven.

Although New Haven is home to a tremendous number of health resources, as a community, we do not have a comprehensive, planned, identifiable public health policy on women's health, nor do we even have an informal priority to identify gaps in services and specific strategies for women. Human or financial resources have not been available to study women's health needs as they should be studied.

We have the infrastructure for and do collaborate on many health matters, but we need to do more in the area of women's health. We are interested in developing a women's health agenda starting with a formal assessment of New Haven women and their health needs. In addition, we wish to capitalize on existing successful grassroots efforts to reach women in their respective environments.

Specific needs of women with disabilities are even harder to determine. How many women with disabilities are there? How many are victims of domestic violence in New Haven? Those in positions to estimate do not agree on the numbers of people with disabilities. Do we use the Census Bureau's definition, the definition of a person with a disability included in the Americans with Disabilities Act, the Social Security Administration's definition, or self-identification by an individual. We do not have good information on the numbers of people with disabilities or, in fact, do we have a commonly understood definition of disability. We need to address these issues and find out who and where these women with disabilities are. We need to do all this on the national level, but it is even more urgent on the local level where we are the people that those in need first find.

Cordelia Gilkyson, C.M.T. *The Endometriosis Association*

Endometriosis is a condition that affects millions, or approximately one in six women that we know of in North America and countless others all over the world. Little help has been available until very recently. For what I had a minor laparoscopy and laser surgery for, some doctors are still prescribing hysterectomies and extreme hormone therapy treatments, which often create more side effects than the endometriosis itself. Thousands of women are walking around in pain today not knowing why, and very often being misdiagnosed or mistreated by their doctors, for lack of information on causes and treatments. There are no known causes for endometriosis, only theories by the women who have experienced it in their own lives. It is greatly affected by diet, lifestyle, and state of mind as so many health issues are, but one often wonders about the effects of our environment on the sensitive reproductive systems of women.

Treatment options are limited. It must become a topic that is discussed within school systems' health programs, that is required continuing education for MDs and OBGYNs, and that has readily available information for the public.

We need more research into the effects of our environment on women's health, primarily chemical exposures, household and cosmetic product ingredients, foods, pesticides, and all potentially toxic or hazardous compounds. Despite limited scientific information, there is evidence of the reproductive toxicity of some substances in wide commercial use. Some studies have shown dioxins and PCBs to be directly linked to endometriosis and infertility, as well as some 45 chemicals widely distributed to the U.S. government, including 35 pesticides and ten industrial chemicals as shown by a study done by the University of Wisconsin. These same chemicals can damage one's body by imitating natural hormones, binding to receptors on fetal cells and altering the genetic instructions. These imitations can then potentially "derail" human development, permanently distorting its reproductive system.

Knowledge is the first step. Educate our doctors. Continue research on causes and treatments. The Endometriosis Association reports that 70 percent of women diagnosed with endometriosis were initially told by their doctors that there was no physical reason for their pain. Of women of color diagnosed, 40 percent were told they had a sexually transmitted disease.

The prevalence of endometriosis is rising in younger women, but few of them know what they're dealing with or how to begin to treat it. Although the condition affects millions of people, it does not garner the resources that more lethal diseases do. Between 30 and 40 percent of women who are treated for infertility have endometriosis. Knowing that endometriosis is one of the leading causes of infertility, I would like to see more funding allotted towards research in the areas of fertility, environment, and women's health.

Linda A. Gonzales, M.A. *Consultant, New Mexico Disability and Health Program*

Health issues for women with disabilities are the same as for all women. They are concerned about pregnancy, breast and cervical cancer, diabetes, aging, osteoporosis, high blood pressure, stress, and heart disease. They need to be concerned about weight, nutrition, and exercise. The difference is the ongoing presence of a major disability around which these health concerns constantly revolve. If these health concerns become health conditions, they are, in fact, secondary to the primary disability. Secondary conditions is a term that is relatively new to persons with disabilities. The list of health concerns includes:

1. Conditions that may be a direct result of the disability such as dicubitus ulcers, spasticity and urinary tract infections in women with spinal cord injury, or memory loss or disorientation in a woman with a head injury.

2. Conditions that may be exacerbated or more likely to occur as a result of the primary disability such as weight gain, high blood pressure, poor circulation with mobility impairments. Examples of the disabilities that invite a more sedentary lifestyle include blindness, amputation, kidney failure, and other secondary conditions in a woman with diabetes.

3. Conditions that extend to environmental factors include a woman with a severe hearing impairment or deafness who cannot adequately communicate with her doctor, a woman who skips her annual pap tests because she can no longer get up on the examining table, physicians who no longer weigh their patients in wheelchairs.

4. Conditions that occur as a result of living with a disability in an able-bodied world, such as being different, feeling devalued. These women have a greater potential for greater stress, depression, isolation, and feelings of loss, anger, and resentment. They must deal with issues of attractiveness, self esteem, and social interaction.

The disability causes a strain on relationships, sexuality, and child rearing.

Research issues for the future include obtaining baseline data on secondary conditions in women with disabilities:

- Women who use wheelchairs. Are they receiving primary and preventive care and screenings at the same rate as the general population of women? (1993 DHP survey says they are not.)

- What are the risk factors related to common secondary conditions in women (i.e., dicubiti, UTI)? Research is needed to provide for information on alternative methods of preventing the recurrence of these conditions.

- What are the reproductive and aging issues for women with disabilities?

- What impact do lifestyle changes have on women who become disabled over a period of time? (i.e., sedentary, inactive, less mobile). Are these women more predisposed to acquiring chronic conditions because of these changes?

- Identify areas of collaboration and work with scientists/researchers in other areas of disability rehabilitation (NIDRR, RSA) and disability and health (DHHS: CDC grants to 15 states to develop a scientific base of information for the disability population). Women's health issues are a priority in many states. Also, identify any other areas where research efforts may overlap.

- Conduct policy research on health services/providers and public recreational/physical fitness facilities that readily accommodate people with disabilities. What impact do these factors have in the overall health and wellness of women in particular (i.e., gynecologists, clinics, women's fitness programs)?

Women with disabilities must be involved in all aspects of research planning and implementation. The disability rights and independent living movements stress the value and importance of consumer involvement. Be aware that people with disabilities are proactively concerned about and involved in the future of their health care: managed care, the right to die movement, organ donor priorities, assisted suicide, and women's health issues.

Janet Greenwald *Citizens for Alternatives to Radioactive Dumping*

Since the beginning of the nuclear age, over 50 years ago, women and children and veterans have paid a heavy price in terms of health for whatever security we gained through the development of the bomb. Though the plutonium experiments were brought to the nation's attention by the *Albuquerque Tribune*, the stories of the survivors of uranium mining, workers at Los Alamos, atomic veterans, and downwinders are little known. Through my 17 years of experience in dealing with these survivors, along with my association with researchers and health professionals concerned about this issue, I have what I believe is interesting information, both scientific and anecdotal.

Barry Halber, M.P.A. *Wilbar Health Productions*

For more than 30 years, research dollars have been spent in the U.S. and other countries concerning the problems associated with choosing hysterectomies. However, by age 60, one in three American women have had their uterus removed (Italy, 1 in 6; France, 1 in 18); that is 560,000 women a year at a cost of $3 billion.

Women today are not fully informed concerning these problems and options; that the public health (physical and emotional) and economic impact of these decisions are staggering with enormous quality of life implications for the 21st century woman in the United States.

Women's decisions may reflect a gap in knowledge due to a lack of easily understood information, population differences, race, culture, ethnicity, and economic factors that impact their interaction with physicians. Someone should pull together the various reports and findings and make them available (i.e., annotated bibliography) on a continuing basis to women of all ages through regional and local organizations (i.e., educational, social, health, business).

More importantly, information should be widely disseminated to all women in an easily understood format so that these basic comparative charts illustrate differentiated symptoms, diagnostic techniques, assessments, risks, treatment options, self-help programs. Each woman can utilize these charts to reflect more carefully, openly and privately with their physicians and family members. A toll-free telephone number should be activated by the NIH Office of Research on Women's Health and encourage the participation of the College of Obstetrics and Gynecology and the American Academy of Family Practice.

Local physicians should be encouraged to participate in local and regional seminars and discussions with interested and concerned women and family members. This might coincide with the ten regional HHS offices and include a collaborative effort of national health foundations that share these interests (i.e., the Robert Wood Johnson Foundation, the Henry J. Kaiser Foundation). Dissemination of information should include a full spectrum of local organizations. New research findings should be updated annually and made part of this continuing effort.

Ladies and gentlemen, we are accountable as individuals and through our organizations for both our commissions and omissions. With this cooperative and focused approach, our efforts can be both feasible and successfully implemented so that women can have truly informed choices.

Albert C. Hergenroeder, M.D. *Baylor College of Medicine*

There are gaps in our current understanding of prevention of osteoporosis with respect to young women and hypothalamic amenorrhea/oligomenorrhea, including women with eating disorders and athletes. These include:

1. The vast majority of bone mineralization in females occurs by the middle of the second decade; however, the normal acquisition of peak bone mass in late maturing and minority females has not been established.

2. Even though osteoporosis is not as great a problem in the African-American female population as it is in the European-American population, it is nonetheless a problem and there is no research addressing the natural history of bone mineral acquisition in young African-American women at risk for premature bone mineral loss.

3. Premature bone demineralization occurs in women with hypothalamic dysfunction manifest as amenorrhea and oligomenorrhea, associated with athletics, dancing, and eating disorders. Bone demineralization will

be occurring soon after the amenorrhea develops. Treatment to prevent premature bone loss and promote bone mineral accretion should begin soon, probably within 6 months after amenorrhea occurs. However, the criteria to commence estrogen replacement therapy in young women are not established. The information available is from European-American women receiving short term therapy.

4. Women who recover from anorexia nervosa at a young age (<15 years) can have normal total body bone mineral, but regional (lumbar spine and femoral neck) bone mineralization may remain low. The longer the anorexia nervosa persists, the less likely it is that the bone mineral will return to normal. Females with anorexia nervosa need to be rehabilitated early in the disease to maximize bone mineral accretion. Currently a gap exists in available knowledge and its application in practice. Physicians and other health care providers need more training in recognizing women at risk for premature bone loss and advising them accordingly.

5. Conjugated estrogen, in doses that improve bone mineralization in postmenopausal women and in combination with medroxyprogesterone, has not been shown to consistently improve BMD in young women with hypothalamic amenorrhea. Treatment with oral contraceptive pills has been demonstrated to have a beneficial effect on bone mineralization in young females with hypothalamic amenorrhea, however long studies with an amenorrheic and oligomenorrheic subjects are needed.

6. Osteoporosis is a major cause of morbidity and mortality. Peak bone mass is a major determinant of the risk of osteoporosis and the second decade is the critical period of peak bone mass acquisition; thus those who provide health care for adolescents and those concerned about preventing osteoporosis need to join forces to understand the factors which affect bone mineralization during this period and develop long-term treatment strategies.

Penelope Kegel-Flom, Ph.D. *Association for Women in Science*

ORWH was charged to "increase the number and enhance the career development of women in biomedical science." The Association for Women in Science (AWIS) is a professional society dedicated to "achieving equity and full participation for all women in science and technology." As past president of AWIS, I want to tell you about AWIS's recent study, "Cultivating Academic Careers: Warming up the Chilly Climate for Women in Science," funded by the Alfred P. Sloan Foundation.

The AWIS study identifies barriers to the recruitment, retention, and advancement of women scientists. Strategies for eliminating these barriers, and thereby "warming up" the chilly climate for women scientists, are among AWIS's recommendations. Dissemination of our findings, we anticipate, will help institutions and government agencies, such as NIH, change the environment for women scientists in ways that will increase their entry into science and advancement in their careers.

Differences in the academic advancement of women scientists are well documented. Compared to male colleagues, women scientists are paid less, promoted less often, more likely to be unemployed or underemployed, receive fewer prestigious awards, participate less in science policy and funding decisions, and are, overall, sparse at the top. Cited reasons for these disparities are: lack of mentoring from senior scientists; exclusion from the inner circles of departmental politics and influence; isolation; conflicts between professional and personal lives; and frank gender bias.

Academic climate for women scientists was the focus of the AWIS research. Onsite visits were made to the biology, chemistry, and mathematics departments of three different institutions: Large Public Research University, Small Liberal Arts College, and Historically Black University. Visits were preceded by assessment of institutional policy regarding recruitment, hiring, and promotion of women faculty, and by in-depth surveys of science faculty and students.

What did the AWIS study find? *First*, issues related to barriers for women were identified: department recruitment and hiring practices, tenure and promotion, mentoring, family and work, communication between faculty and administration, informal networking, and university-supported initiatives for women faculty. These issues applied regardless of size or character of the institution. *Second*, strategies to address these issues emerged. For example, recruitment and retention of women scientists, we found, requires establishing clear departmental goals and timetables for recruitment and hiring, designating slots for women, equitable hiring packages, and departmental accountability for improvement in hiring and retention of their women scientists. In addition, the institution needs policies that change, i.e., "warm up" the environment for women scientists. Adequate child care services, flex-time, family leave, extended time to tenure, dual career and joint position options, and spousal hiring policy and procedures are essential. Students in particular emphasized that their willingness to enter and continue in a science career depended on being able to have a career and a family, without "penalty" in their careers.

The issues raised in the AWIS study reflect those reported in other studies; together, the message is resoundingly clear: *equity for women* is more theoretical than actual.

ORWH of NIH has provided strong national leadership for change in research on women's health. NIH can also lead the nation in the direction of major climate change in the science workplace, one that will benefit all scientists. NIH can ensure: (1) that its intramural research programs create and maintain environments that eliminate discrimination; it can mandate "policies-without-penalty" that allow flexible work schedules, family leave, and dual career opportunities; (2) that women and minority scientists are aggressively and equitably recruited, hired, and promoted; (3) that external training programs for young scientists and health professionals expand; and (4) increased visibility of its women and minority scientists, particularly through appointment to top-level, decision-making positions.

More women and minorities will enter and advance in science careers as NIH continues to initiate a change in climate. And, as with the Women's Health Initiative, others will again follow the lead of the National Institutes of Health.

Gwendolyn Puryear Keita, Ph.D. *American Psychological Association*

The APA would like to convey its deep appreciation for Dr. Pinn's recognition of the importance of psychosocial and behavioral factors in women's health and the inclusion of behavioral and social scientists in the development of the new women's health research agenda. We are the largest scientific and professional organization representing psychology in the United States. APA's membership includes more than 151,000 researchers, educators, clinicians, consultants, and students. APA has a long history of involvement in women's issues, in particular supporting and encouraging behavioral and social science research to address women's health.

Despite increased focus on medical and epidemiological aspects of women's health, research has not adequately addressed psychosocial and behavioral factors that contribute to health status. In May 1994, APA, in collaboration with a number of federal agencies and professional organizations, sponsored an interdisciplinary conference titled "Psychosocial and Behavioral Factors in Women's Health." The purpose of the conference was to highlight the extensive research implicating behavioral and psychosocial factors in a number of major chronic diseases and conditions that influence women's health across the life span.

The "Research Agenda for Psychosocial and Behavioral Factors in Women's Health" evolved out of the conference. It was developed by the conference advisory committee, which included experts from across disciplines, institutes, and federal agencies — including ORWH — and represented a broad range of women's health concerns. The Research Agenda builds on the growing body of knowledge in women's health and articulates a set of priorities for the next generation of research studies.

The Research Agenda defines research priorities pertaining to specific diseases and health practices that greatly affect women. The diseases included are those that show high mortality or morbidity rates for women and that may cause great physical disability, lowered financial resources, and poorer quality of life. Some of the priorities delineated support important priorities for women's health identified at the beginning of this decade in the U.S. Department of Health and Human Services' *Healthy People 2000*.

APA believes that consideration of future research and funding needs for women should be made 1) with full awareness of the issues of concern to women's health, 2) with knowledge of what research has already shown, 3) with knowledge of what questions remain unanswered, and 4) with a full appreciation of the behavioral and psychosocial factors that impact each health issue. Our Research Agenda was developed with these factors in mind. We, therefore, propose that ORWH use our Research Agenda as the foundation upon which ORWH builds its new research agenda. This would avoid duplication of efforts and enable women's health researchers, federal agency personnel, and policy makers to most effectively address women's health research and would go a long way in furthering the much-needed federal commitment to improving the health of America's girls and women.

Daniel Kerlinsky, M.D. *Physicians for Social Responsibility*

The Environment Committee of Physicians for Social Responsibility, a national organization of 15,000 members, supports the prevention of nuclear war, reduction of violence, and the protection of the global environment. The organization is particularly concerned with the effects of toxic environmental chemicals during the prenatal period. The issue of environmental toxicity in the prenatal period is important to ORWH for several reasons:

- Toxic exposures during fetal development produce effects that last a lifetime. Birth defects, mental retardation, and impaired reproductive ability are some of the lifelong effects of in utero exposure to toxins. Each of these has profound impact on self esteem, social functioning, vocational abilities, and family life. The more subtle toxic effects on information processing, emotional relatedness, attention and aggressive behavior may be difficult to study. Having a single, handicapped child changes every aspect of family life. However, toxic environmental exposures are likely to produce multiple lifelong impairments in several children in the same family.

- Sensitivities during this period are orders of magnitude greater than in later life. The developing fetus is much more sensitive to toxic chemicals than adults are. Dioxin exposure shows that regulatory genes, growth factors, protein transcription, and multiple hormone systems can be affected by these chemicals. These effects can occur at very low concentrations. Hypoplasia, a decrease in cell numbers, occurs in lymphoid tissue; dysplasia, the abnormal growth or development of an organ, occurs in ectodermal tissue in humans. It is not necessary to kill a cell during fetal development to affect brain development; an impaired energy metabolism in a cell may be sufficient to lead to altered connections. These sort of effects appear functionally years later when complex functions, such as sustained, voluntary attention, require the coordination of many brain areas.

- Multiple organ systems are affected by prenatal toxins. Many organ systems are affected by exposure to toxic chemical exposure in utero. This leads to more complex illnesses, such as asthma, disorders in liver metabolism, and multiple drug sensitivities. Immune system suppression may further complicate the presentation and management of these cases.

- Women bear the brunt of raising CNS and behavior disordered children. Mothers are directly impacted by the behavior problems of their children. The increased stress that these children experience in their early years may be followed by physical traumas as they get older. Male children exposed to toxic chemicals show increased aggressive behavior as they enter their teenage years.

- In utero exposure to environmental chemicals may have profound effects in wildlife populations, which may in turn, affect human populations. Population reductions in wildlife due to reproductive failures have been profound. Decreases of 80 percent in populations of birds and mammals over just a few years have been reported. These raise concerns about human reproduction as humans are not particularly resistant to the toxic effects of the chemicals to which these population crashes are attributed.

- Proposed solutions to dealing with the threat of prenatal toxins include regulating and restricting the use of toxic chemicals; long-term research support; medical and community education efforts; and government outreach and support to women whose occupations expose them to toxic chemicals.

Wilhelmina A. Leigh, Ph.D. *Joint Center for Political & Economic Studies*

My statement addresses population differences due to race/ethnicity and their influence on women's health. One health behavior (help seeking in the managed care environment) and several health outcomes (low birth weight, hypertension, osteoporosis, and Alzheimer's disease) are the specific foci of my statement. The following questions summarize my statement.

- *Health behavior:* How will populations with little education, little knowledge of English, and little knowledge of health conditions, recommended preventive tests, and the like, respond in the managed care environment?
- *Low-birthweight infants:* How is the incidence of low-birthweight infants born to African-American and Asian Indian women explained? What are the protective factors for births to first generation Mexican-American women?
- *Hypertension:* What physiological and psychosocial mechanisms underlie the high rates of hypertension, heart disease, and death among African Americans, Native Hawaiians, and Filipinos?
- *Osteoporosis:* Is childhood nutrition implicated in osteoporosis? What behaviors and factors could be preventive for osteoporosis among Asian women, among whom the incidence is high?
- *Alzheimer's disease:* What is the relationship between the incidence of Alzheimer's disease and aging among women of color? Are the oldest old women of color more or less likely to get the disease than younger old women of color?

Susan Lewis *Independent Living Research Center*

As a woman with a spinal cord injury (quadriplegic) there are many areas or gaps in knowledge relating to health for women with disabilities. After sustaining an injury at 24 (a time when thoughts of education, careers, marriage, and families enter the picture), I entered a different world. A world where my independence and freedom were taken away from me.

The medical professionals did not provide the needed information, education, or financial resources necessary for transitioning me from the hospital back into my home. As a result, I ended up in a nursing home for 8 years of my young life. I lost control of every aspect of my life.

After the assistance, support, and encouragement from an employee of the Division of Vocational Rehabilitation I was able to move out of the nursing home and return to school for an education.

Living in the community and regaining my independence I have learned that the following issues affect women with disabilities:

- Lack of information for individuals and their families. Increasing information increases choice and individual empowerment.
- Adaptive equipment is not always accessible and is often times very expensive. Having access to adaptive equipment eliminates limitations.
- More services are needed, especially at the initial phase of an injury. Attendant services are of major importance but in most cases not easily accessible or affordable. They are important in maintaining quality of life and for reducing risk of developing infections and other health problems.
- Health and Auto insurance issues faced by women with disabilities. Auto insurance increases because of being a “high-risk” driver, and health insurance is not always accessible. If it is, there is no guarantee that it will assist with payment of medical assistance.
- Women with disabilities face extreme financial issues. The cost of living with a disability puts extra stress on individuals and families.
- Complicating the issues of women’s health is the fragmentation and under funding of a variety of federal and state programs that pay for a range of services that people with disabilities need to become independent. In addition, more of these programs contain disincentives to employment, which keeps women with significant disabilities out of the work force and dependent on services and programs.

These are just a few issues that women with disabilities face living in our communities. These areas need to be addressed so those women with disabilities can live a quality life in our communities.

Washington, D.C. Liaison

Rosemary Locke *Y-ME National Breast Cancer Organization*

In 1996, Y-ME National Breast Cancer Organization and other cancer patient and provider organizations filed a citizen petition urging the Food and Drug Administration (FDA) to ease its restrictions on access to silicone gel breast implants for women with breast cancer or those at high risk for the disease. The petition relied on the impressive body of sound scientific evidence related to silicone gel implants that has been produced since the FDA severely limited access to these medical devices 5 years ago.

Women requiring mastectomies following a diagnosis with breast cancer face the difficult and very personal decision whether to have reconstructive surgery. Y-ME and others strongly believe that women with breast cancer have the right to choose whether they want implants and to select the product that will give the best cosmetic outcome for reconstruction. In order to make this decision, we must have as much clear and accurate information about the safety of these products as possible.

Unfortunately, women have great difficulty obtaining accurate information. Many women increasingly rely on the media to assist them in making health related choices. But sadly, for the most part, the media has presented sensationalized stories about women with breast implants using anecdotal accounts instead of scientifically valid studies looking for a causal relationship between breast implants and illness.

FDA, the source informed consumers should normally rely on, continues to downplay the overwhelming scientific evidence that indicates no clinically relevant risks associated with these devices. Moreover, two official FDA documents send a mixed message to consumers. This creates fear and confusion for women considering implants as well as those who already have them.

FDA breast implant policies have broader implications relating to the regulation of and access to medical devices used in the treatment of other cancers. The threat of overly burdensome regulations and litigation have an intimidating effect on the research and development of potentially life-saving medical products.

Because the FDA failed to address adequately our concerns, the following cancer organizations joined Y-ME in the attached citizen petition: American Cancer Society (ACS), American Society of Clinical Oncology (ASCO), Cancer Care, Inc., Candlelighters Childhood Cancer Foundation, National Alliance of Breast Cancer Organizations (NABCO), National Coalition for Cancer Survivorship (NCCS), Society of Surgical Oncology, and US TOO International (prostate cancer organization).

We believe that this document will provide a valuable tool for the Office of Research on Women's Health as it assesses issues relevant to breast implants, other medical devices, and scientific research.

Ann Martin-McAllen, M.S., Ph.D. (Candidate) *Self (Presented by Sheena Cameron)*

Fibromyalgia is a topic of importance to women's health. I am currently studying the connection of stress, personality and coping style in women who have been diagnosed with fibromyalgia syndrome (FMS) for my dissertation. I also am an FMS survivor.

I was diagnosed with FMS numerous years after several traumatic experiences, two of which were automobile crashes. I experienced many problems in trying to get a diagnosis — I saw many doctors of various specialties, had many examinations, took a great variety of tests, yet they stubbornly refused to believe that it was anything but just my imagination, because I "looked perfectly healthy." Before obtaining a diagnosis, I had gained 80 pounds, was so fatigued at times that I could hardly function, was in tremendous pain throughout my body which at its worst caused me to depend on my husband to perform almost every task of daily living.

Once diagnosed I knew I had achieved the first step in regaining my health or at least becoming functional again and hopefully would be able to recapture my life and my future. What followed my diagnosis was a continued quest for treatment modalities that would restore my health or at least allow me to reclaim my life and my relationships.

FMS is defined as "a form of nonarticular rheumatism characterized by widespread musculoskeletal aching and stiffness, as well as tenderness on palpation at characteristic sites called tender points."

FMS occurs predominantly among females, with only 5 to 20 percent of the cases among males. FMS occurs most commonly in the age group of 30 to 50 years, but some juveniles and elderly also are afflicted. Most patients are Caucasian, but FMS is also found among the Japanese and South African blacks.

The reason this syndrome is of such concern is that FMS dramatically affects the lives of its victims in a wide range of ways. The range of impairments include: muscle pain, functional disability, poor physical fitness, work disability, psychological distress, decreased quality of life, and relationship problems. The lack of information and understanding by the public and the health care community has caused many women to suffer needlessly, virtually having their lives destroyed. Women have been told and are still being told that there is really nothing wrong with them because nothing shows up in tests and they look well. This attitude has caused family members to doubt the seriousness of the condition and this only adds further suffering to the individual.

In summary, millions of women suffer from FMS. Many have been unable to obtain a diagnosis because of the confusion within the medical community regarding FMS and the stigma that still exists where women's health is concerned. Thus we must call for a greater focus in research of the etiology and treatment of FMS. We have a responsibility to take women seriously, believe them, and trust that they know their bodies; to not dismiss their complaints as being neurotic. This can begin with the use of behavioral medicine. Using behavioral medicine, women can be taught to recognize how their behavior affects their lives and their health especially; how our culture affects our attitudes and that we as women do have choices in our behavior.

Ann McCampbell, M.D. *Chair*
Multiple Chemical Sensitivities Task Force of New Mexico

I am a physician disabled with Multiple Chemical Sensitivities (MCS). I am also the Chair of the Multiple Chemical Sensitivities Task Force of New Mexico, a statewide advocacy organization for people with MCS. Because this illness primarily affects women, I encourage the Office of Research on Women's Health to make research on MCS a high priority.

In-depth research on MCS is urgently needed and long overdue. Since MCS was described in the 1950s, its prevalence has grown to near epidemic proportions, yet this illness continues to be virtually ignored by the medical and scientific communities. The fact that the vast majority of MCS sufferers are women has undoubtedly contributed to the tendency for MCS to be dismissed as hypochondriasis and hysteria. Efforts by the chemical industry, with its vested interest in maintaining doubts and controversy about MCS, have also contributed to lack of research in this area. Clearly, it is time for government to declare war on MCS, as it has on cancer, and commit to solving the mysteries of MCS, developing effective treatments, and implementing prevention programs.

Martha A. Medrano, M.D., M.P.H. *Associate Director*
Medical Hispanic Center of Excellence

We have organized a Hispanic Faculty Association within our institution to identify and address issues of Hispanic Americans. The issues we have identified for Hispanic women in academia are as follows:

- Early in their careers, Hispanic women faculty are heavily involved in clinical services and not having an opportunity to be involved in activities that will assist their tenure and promotion.
- Hispanic women faculty are sometimes written into grants requesting funding to research Hispanic communities, but have limited influence in the project. When the grant is funded, they are not notified and therefore not involved in the project.

The solutions to the above issues are:

- Funding of postgraduate fellowship opportunities for women of color in academia.
- All grants targeting research in minority populations should have, at a minimum, one co-investigator involved through the life of the grant, who is representative of the population being studied. This would ensure sound, culturally and gender sensitive research design, methodology, implementation, and reporting of results. This would also assure that female minority researchers have opportunities to be involved in research projects.

Holly Neckerman, Ph.D. *Navajo Division of Health*

It is essential that the health concerns of the Navajo woman are heard. The Navajo Nation stands out from other Indian tribes and other ethnic groups. For the most part, Navajo people are both physically and geographically isolated. To fully appreciate the urgency of the health problems affecting the Navajo women, it is essential that you understand who the Navajo people are and the conditions in which they live. The Navajo Nation is the largest American Indian reservation in the United States, yet many people lack complete plumbing or kitchen facilities, or working telephones. The rates of unemployment and poverty are much higher than other parts of the country and other ethnic groups. Four health issues are of critical concern: gestational diabetes, chlamydia, breast and cervical cancer, and domestic violence.

Gestational diabetes. Research and clinical practice indicate that gestational diabetes is an urgent problem among Navajo women. One study found that the prevalence of gestational diabetes was 3.4 percent. Currently, there is no coordinated effort to provide adequate education, recruitment, monitoring, and followup for women with gestational diabetes. The Navajo Nation is seeking funding to develop a coordinated, comprehensive, and multidisciplinary approach to patient education, recruitment, and care to women with pregestational and gestational diabetes.

Chlamydia. Although the number of syphilis and gonorrhea cases has decreased since 1975, chlamydia is fairly new to the Navajo Nation. In 1986, there were 44 cases and in 1996, there were 1,305 cases. The Navajo STD Program provides STD/HIV counseling, referral for STD testing, and HIV testing and treatment referrals. While they do conduct surveillance activities, they are a paper-and-pencil operation. Our recommendations include more up-to-date treatments and more prevention education aimed at young adults.

Breast and Cervical Cancer. The incidence rates for breast and cervical cancer are not higher than other ethnic groups across the United States, yet the 5-year survival rate is much lower because of the advanced stage of the disease upon detection. One year ago, the Navajo Breast and Cervical Cancer Project was funded by the CDC. We are moving forward with a plan to increase access and availability of breast and cervical cancer screening among older, underserved women with the hope of saving lives and increasing survival rates.

Domestic Violence. Domestic violence is a clear problem among Navajo women and demands a collaborative and comprehensive solution. In an area with too few police to cover such a large geographic area and too few people having telephones to call for help, there is really a need to go beyond the criminal justice model for the prevention of domestic violence. The Department of Social Services has funding to tackle the criminal enforcement aspect of this problem, yet we need a comprehensive approach to address the problem in its entirety.

Like the rest of the United States, we must move beyond a piece-meal approach towards the understanding, prevention, and treatment of women's health issues. Yet an additional problem impedes progress. There is a severe shortage of Navajo medical, health, and research professionals. Additional training opportunities will give the Navajo people the necessary tools and knowledge such that they can come to the table to voice the concerns, ideas, and visions for the good of the Navajo people.

Women's Health Center of Excellence
Electra D. Paskett, Ph.D. *Bowman Gray School of Medicine*

Approximately one million persons in the United States are diagnosed, and over one-half million die of cancer each year. A disproportionately greater number of incident cases and deaths are among the socioeconomically disadvantaged.

African Americans comprise about one third of the poor and have the highest overall age-adjusted cancer incidence and mortality rates of any population group in the United States. Of particular concern are breast, cervical, and colorectal cancer since screening exams, when used regularly, can reduce mortality.

Research conducted by investigators at the Women's Health Center of Excellence at the Bowman Gray School of Medicine have focused for several years on improving rates of screening exams among low-income, predominately African-American women. One of the most recently completed studies, the Forsyth County Cancer Screening Project, was an NCI-funded study to improve breast and cervical cancer screening among women who resided in low-income housing communities. The end of study survey collected information on knowledge, attitudes, and practices related to breast, cervical, and colorectal cancer. These data provide insight into differences in screening behaviors among African-American and white women who have a relatively similar low socioeconomic status.

A random sample of 424 women, stratified by city and age group (40 to 64; and 65 and older), from the housing communities was selected to participate in the end of study survey by simple random selection. Of the 300 women who participated in this cross-sectional survey, 79 percent (N=237) were African American and 21 percent (N=63) were white. African-American women in the sample were younger (average age 66 years) compared to white women (average age 73 years) ($p<.001$).

In general, screening tests for breast, cervical, and colorectal cancer were underutilized by the women and racial differences in screening rates were observed. Only 52 percent of African-American women and 40 percent of white women had had a mammogram within recommended age-appropriate guidelines. About 60 percent had had a Clinical Breast Exam in the last year although about 80 percent had visited a physician in the last year for a regular check-up. Fewer white women had had a Pap smear in the last year, but African-American women had achieved the 80 percent goal set by the year 2000 objectives. Colorectal cancer screening test utilization rates were low among both groups of women. After adjustment for significant factors, important issues related to obtaining regular screening exams included the receipt of regular check-ups, and knowledge, beliefs and barriers related to the specific screening test regardless of race. These data suggest that efforts to improve mortality rates from these cancers among low-income women should include tailored messages to improve beliefs and convey understanding of risk. These efforts will assist in bringing us closer to the Year 2000 goals for all women and help to reduce the disproportionate cancer mortality rates among low-income populations.

Sally Piscotty *The National Association of Women's Health Professionals*

The National Association of Women's Health Professionals (NAWHP), a membership organization of women's health administrators, health educators, and clinicians, works at the local level to disseminate the results of scientific studies and to provide gender expertise in the treatment and education of women.

NAWHP recommends that research be conducted to examine:

- The effectiveness of health education methods, focusing on the role of psychosocial determinants of effectiveness.
- The risks, benefits, and effectiveness of alternative medicine practices.

Health education. Information and health education can enable a woman to avoid major risks, practice prudent self care, and seek timely medical interventions. Members of NAWHP and others across the country who are measuring the effectiveness of their health education programs have found that they not only improve the health status of women, but that they also reduce long-term health care costs. For example, a breast health education program offered by St. Charles Medical Center in Bend, Oregon has successfully demonstrated that education and community outreach has resulted in early diagnosis of breast cancer with a 75 percent Stage I diagnosis as compared to a national average of 49 percent. The cost of treating one early-stage breast cancer is approximately $12,000; late-stage treatment is estimated at $145,000.

While the impetus and purpose of many women's health centers, clinics, and service lines is to help women to be informed health care consumers and to give them the knowledge they need to take care of themselves, we currently teach women about their health without scientific evidence regarding the suitability or effectiveness of the education. Studies suggest that women learn differently than men and that behavior change is elicited in gender-specific ways. Group education issues, relational development, and attitude sets influence a woman's learning as do demographic variables including ethnicity, race, age, and socioeconomic background. Health care providers focusing on prevention need a better understanding of the impact of these issues so that they can bring information to their patients in a way that leads to the best health outcomes.

Although women's health providers across the country are offering health education programs to women and are achieving favorable outcomes, we do not have a clear scientific understanding of which programs work best for which women and why. Research on this issue would help NAWHP and others to improve health outcomes for women through primary and secondary prevention practices.

Alternative medicine. In 1993, David Eisenberg, et al. published results of a study that found that, "Roughly 1 in 4 Americans who see their medical doctors for a serious health problem may be using unconventional therapy in addition to conventional medicine...; 7 out of 10 such encounters take place without patients' telling their medical doctors that they use unconventional therapy." Further studies have shown that women use unconventional therapy or alternative medicine more often than men.

Professionals in women's health currently provide their patients with alternatives to conventional medicine. NAWHP members offer massage, therapeutic touch, yoga, acupuncture, natural hormones, and homeopathy. Data on NAWHP member surveys show that patients regularly request information about alternative health methods, yet, again we have no scientific data to document the effectiveness or the ineffectiveness of various alternative methods.

Charles Ponte, Pharm.D., C.D.E., B.C.P.S., F.A.S.H.P., F.C.C.P.
Professor of Clinical Pharmacy and Family Medicine
West Virginia University Schools of Pharmacy and Medicine

I shall discuss my vision of the role of the pharmacy profession and its relationship to women's health issues. The role of the pharmacist has changed from the earliest compounding of healing medicaments to the provision of more sophisticated care. Since 1990, the pharmacy profession has come to embrace the notion of pharmaceutical care. This paradigm shift espouses a new philosophy for the profession. The pharmacist has a shared and equal responsibility with the physician and other health care providers to guarantee suitable outcomes and quality of life indicators stemming from a person's drug therapy. Ongoing research efforts are underway to decide the clinical and economic benefits of pharmaceutical care to both patients and the overall health care system.

Important gender differences do exist which may affect the quality of health care received by women. Sex discrepancies are found between diagnostic and treatment decisions, drug prescribing patterns, susceptibility to poor health care, communication with health care providers, recruitment for clinical trials and even drug action and metabolic fate.

The pharmacy profession is beginning to recognize the unique health care needs of women. Both pharmaceutical care efforts and scientific inquiry are being directed toward solving gender-specific, drug-related problems. Curricula in colleges/schools of pharmacy reflect an increased awareness and sensitivity to women's health care issues. Professional associations and publications are devoting more educational programming and editorial space for women's health care topics. My own research has shown that many pharmacists are engaged in counseling women about their unique health care concerns and that women tend to be proactive in requesting advice from the pharmacist. Notably, women want the pharmacist to be an active participant in their health care education about prescription and non-prescription drugs (e.g., hormone replacement therapy, feminine hygiene products, contraceptives, vitamins).

Despite these positive efforts, the pharmacy profession needs to continually seek a better understanding of the role of gender and its overall influence on the provision of pharmaceutical care. At the national level, there still remains a need to more thoroughly understand the attitudes of pharmacists regarding women's health issues and to discover the kinds of pharmaceutical care services rendered to women. These and other "pharmacogender" research endeavors will better define the profession's future initiatives aimed at women. Such initiatives could include focused disease state management strategies (e.g., diabetes mellitus), curricula revisions, outcomes development, and public policy framing. Collective involvement by pharmacists (the most accessible health care provider) in the women's health care arena could result in an improved health status for women and its attendant socioeconomic benefits.

Linda Ransom *Self*

I am the mother of 10-year-old, Tara. Tara is dependent on a shunt made of silicone to control hydrocephalus. The current litigious climate in the United States endangers the supply of raw materials for her shunt and other life-saving and life-enhancing implantable medical devices such as pacemakers, hip and knee joints, and cataract lenses. With the shunt, Tara is an accomplished young lady who deserves the chance to live to become a productive woman. Without shunts and other medical devices, Tara and many others will face painful deaths. Although Tara has had five shunt-related surgeries, we know that the day will come when she needs another replacement or revision if for no other reason than growth. The medical technology to save her exists, but the availability is threatened. We cannot continue to allow lawsuits to dictate the medical options available to women today. This will increasingly impact and overlay all areas of women's health in the near future unless something is drastically changed. Since women live longer lives, they can expect to need more devices, making this very much a woman's issue.

Joan Y. Reede, M.D., M.P.H., M.S. *Harvard Medical School*

As assistant dean for Faculty Development and Diversity at Harvard Medical School, I wish to share with you the history of this department and how we have addressed the issue of minority underrepresentation in the biomedical sciences. The Office for Faculty Development and Diversity was established in 1995 to:

- Provide leadership, guidance, and support for academic and professional career development, and
- Promote increased recruitment, retention, and advancement of underrepresented minorities and women.

Historically, African Americans, Mexican Americans, Puerto Ricans, and Native Americans have been chronically underrepresented in the biomedical sciences. The rise in minority medical student enrollment in the late 1970s should have resulted in a concomitant increase in the representation of minority physicians, scientists, faculty, and leaders in the 1980s and 1990s.

Between 1971 and 1994, there was an increase in the number of minority medical faculty from 1,001 to 2,813 — an increase from 3.4 to 3.9 percent when compared to total faculty. The Association of American Medical Colleges attributes part of this growth to the accreditation of three predominantly minority medical schools. In fact, six of the 125 medical schools in the United States account for approximately 27 percent of all underrepresented minority faculty. In essence little progress has been made.

If underrepresented minority students are to become future leaders in our academic medical centers research institutions, industry and government, they must be informed of educational, training, and employment opportunities and must be encouraged to pursue positions where they can become change agents.

Harvard Medical School (HMS) has created a system of programs designed to address minority faculty underrepresentation. In May 1990, the Minority Faculty Development Program (MFDP) was established. This program became part of the Office for Faculty Development and Diversity in 1995. The four goals of MFDP were to: (1) increase the number of medical school minority faculty; (2) increase the number of minority professionals who enter graduate medical education programs at HMS-affiliated hospitals; (3) establish program models for the development of minority faculty, with an emphasis on mentoring; and (4) develop outreach precollege and college programs.

Reviewing national, regional, and local efforts to increase minority participation and advancement in the sciences revealed three recurring obstacles to achieving these goals. First, there has been poor communication of information pertaining to prerequisites for entry and advancement, poor communication on available supports such as targeted programs, scholarships, research supplements, and fellowships and insufficient understanding on how to get through the bureaucracy. The second obstacle has been the ongoing lack of continuity in advancing students, trainees and professionals from one stage to another along the career pipeline. Succinctly stated, in the development and implementation of programs, "the right hand often does not know what the left hand is doing." Third, there is an absence of evaluative data on the effectiveness of strategies and outcomes achieved.

Having determined these obstacles, programs were designed that furnished information about training opportunities and funding resources; provided students exposure to academic health centers, research experiences, and faculty role models; improved the preparedness of students, residents, and junior faculty to make informed career decisions; and promoted the development of mentoring relationships and supported the building of student and professional networks that cross disciplines, departments, and institutions. A brief description of several programs follows.

Precollege. At the precollege level, MFDP implemented programs that include the development of science curricula used in middle and secondary classrooms; through the Teacher Institute, the training of science teachers in both laboratory techniques and the use of the case study method; and through Project Success, hands-on, mentored research experiences for high school students.

College. Students completing the precollege program can continue in Project Success while in college. They can also be linked to research programs at HMS-affiliated hospitals, in private industry and at other academic and research institutions. In addition, MFDP sponsors a health policy summer research program for college students who attend Minority Access to Research (MARC)-funded historically black colleges and Hispanic-serving institutions.

Medical Student. Through the Visiting Clerkship Program (VCP), another MFDP project, more than 250 underrepresented minority students from U.S. medical schools have participated in the HMS Exchange Clerkship Program. Along with financial support, this program informs students about residency and fellowship training opportunities and provides career guidance from senior faculty. VCP's success is measured not merely by the number of student participants who become HMS residents, but by whether students become better informed about existing academic training opportunities and the impact their current choices will have on future career options.

Biomedical Science Careers Project. In conjunction with the Massachusetts Medical Society and the New England Board of Higher Education, MFDP founded the Biomedical Science Careers Project (BSCP). BSCP is a not-for-profit organization that provides New England minority trainees, junior faculty, and students (from high school through graduate school) with mentors, career guidance, and comprehensive information on programs and opportunities. BSCP is supported by a collaboration of area professional societies, teaching hospitals, biotechnology companies, community and 4-year colleges, universities, high schools, and private industry.

Since its inception, this organization has initiated several activities including the publishing of the *New England Resource Directory of Science Programs*, producing a newsletter — *In Touch with BSCP* — distributed to more than 2,500 students, teachers, guidance counselors, administrators, and community organizations, as well as sponsoring regional conferences that have brought together more than 1,500 minority students and professionals with senior advisors and mentors.

Fellowship. During the implementation of the above programs, major changes continue to occur within the areas of academic medicine, health care, public health and health policy. These changes include: movement toward increased enrollment in managed care, increasing emphasis on quality and outcomes, persistent disparity in health status among various ethnic and racial populations, shifting support for graduate medical education, and increased competition for research dollars.

In this changing environment as policies are developed, priorities are set, and funding is allocated, it is imperative that minority physicians and scientists be included in the decisionmaking process. Failure to include minority individuals, as leaders with recognized expertise and the power to make decisions, will result in solutions that are exclusionary, shortsighted, and continue to be less than effective.

Recognizing the need to proactively prepare physicians to assume leadership roles in this era of change, MFDP, through a collaboration between Harvard Medical School, Harvard School of Public Health, and the Kennedy School of Government, has established The Commonwealth Fund/Harvard University Fellowship in Minority Health Policy. This is a 1-year, full-time, academic, degree-granting program designed to create physician-leaders, particularly minority physician-leaders, who will pursue careers in health policy, public health practice, and academia. A total of 25 fellowships will be awarded over a 5-year period.

The Fellowship has five primary objectives:

1. To enhance the leadership skills of physicians, preparing them to identify, analyze, quantify, and develop solutions to public health problems and offering them substantive knowledge in health policy, financial and organizational management, communication, politics, economics, and ethics, while creating a network of physician-leaders capable of advancing successfully among the public, nonprofit and academic sectors;
2. To provide rigorous academic training, including both academic work leading to a master's level degree in public health and advanced leadership training beyond it;
3. To develop physician-leaders who will, over time, improve the capacity of the health care system to address the health needs of minority and disadvantaged populations;
4. To enhance the health leadership training offerings at Harvard institutions; and
5. To remedy the underrepresentation of minority physician-leaders who are well-trained academically and professionally in clinical medicine, public health, health policy, and health management, and who are prepared to pursue careers that bridge the academic and public service arenas.

Over the past 7 years, the Harvard Medical School Office for Faculty Development and Diversity and the Minority Faculty Development Program have made substantial strides in trying to increase the numbers of minority students pursuing biomedical careers, residents in academic training programs, and physicians preparing for leadership roles. In addition, individual counseling and career development programs have been provided for fellows and junior faculty. Next steps include increasing the availability of mentors and addressing issues of promotion and retention.

Karen C. Renick *Board of Directors, DES Action USA*

The Health Legacy for Women of the DES-exposed Population

The National Cancer Institute estimates that only 50 percent of the 10 million DES-exposed people are aware of their exposure today. This lack of awareness is hardly benign. It translates into a public health crisis which is both serious and complex. It means that millions of Americans were exposed to a toxic drug without knowing it. Accordingly, this population has no idea that their health, and ultimately their lives, may be in jeopardy because of a dangerous drug administered decades ago. At present, they are not receiving the critical information they need regarding screening and followup medical care.

Today the hazardous effects resulting from *in utero* exposure to DES are well known. For DES daughters, these effects include clear cell adenocarcinoma of the vagina and cervix, structural malformations of reproductive organs leading to infertility and pregnancy disasters, and effects on the immune and other bodily systems. Women who took DES during pregnancy face an increased risk for breast cancer, and DES sons have an increased risk for reproductive tract abnormalities.

These health effects are compelling reasons for addressing the needs of the DES-exposed population. Furthermore, research on the effects of DES are far from conclusive and the serious health consequences faced by all DES-exposed women require further research to determine both long-term effects and appropriate treatment.

DES is an important model to consider as we face the question of the inclusion of pregnant women in clinical drug trials. DES is also a well-known and significant example of a hormone disrupter. With today's widening appreciation of the power of estrogens to affect our bodies, we need to follow through and learn as much as possible to understand the full implications of long-term, worldwide exposure to endocrine disrupting chemicals.

DES Action poses the following research questions: (1) Will there be a new peak of clear cell vaginal or cervical cancers as DES daughters reach menopause? (2) Will DES daughters, as we age, develop an increased rate of breast cancer as animal studies seem to suggest? (3) Should DES daughters be candidates for hormone replacement therapy during menopause? (4) What are the long-term effects of fertility drugs on a population already exposed to synthetic estrogen in utero? (5) What are the effects of DES on the endocrine, skeletal, cardiovascular, neurological, and immune systems? and (6) What are the risks for the third generation exposed to DES?

Colonel Irene M. Rich

Director, Research Area VI
U.S. Army Medical Research and Materiel Command

In the last few years, targeted Congressional biomedical research funding to the Department of Defense (DoD) has resulted in significant advances in women's health research. The DoD Breast Cancer Research Program (BCRP) is the largest of these efforts. The program aggressively seeks to identify gaps in breast cancer research funding, enhance previous accomplishments, and contribute to a comprehensive national effort that will benefit all citizens through scientific innovation and technology transfer. The BCRP has funded research at 828 institutions in the U.S. and abroad with a variety of funding categories to support basic and clinical research projects, training grants, and infrastructure enhancement awards. Programmatic goals include addressing the needs of minority, elderly, low-income, rural, and other underserved populations.

The BCRP fosters partnerships, collaborations, and interdisciplinary studies at several levels. BCRP stakeholders include key scientists, national leaders, and consumers from government, academic, and consumer advocacy organizations. Two consumers are assigned to each scientific peer review panel. The Idea Award Philosophy was created to stimulate and reward speculative but promising and creative ideas. Internet Web sites, the Arden Knowledge Management System (AKMS), and multidisciplinary meetings are the primary research dissemination modalities.

FY 93/94 BCRP Research Achievements. To date, projects have resulted in the publication of 380 manuscripts. BCRP-funded research has been presented at more than 300 national and international meetings, and investigators currently hold 9 new patents or licensures. Several BCRP infrastructure projects are acquiring breast cancer survival data and morbidity and mortality information, and are identifying women at high risk for the disease. Single- and multi-center clinical trials have been initiated to aid in the diagnosis/detection of breast cancer. Advances have been made in the detection of cellular abnormalities in breast cancer. Funded BCRP investigators have made progress in drug trials for therapy, treatment, and aftercare. Some examples of BCRP-funded projects on quality of life include pain management, benefits of counseling, access to care, and care following treatment; some results indicate the need to further address specific concerns and issues of ethnic groups.

Investigators funded by the BCRP have developed model systems that can characterize mechanisms involved in the pathology of breast cancer, tumor progression, and metastasis. BCRP researchers have shown that increased breast cancer risk is associated with high sunlight exposure, high residential solar radiation, and high dietary Vitamin D intake. Eleven new mutant strains have been developed and 10 new breast-related cell lines have been developed.

Emerging Breast Cancer Research Issues. Increased sensitivity to the spectrum of issues surrounding patient care including psychosocial, sexual, quality of life, and cultural dimensions is needed on all fronts. Breast cancer prevention must address genetics, environment, and lifestyle. Answers to questions of hormonal deprivation/replacement and childbearing for the patient with breast cancer remain elusive. Improving access and utilization of health care services, especially to underserved populations, remains a major challenge. The explosion of diagnostic and treatment complexities demands improved education and information services, enabling each patient to have optimal resources for decisionmaking. Consideration of the ethical dilemmas posed with each new diagnostic and treatment advancement must become standard practice. The most important systems issues are enhanced coordination among all agencies and researchers and the creation of additional national infrastructures to support technologies and rare specimens.

Other DoD Women's Health Research Programs. The goal of the Defense Women's Health Research Program is to combat health problems unique to military women, that are especially prevalent among military women, or that have a large impact on mission performance. Other programs include the DoD Osteoporosis Research Program and the DoD Ovarian Cancer Research Program.

The DoD is a relatively new player in the women's health research arena. The traditions of focused military determination and operational capabilities and the infusion of creative science management to expediently and responsibly fund the most urgently required research have enabled the DoD to become a catalyst for new insights, technologies, and partnerships across the spectrum of women's health research issues.

Peggy Roberts, M.D. *Self*

As a practicing primary-care physician for 20 years, I spend less time preventing injury, cancer, and chronic disease and more time helping people manage symptoms and dysfunction from these conditions and overcoming barriers to their care. I value opportunities to reinforce healthier lifestyles, safety, and stress reduction, and to encourage health maintenance and well-person exams for screening and further education. I feel that knowledge of one's state of health and of preventive measures, along with detection of possible disease and injury, can give individuals choice in further evaluation and treatment options. However, much early detection does not represent prevention or even secondary prevention as claimed by some well-known health campaigns.

True primary prevention means limiting the incidence and extent of disease and disability in the first place and supporting our body's own homeostatic mechanisms for maintaining health and healing. One way we can help prevent the increasing rates of many malignancies, reproductive disorders, and infertility, as well as some chronic diseases in women, is to understand and respond to the growing evidence of the deleterious effects of toxic chemical and pollutants in the environment on our own health as well as on that of wildlife around us.

I wish to focus on a review of environmental components of women's health and their effects during a woman's life span. I strongly recommend that ORWH study the texts and include specific research recommendations from recent and upcoming reports on known, environmentally related women's health conditions.

In studies and by testing of mutagenicity in animals, natural as well as man-made chemicals and radiation have been found to act directly and possibly indirectly as environmental triggers of cancer. Chlorinated hydrocarbons, herbicides, and heavy metals can mimic estrogen in our bodies. These toxic chemicals can also have other endocrine-disrupting activity and genetic-damaging effects in susceptible individuals; they are lipophilic and accumulable in fat tissue throughout life. In utero exposures to these toxic chemicals can cause fetal loss, birth defects, and neurologic developmental deficiency or even delayed immunological effects. Skeletal and nervous systems can be affected during times of growth, including in utero development. Asthma and autoimmune diseases are often more active during pregnancy and may be susceptible to adverse effects of hormonally active environmental toxicants.

For women, occupational exposure to chemicals and chemical processes can adversely affect fertility, cause pregnancy abnormalities, and increase risk of cancers. Obtaining more demographic information through ongoing studies such as the Women's Health Initiative and the Nurses' Study may help show whether occupational or recreational exposures to environmental toxicants play a role with other risk factors.

There is certainly abundant evidence of adverse effects and risks for women from exposure to environmental toxicants throughout their life spans, along with a need for more education and for continued research on ways to diminish the impact from these exposures. As a public-health-minded primary-care physician, I feel it is prudent and precautionary to advise a reduction of much environmental exposure to these toxicants for women, as well as for all individuals in families and communities and nations, in order to prevent known disease and disability.

- We can insist on our right to cleaner air and water and on our right to know what kinds and levels of toxins are produced and released into the environment in our home, work, and communities.
- We can require that chemicals be tested for endocrine-disrupting activities and possible indirect carcinogenicity and that containers be so labeled and the public informed.
- We can advocate for zero chlorine and dioxin discharge from all industry, including medical work incineration, and also for removal of chlorine from paper production.
- We cannot support the use or production of known toxic chemicals and drugs, including cigarettes, nor their exportation to other countries.
- We can avoid using pesticides and practice integrated pest management at home and in our communities.
- We can eat organic, pesticide-free foods, with more vegetables, grains, beans, and fruit, and less fatty animal and fish products, thus minimizing body fat and potential toxic chemical burden.
- We can support education and outreach for affordable and safe home, work, and community environments for all persons in our country and abroad.
- We can ensure access to good health care for all.
- We can reduce waste and encourage recycling, relying less on petrochemicals, and supporting development and use of alternative, biodegradable and non-toxic chemicals and materials.
- We can continue further study, education, and outreach on the effects of the environment on our health, as well as on global health, and move towards less deleterious and more harmonious ways of living on and with this earth.

Gail Robin Seydel *Action for Women's Health*

The links between women's health and industrially produced environmental contaminants is an extremely serious concern that must be addressed in future research and in outreach and educational efforts in large and small, urban and rural communities. Understanding the links between health and environment has been popularized by the women's cancer movement in light of the fact that approximately 70 percent of women with breast cancer do not have the established medical risks and the breast cancer gene only accounts for about 5 percent of women. Looking for answers to what can be called a plague on our nation's women, that grassroots movement spotlighted the research and work of scientists and doctors, including Ana Soto, Mary Wolfe, Devra Lee Davis, Theo Coburn, and many others as it searched for answers.

More work must be done in this area if we are to prevent breast cancer as well as address a host of other women's health problems. With over 70,000 chemicals in our air, water, soil, food, household products, feminine hygiene products, cosmetics, etc., that have yet to be tested for endocrine-disrupting effects, both individually and in combination, every woman is at risk from the toxic soup in which we live. The fact that organochlorines, as well as other chemicals, heavy metals and radioactive materials can cross placenta barriers and affect the first environment all humanity experiences, our mother's womb, makes this research of immediate importance to the well being of future generations.

Exposure to environmental contaminants has been shown to cause health problems, including all kinds of cancers, infertility, other reproductive disorders, endometriosis, birth defects, behavioral and learning disabilities, diabetes, and other health problems in test animals with exposure levels within which those we women currently experience. Most affected are poor women and women and communities of color. Here in New Mexico this is of great importance with Native American and Hispanic peoples being a large proportion of our population.

A variety of research, regulatory, education, and outreach opportunities and suggestions to respond to and combat the above ills will be presented as part of my testimony.

Cynthia M. Shewan, Ph.D. *The American Physical Therapy Association*

The American Physical Therapy Association appreciates the invitation to participate in the development of a research agenda for women's health research in the coming decade. The Association believes that research is especially needed in the following areas:

Environmental. The workplace should be studied to identify and correct health hazards for women as well as men. In particular, research is needed to identify practical, effective ways to protect workers from job-related musculoskeletal risks, including repetitive stress syndrome. This research area is particularly important because musculoskeletal disorders are the country's most costly category of workplace injury and illness.

Recreational and Sports-related Injuries. As more women participate in recreational and organized sports activities, investigations into the prevention, causes, and treatment of musculoskeletal injuries, especially knee injuries, are needed.

- Emphasize continuing research into the prevention of osteoporosis and hip fractures, including designing effective strategies to instill good exercise habits.
- Study the influence of exercise and physical activity on balance activities, including the prevention of falls.
- Conduct additional research on the benefits of exercise for the prevention of disease and disability.

Chronic Conditions

- Increased research is needed on chronic conditions and diseases, such as cancer, stroke, diabetes, and chronic pulmonary disease, that impact the quality of life of older women in the U.S.
- Additional research is needed to improve urinary incontinence treatments, including behavioral techniques, muscle exercises, and biofeedback.
- Cardiovascular disease, especially in women over age 50 years, continues to have a major impact on women's health. Research on the etiology, prevention, and treatment of cardiovascular disease and cardiac rehabilitation for women is needed.
- Osteoarthritis has disabling effects on the musculoskeletal system. Research is needed to identify the most effective way to reduce musculoskeletal impairment and improve function.
- Osteoporosis affects an estimated 20 million Americans and is most common in the elderly and in postmenopausal women. Additional research on the prevention and treatment of osteoporosis, including studies on the effectiveness of weight-bearing and weight-training exercise, is indicated.
- Diabetes is associated with long-term complications that affect almost every major part of the body. Additional research is needed, including the prevention and treatment of foot ulcers, due to both neurologic and vascular complications.

The mission of ORWH should be expanded to monitor funding for women researchers and career opportunities, and to ensure equality and the elimination of career barriers for women.

Susan M. Shinagawa *Self/Intercultural Cancer Council*

Breast cancer incidence and mortality rates in Asian Pacific Islander (API) women are consistently reported to be among the lowest for all women in the United States. These low rates for API women compared to all other ethnic groups have led to the belief among health care providers, public health policy makers, governmental agencies, and the general population that API women are not at risk for breast cancer. But these statistics are skewed. They have perpetuated a dangerous myth and provided justification for an outcome all too familiar to API communities — once again, when health care dollars are allocated, we are left out of the equation.

Currently, reported breast cancer statistics for API women are skewed because API populations have (1) the highest immigration rates at nearly 70 percent, (2) immigrating from their native countries with the overall lowest breast cancer incidence and mortality rates in the world, and (3) have the lowest median age of all U.S. populations (risk of breast cancer increases with age). As the current API population ages, acculturates, and increases due to fertility, the reported incidence and mortality rates will begin to show a steady increase. Yet, the rapid growth of API populations fueled by immigration over the next 10 to 15 years will prevent the statistics from depicting an accurate picture of breast cancer risk in APIs. And the trend to study cancer in API populations as an aggregate group only obscures the reality of breast cancer risk, incidence, and mortality in our many diverse and divergent subpopulations.

In fact, while the ACS reported last year that U.S. cancer deaths are declining, cancer deaths have actually increased at a faster rate among APIs than any other U.S. racial/ethnic population. Between 1980 and 1993, cancer death rates for APIs more than doubled (290 percent for males and 240 percent for females), representing the highest percentage increase in the U.S.

These inaccuracies are now reflected and will continue to be reflected in the lack of knowledge about actual female cancer risks among API women, and the paucity of health care research, funding and programs targeted to (breast) cancer outreach and education in API communities, which will continue to result in late stage diagnoses with a disproportionately high mortality rate. The myth that API women are *not* at risk for breast cancer (1) promotes a false sense of health security among API women, (2) creates the illusion among health care providers and policy makers that there is a lack of need for breast cancer education, screening, diagnoses, treatment and support among API populations, and (3) validates the arguments that justify policies precluding the utilization of resources to provide for the overall spectrum of breast cancer in API populations.

In addition, the perception among health care providers and public health policy makers of APIs as the "model health minority" (another well established myth in the American medical and political milieu — that APIs take care of themselves and do not require preventive and first-line health services) only serves to exacerbate this situation, resulting in a lack of culturally competent outreach and intervention for these diverse populations.

Utilization of demographically based projections of API cancer research and incidence/mortality rates are critical and necessary tools in developing sound public health policies for U.S. API communities. In addition, the immediate development and implementation of a multifaceted effort to educate API women on healthy lifestyle interventions and early detection methods; the education of health care providers and public health policy makers about actual breast (and other) cancer risks in API communities; and a culturally competent, community relevant, and language appropriate U.S. health care system is imperative to preclude a virtual (breast) cancer epidemic in API communities over the coming decades.

Susan Silverton, M.D., Ph.D. *American Association of Dental Schools*

Dental and oral diseases affect most older Americans; 99.5 percent of Americans 65 years and older have had cavities and 40 percent of these elderly Americans have lost all of their teeth. Of those who are poor, a disproportionate number are also edentulous. In the edentulous elderly population, only 10 percent had a yearly dental visit. In addition, those in poorer health or limited by disability have fewer regular oral health followup visits. By the year 2000, it is estimated that $62.3 billion will be spent yearly on dental services. Yet, only 15 percent of those 65 and older have dental insurance.

Gender-specific data on women shows that increasing age is accompanied by an increase in the edentulous population. While women aged 45 to 54 have only a 12 percent prevalence of complete loss of teeth, 46 percent of women over 75 years of age have lost all their teeth. The loss of teeth does not signal an end to the need for oral health care. In fact, the health problems of edentulous patients demand continued care. The vast majority of nursing home residents are women. New nursing home regulations on oral health care have been in place for 2 years, but oral health screening is not standardized and no provision is made for coverage of oral health care costs unless the service required is an emergency or is covered by Medicare.

Oral Health Diseases of Postmenopausal and Elderly Women. Oral conditions may undermine an elderly person's quality of life. Several of the most common oral health diseases occur more frequently in elderly women. These include temporomandibular disease; trigeminal neuralgia; atypical facial pain; pemphigus; burning mouth; discoid lupus erythematosus; and oral cancer.

Oral Manifestations of Systemic Disease. Sometimes, oral symptoms are the prodrome of systemic disease. Some examples of systemic diseases that oral health care practitioners recognize and treat include anemias; multiple myeloma; Paget's disease of bone; and diabetes mellitus.

The Traditions of the Oral Health Practitioner Include Prevention and Screening. Oral health practitioners have a tradition of providing effective preventive health care. Eighty percent of general practitioners are trained to take a comprehensive medical and oral history, blood pressure and any other diagnostic tests which are required for risk assessment prior to the surgical treatments of health care. Preventive counseling highlights caries and periodontal care. Dental care practitioners also include information on smoking and tobacco cessation (oral cancer risk), and nutrition counseling. In older or more medically compromised populations, dentists are competent to take blood pressures and recommend a physician followup for hypertension control.

Oral Health in the Medical Curriculum. Although there is considerable overlap in the knowledge base of physicians and oral health practitioners, there are also barriers in the education and training of these practitioners that limit the integration of oral health care and general health care. However, these barriers are being challenged. Ongoing surveys and reports of the medical and dental curriculums should lead to reevaluation of the gaps between the training of health care and oral health care practitioners. One goal should include structuring the respective curricula to provide linkages between the disciplines of medicine and dentistry. Curricula can be designed to decrease the knowledge gaps and to lower barriers to the practice of integrated care. As far as practice integration is concerned, integrated medical and dental services are now beginning to be offered in some managed care settings. Working together on the same patients should help oral health and health care practitioners achieve better integration of oral health and health care for women.

Recommendations for Oral Health and General Health Care for Postmenopausal and Elderly Women.

- Improve science transfer/education of the public; and
- Strengthen the linkages between oral health and general health.

Linda C. Skidmore, M.S.

Committee on Women in Science and Engineering
National Research Council

CWSE is the one unit of the NRC that focuses on the retention of female scientists, engineers, and technicians (SETs) in science-based education and employment. This Committee has the broad mandate to increase the participation of women in the scientific and engineering (S&E) labor force. Despite women's increasing participation in the S&E work force during the past decade, the rate of increase of the participation by women of color (minority women) in both post-secondary S&E education and science-related careers remains fairly constant.

- At the undergraduate level, according to NSF (1996), "underrepresented minorities — blacks, Hispanics, and American Indians — are as likely to earn bachelor's degrees in science and engineering as they are to earn bachelor's degrees in other fields." In 1993, the rates ranged from 7 percent for blacks, 5 percent for Hispanics, but only 0.5 percent for America Indians. However, the rates were even lower for undergraduate women of color: of all S&E baccalaureate awardees, only 3.9 percent were black women, 2.5 percent were Hispanic women, and 0.3 percent were American Indian women.

- 1996 data available from NSF reveal that "minorities earned 17 percent of master's degrees in science and engineering in 1993, compared with 13 percent in 1985;" however, no change was found for American Indians and the increase for both blacks and Hispanics was only 1 percentage point. At the same time, women were 35.8 percent of all S&E master's degree holders in 1993. Women of color were almost lost among the "17 percent" figure, for they comprised a smaller group of S&E master's degree holders that year: 2.3 percent were black women, 1.5 percent were Hispanic women, and 0.2 percent were American Indian women.
- While the basic biomedical sciences, behavioral sciences, and nursing remain attractive to women, oral health research and health services research have recruitment rates less than half of that for basic behavioral sciences. At the same time, women comprise about one-third of the participants in NIH's Medical Scientist Training Program (MSTP), which produces physician-scientists.
- Among S&E doctorates, the committee found significant underrepresentation of minorities (particularly minority women) in all other research areas, noting an "alarming shortage of researchers" of all racial ethnic groups in oral health; in that field, participation by black women and men actually declined about 1 percentage point, to 2.6 percent, between 1986 and 1993. In fact, blacks and Hispanics were underrepresented in all five areas as well as among physician-scientists. Native Americans were particularly underrepresented among the behavioral science research personnel. Representation by Asians typically reflected their percentage in the total U.S. population; however, the study found that they were underrepresented in the behavioral sciences but overrepresented in oral health research.
- Little difference is found in S&E employment: women are most likely to hold part-time research positions and to be concentrated at the rank of assistant professor. For instance, in 1993, women comprised only 13 percent of physician-scientists and less than 19 percent of oral health researchers. Among research faculty, women were most likely to be found in the lower ranks in the basic biomedical sciences and the behavioral sciences, although they comprised about 40 percent and 55 percent, respectively, of researchers in those two areas.

As a result of the drastic underparticipation of women of color in the technological work force of the United States, the National Research Council's Committee on Women in Science and Engineering examined, during its third national conference, both the quantitative information about their underparticipation and qualitative data that reflected the experiences common to many minority women interested in pursuing science-based careers. Information presented here is drawn from the transcripts of that conference, "Diversity in Science: Perspectives on the Retention of Minority Women in Science, Engineering, and Health-Care Professions."

Anne Stansell *United Silicone Survivors of the World*

Contemporary health care services must work to bridge the gap between the legitimate illnesses suffered by women with silicone breast implants and the manufacturers who say, “nothing’s wrong.” Manufacturers of silicone breast implants spend millions of dollars on media advertisement, stilted research, and grants to medical schools. The results are misled consumers, erroneous findings, and large profits!

The truth is found in the recipients of silicone breast implants: their failing health, their frustrated attempts to achieve credibility, and the truth is found in real evidence. There is a need for support and communication among the medical practitioners who can work free of excessive pressure and beyond the biases of previous research that was funded and influenced by silicone breast implant manufacturers, such as the Harvard and May studies.

We want to share the over 1,300 peer reviewed, legitimate medical research articles available, one of which is by Robert Garry, M.D., immunologist and microbiologist and author of more than 200 articles on autoimmune diseases. The challenge to the medical researcher: identify and name “like-syndrome” diseases which mimic classic diseases.

We must focus on the women and question the practice and motives of the manufacturers. Silicone disease is showing up in the second generation: the children of women with breast implants. Silicone is not biologically nor chemically inert. Silicone breast implants are not lifesaving devices but life-shortening devices and banning all silicone devices is medical blackmail!

Leah Stiemel, M.D. *New Mexico PreNatal Care Network*

Prenatal care is one of the best examples of preventive care and represents the best investment of the health care dollar. Prenatal care offers the best hope for improved pregnancy outcomes and thus represents one of the most important components of obstetrical care. Women who do not receive early and continuous prenatal care have three times the rate of low birth weight babies. Several preventable factors increase the risk of delivering a low-birthweight baby, including lack of prenatal care, maternal smoking, use of alcohol and drugs, pregnancy before the age of 18, and lower socioeconomic and educational levels. Low birth weight is a primary predictor of costs: as birth weight falls, costs increase. An estimated more than $6 in neonatal intensive care costs could be saved for every $1 spent on prenatal care.

New Mexico continues to rank next to last in the nation for the percentage of women who receive the recommended level of prenatal care. In 1995, only 52.6 percent of pregnant women in our state received adequate prenatal care. New Mexico still must make considerable improvements to reach the Healthy People 2000 goal of 90 percent of pregnant women receiving prenatal case in the first trimester of pregnancy.

There were 26,914 births in New Mexico in 1995. Of these births, 11.6 percent were born to women who received late (third trimester) or no prenatal care compared to a national rate of 6 percent. Ethnic and racial differences exist when it comes to receiving adequate prenatal care in our state. In 1995, 61 percent of Anglo women who gave birth received adequate prenatal care, while only 48 percent of Hispanic women received adequate prenatal care, and 40 percent of Native American women received adequate prenatal care.

In addition, the number of babies born to teen mothers New Mexico in 1995 was 18 percent; New Mexico ranks 49 in the U.S. for teen birth rate (ages 15 to 17). Of these teen mothers, only 35 percent received adequate prenatal care.

Why such dismal figures for New Mexico? Barriers to accessing adequate prenatal care are similar to access to health care for anyone in New Mexico. In a largely rural state, there simply are not enough health care providers; 30 of the 33 counties are designated health care provider shortage areas. Rural women struggle with traveling long distances for health care, and lack public transportation to get to appointments. New Mexico is culturally diverse, so language and cultural barriers affect access to health care. Finally, a high level of poverty and lack of health care insurance influence access to health care.

New Mexico has established two programs to improve health care access for women: the County Maternal Child Health Program and the Community Health Worker model. The Maternal Child Health Plan Act was passed by the New Mexico Legislature in 1991 to encourage the assessment and prioritization of maternal child health needs and the formation of a maternal child health council at the county level. The Community Health Worker Model is appropriate for New Mexico because it utilizes local resources to take basic education and health services to the client in their home.

New Mexico sits in a vulnerable position with regard to health care for pregnant women, putting its women and future children at a real disadvantage for a healthy birth, and potentially costing New Mexico millions of dollars. Efforts must be increased at all levels, state, county, and local, to change our states' poor ranking in this area. Prenatal care provided in a timely, continuous and regular manner, assists the woman in monitoring the progress of her pregnancy, provides her with essential health information to make sound decisions for herself and her baby, and reduces her risk of having a low-birthweight baby. Improved prenatal care is important for New Mexico's future.

Cecilia Téllez *Self*

Not only are lesbians subject to the same barriers to health care as other women, but they are also subject to barriers that are unique to their sexual orientation. Anti-gay bias within the medical community hinders the ability of lesbians to obtain comprehensive, quality health care. Examples of negative experiences include heterosexual assumptions and bias during the medical interview; perceived health care provider discomfort in treating lesbian patients; homophobic comments; repulsion; ignorance; and inferior care such as rudeness, intimidation, a rough physical exam, and hostility toward the lesbian patient, her partner, and/or her children. Many lesbians conceal their sexual orientation out of fear of disapproval, hostility, suboptimal treatment, or breach of confidentiality resulting in losing her job, home, educational opportunities, insurance, or custody of her children.

Our study is the first large study done on physician attitudes since 1982. We found substantially less homophobia among physicians than previously reported. We found that the most homophobic specialties were, in ranked order, general practice, orthopaedics, surgery, and pathology/radiology as a group. The four most homophilic specialties were psychiatry, pediatrics, emergency medicine, and family practice. We found that gender; specialty; urban versus rural practice; and association with lesbian and gay relatives, friends, colleagues, and patients were associated with physician attitudes. Ethnicity was not associated with attitudes toward homosexuality. Physician homophobia was separate from issues of fear of AIDS. Although anti-gay bias among physicians is decreasing, it persists as a threat to the quality of patient care to the lesbian population.

Health Concerns. Lesbians have the same gynecological and non-gynecological health concerns as other women; however, lesbians also have unique health concerns. Although the risk for sexually transmitted diseases is lower for lesbians, those who have or have had sexual encounters with men are at risk for herpes viruses and human papillomavirus, and can transmit these infections to their female sexual partners. Most lesbians with HIV infection acquired it from injecting drug use or from having sexual relations with men. It is assumed that transmission of HIV between lesbians is rare; however, few or no studies document the rate of female-to-female transmission.

Lesbians are less likely to have an annual gynecological exam than other women. They are probably at higher risk for breast cancer, ovarian cancer, and endometrial cancer than other women because they are more likely to be nulliparous. Lesbians who have never had vaginal intercourse with a man have a lower risk for cervical cancer than women who have or have had male sexual partners.

Sexually active lesbians are just as likely as other sexually active women to have traumatic penetration from digital, manual, sex toy, or penile penetration of the vagina or anus or from sadomasochistic activity. They also can have the same sexual dysfunctional problems that other women have.

Lesbian Families. A lesbian's family may consist of her partner, members of her family of origin, children, friends, or any number of diverse combinations. The partners of lesbians may be left out of family events or health care decisions made by lesbians' families of origins.

Having children from a known donor either through insemination or heterosexual intercourse can potentially set up a lesbian mother for custody battles. In addition, many clinics continue to refuse insemination services to lesbians. Having children from any donors not screened for HIV puts the lesbian mother and her offspring at risk for HIV infection. Many states and adoption agencies do not permit known lesbians to adopt children, making it a limited alternative for having children.

Pregnant lesbians may not have support from their families of origin. Role models and support systems are lacking for nonbiological lesbian parents. If the nonbiological lesbian parent is even allowed in the delivery room, she and the biological mother may not be allowed to have the same level of intimacy as heterosexual partners in labor.

Mental Health and Psychosocial Issues. Lesbians do not have any more mental illness than other women, although they do have unique concerns related to their sexual orientation. They risk being rejected by their families of origin, friends, co-workers, and society at large. They risk losing their jobs, their homes, their custody rights of their children because of their sexual orientation. They are at risk for hate crimes, verbal abuse, physical assault, sexual assault, and murder. Coming out can even be stressful enough to lead to depression, self-harmful activities, and/or suicide. No research supports the suggestion that psychosocial development of children with lesbian parents is compromised compared to those who are not raised by lesbian parents.

My recommendations may be considered quite ambitious, but I hope that some, if not all, of them will be put into effect.

- Develop curricula, in conjunction with lesbian health experts and activists, on appropriate and sensitive bedside manner with lesbians, lesbian sexuality, and on health, family, and psychosocial concerns unique to lesbians for medical, nursing, and other health care schools to incorporate into their programs.

- Develop continuing education and re-certification curricula, in conjunction with lesbian health experts and activists, on appropriate and sensitive bedside manner with lesbians, lesbian sexuality and on updates in lesbian health for physicians, nurses, and other health care providers.

- Develop a quarterly newsletter to notify all health care providers of changes and updates in lesbian health.

- Develop a widespread campaign (to include patient literature; newspaper, magazine, radio, and television announcements; and health fairs and lesbian events), in conjunction with lesbian health experts and activists, for lesbians of all ethnicities and languages, ages, and educational and economic backgrounds on what they should expect from health care providers and on their rights as patients.

- Develop a widespread campaign (to include patient literature; newspaper, magazine, radio, and television announcements; and health fairs and lesbian events), in conjunction with lesbian-health experts and activists, for lesbians of all ethnicities and languages, ages, and educational and economic backgrounds on the importance of routine and preventive gynecological and non-gynecological health care, and to dispel myths that lesbians have about their health risks and lack of health risks.

- Develop outreach strategies on how to inform and update all lesbians on health, family, and psychosocial concerns unique to lesbians.
- Develop patient education materials to inform lesbians of all ethnicities and languages, ages, and educational and economic backgrounds on lesbian sexuality, and on health, family, and psychosocial concerns unique to lesbians and not unique to lesbians.
- Develop workshops on how health care providers can encourage lesbians of all ethnicities and languages, ages, and educational and economic backgrounds to access health care.
- Develop Lamaze, childbearing, and child raising classes for lesbians of all ethnicities and languages, ages, and educational and economic backgrounds.
- Develop workshops for domestic violence and sexual assault workers to better serve their lesbian clients.

Patricia King-Urbanski, R.N., M.S.N., C.C.E., L.C.S.

Associates of Women's Health
Obstetric and Neonatal Nurses

The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), has great interest in women's health research. AWHONN is an organization of 22,000 nurses whose primary practice is committed to the care of women across their life span and newborns. Our central purpose is to promote excellence in nursing practice, education and research in women's health, obstetric and neonatal health care, so as to improve the health and health care of women and newborns. Our program of education, research, practice, and advocacy for the health and health care of women and newborns based in the principles of health promotion, health maintenance, and health restoration serve as testimony to this mission and purpose.

We support and conduct research endeavors that strengthen the scientific basis of nursing practice. We believe that research which seeks to improve the health of women across their life span, such as postmenopausal health and reproduction is vital, as is research which seeks to improve the health of childbearing women and their infants.

Today, many women are single heads of households, care for children and extended family members, and hold one or more jobs outside the home. Research in women's health does not provide information about how the health of women in today's society can be optimized. In addition, as has been widely documented, women have been represented inadequately in clinical trials.

Natural menopause is a normal event in the lives of most women when they are about 50 years old. With a life expectancy of 82, women live one-third of their adult lives after menopause. Yet little research has been conducted on natural menopause and on the health problems of postmenopausal women.

Heart diseases are the leading cause of death in women ages 55 and older. Until recently, however, women have been under represented in studies of coronary heart disease. Among women who have cancer, breast cancer is the leading cause of death among women aged 35 to 54. Research studies on breast cancer dealing with epidemiology, early detection, treatment, psychosocial, and behavioral concerns is essential.

Childbirth is a significant experience for any family. Childbirth generally represents a positive experience; however, recent findings have demonstrated that more women die due to childbirth than has been previously reported. Research must be aimed at improving the safety of the childbearing women. In relation to this, four out of ten American girls under the age of 20 get pregnant every year. Prevention of teen pregnancy is another crucial area in need of further research.

Societal issues such as violence against women and substance abuse are areas that need to be explored to determine effective support and treatment for women. For example, little is known about why some women leave their abusers and others do not. Women have been treated for substance abuse similarly to men. However, research has shown that the effect of substance abuse is different in men and women. Comprehensive investigations are needed to develop effective treatment of women who abuse drugs and alcohol.

In view of these facts, AWHONN supports

- research that focuses on health promotion and maintenance, as well as disease prevention, throughout women's life span;
- adequate representation of women in future studies of health problems, such as coronary heart disease;
- research on health problems that primarily affect women, such as breast cancer and osteoporosis; and
- research on diseases with social origins, such as substance abuse, teen pregnancy prevention and violence, as well as diseases of biologic etiology.

Sandra Welner, M.D. *Self*

There are over 27 million women with disabilities and chronic conditions in this country. These women are of all ages, races, and ethnic backgrounds. Disability does not discriminate. As America ages, all of us may confront a time in our lives where we may experience a decline in our independent functioning. Thus, as we chart new courses for improvements in health care delivery for women with disabilities and chronic conditions, these improvements may affect many of us personally at some point in our lives. What are these gaps that I am speaking of? Certainly you might say there are a lot of advances in health care research, health care policy, and all of these changes and improvements most certainly should be improving health care for women with disabilities and chronic conditions by extension. Unfortunately, this does not happen automatically. Although all women have the same chromosomal compliments, their health care needs may be vastly different from each other and from women in the "mainstream society." I would like to turn your attention to key areas that I feel deserve our attention as we chart new courses for improving health care for all women.

We may take it for granted that medical care, if available, can be obtained. Unfortunately, for women with disabilities and chronic conditions accessibility issues may prevent such medical care from being received. Structural barriers may limit access to facilities where medical care is administered although architectural barriers are improving, not all private doctor's offices and some older facilities may not have made the appropriate structural modifications to allow easy entry for a woman with a disability or chronic condition. These women may be wheelchair users, ambulatory with canes or crutches, or suffer from a debilitating disorder that causes excessive fatigue, making stairs and high curbs a daunting obstacle. Other aspects of physical accessibility should not be overlooked. Some medical offices are not large enough to accommodate a woman in a wheelchair. Examination rooms may not be large enough to accommodate a patient in a wheelchair, an exam table and other exam room equipment permitting the patient and any assistant to have adequate space to get the medical care she requires. Bathrooms in order to be truly accessible must consist of more than a small closet-sized room with a toilet and handrail. Guidelines for true accessibility in structural design are available but may not always be followed.

Frequently suitable equipment is also not available. It is somewhat humiliating to have a woman have to go to a loading dock to be weighed if she is in a wheelchair. Platform scales for wheelchairs are available, however, very few centers caring for women have these on site. Examination tables that lower to wheelchair height are available for purchase with special design tailored to the diversified needs of women with chronic conditions and disabilities. However, these tables are often not found in many centers providing health care to women necessitating extra personnel to lift the patient on and off the examination table. This transferring has resulted in patient's being dropped and suffering further injuries. It is also somewhat humiliating for extra people to hold a woman's legs apart while the health care professional is performing a pelvic examination. Unfortunately, equipment that would eliminate these dangerous and unpleasant experiences is frequently not purchased.

It is not surprising that if a woman cannot find accessible transportation to go to her medical appointments, she will not receive medical care. This seems to be such an obvious barrier but in many locations reasonably priced accessible transportation is unavailable. Some forms of insurance cover transportation to medical appointments, and some do not. There are models in isolated areas across the country for low-cost accessible transportation. However, these programs have not been universally implemented in all locations.

Insurance coverage for necessary medical care may be quite limited for many women with disabilities and chronic conditions, many of whom are not in the work force or are single parents, or may have low paying jobs. There is a real disincentive for a woman with a chronic condition to be employed at a job which does not have health benefits but has an earning level that would make her ineligible to receive publicly funded medical support. Even when insurance coverage is available, the specialized types of care required by women with complex medical conditions may not always be covered by the woman's health plan. The specialists and facilities that are expert in her unique condition are often not among the participating facilities at which she is allowed to receive her care. The false economy of having insurance cover sub-optimal care leading to serious secondary and avoidable complications is obvious to women with disabilities and chronic conditions, but seems to be unrecognized by most health plans.

In order to provide appropriate medical care, the guidelines for what appropriate medical care is need to be determined. Because there has been so little attention focused on research into medical care for women with disabilities and chronic conditions, such guidelines and standards are very poorly developed. The gaps are many from basic medical needs to reproductive health care, to issues surrounding the aging process. To complicate these issues different disabilities affect a woman's health in different ways, so generalizations on what would be applicable to all women cannot possibly apply. Each major disability group requires specific research questions to be asked and answered. In order to map out guidelines for appropriate medical treatment and standards of care, this research must be done. Otherwise it would be clearly impossible for necessary treatment to be ascertained as necessary, or alternatives explored. Some basic concepts pertain to health of women with disabilities and chronic conditions are known but are not being taught to health professionals in any comprehensive fashion, either during their training or in medical conferences and publications.

Twenty-seven million women, that is a large number of women. These women are becoming more empowered because of the backing of federal legislation through the American's with Disabilities Act, Human Rights Acts, and other legislation. These are positive steps. However, these advances do not eliminate the gaps in medical care and medical knowledge that restrict women from receiving appropriate and adequate comprehensive care. In these women, more than in other populations, psychosocial factors may have a significant influence on compounding existing limitations. These limitations could also be improved or eliminated with the acknowledgment of the importance of assistive services to maximize independent functioning and productivity. This goal is a fairly universal one and most women would prefer to be contributing members of society but may need some assistance in doing so. If there is no medical coverage for such assistance, lack of knowledge on appropriate medical treatment, lack of awareness among medical professionals, and economic barriers for self determination women with chronic medical conditions, although desiring to continue to be healthy and productive, may be prevented from doing so.

Joanne M. Williams, R.N.C., C.N.P. *OB/GYN Certified Nurse Practitioner*

Lack of Knowledge Regarding Hormone Levels and Effects on Aging and Disease

It is a known fact that as we age our hormone levels drop, the aging process accelerates and degenerative diseases become more prevalent; i.e., decrease in mental function, decrease in muscle mass, coronary vascular disease, cancer (breast), osteoporosis, diabetes, etc. There is a lack of long term studies regarding the relationship between these processes and all natural hormones, specifically the "super hormones," i.e., DHEA, natural estrogens (estradiol, estrone, estriol), human growth hormone, melatonin, natural progesterone, pregnenolone, testosterone and thyroid hormone. Because most studies are funded by pharmaceutical companies, they are conducted using synthetic hormones. This is an opportunity for NIH to support research that includes natural hormones.

More and more women are wanting natural solutions that produce improved quality of life as they age. Additionally, they are interested in the whole body (holistic) approach, which for many includes natural hormones. It is imperative that we develop a better understanding of these natural hormones and how they impact women's health over their life span.

Caroline J. Yu, M.P.A. *National Asian Women's Health Organization*

I wish to inform you about the most recent efforts of the National Asian Women's Health Organization (NAWHO) to expand the public knowledge about the reproductive and sexual health of Asian American women. NAWHO is the only national agency of its kind that is solely dedicated to improving the health status of Asian women and girls. NAWHO's mission is to empower Asian women and girls through a framework that reflects commonalties and differences within Asian American communities, and ensure equal and adequate access to health care and life advancement opportunities.

In the area of research, NAWHO's goal is to close the major gaps in baseline health information, including gender and ethnic specific documentation, and address the need for reliable and timely data for policies and programs on Asian American women's health. In particular, NAWHO has focused on reproductive and sexual health needs and concerns. NAWHO has found that overall Asian women's sense of risk regarding reproductive and sexual health is downplayed. Many Asian women only seek medical attention when the pain or symptoms of infection became unbearable or interfered with daily functioning.

To further examine these issues, NAWHO conducted a survey of 674 Asian American women in California, a study that has been documented in NAWHO's 1997 publication, *Expanding Options*. The survey sought to analyze the knowledge of, attitudes towards, and use of reproductive health technologies by Asian American women between the ages of 18 and 35 in six California counties with significant Asian populations.

The survey indicates clearly that Asian American women are sexually active and thus face a number of decisions regarding their sexual and reproductive behavior. In brief, the survey found that nearly half of the women surveyed (49.8 percent) had not visited a health care provider within the last year for reproductive or sexual health needs, compared to 3 percent of women in a nationwide Kaiser Family Foundation study. In addition, one fourth of these women have never received reproductive health care in their entire lives. Also, Asian American women are not adequately protecting themselves against pregnancy and sexually transmitted diseases, with 61 percent stating that they did not always use contraceptive methods.

Based on the survey results, NAWHO makes several recommendations to health educators and providers, women's health advocates and activists, and policy makers in the areas of information, services, research, and policy, including the need to make no assumptions about Asian American woman's knowledge and understanding of contraceptive methods or reproductive health in general. These recommendations are detailed in *Expanding Options*, which may be obtained by calling the NAWHO office at (415) 989-9747.

Diana Zuckerman, Ph.D.

National Women's Health Network
Institute for Women's Policy Research

The National Women's Health Network focuses on the need for women to make informed decisions about their health care. We are concerned about a wide array of health issues, but, reflecting the interests of women across the country, breast cancer has been a particular concern. We believe that NIH would do a great public service by focusing greater attention on the unnecessary use of mastectomies in situations where the woman has no evidence of breast cancer, has no evidence of invasive breast cancer, or has a breast cancer that most experts believe does not require a mastectomy.

The history of breast cancer treatment in this country is a history with surgery as its central focus. Thousands of women were subjected to radical mastectomies before it was determined that less radical breast removal was as effective in saving women's lives, and even then, the practice of medicine changed slowly. Mastectomies were also recommended for thousands of women with "fibrocystic breast disease" before research indicated that this was unnecessary. Similarly, when NIH-funded research and an NIH consensus conference indicated that lumpectomies were as effective with Stage I and Stage II breast cancers as mastectomies in saving women's lives, there was still a lag before medical practice reflected those findings. In some parts of the country, it appears that women are still being encouraged to undergo mastectomies in situations where virtually all experts would argue that they are unnecessary. NIH has played an important role in informing doctors and the public about appropriate medical treatment for cancer, and we believe that it is time for NIH to become more actively involved in some of the newer controversies regarding mastectomies.

Breast-conserving Surgeries. Several studies have shown that in certain parts of the country and at more sophisticated medical facilities, women with Stage I or Stage II breast cancer are more likely to undergo breast-conserving surgeries rather than mastectomies. These regional variations were first noted in research published in the early 1990s. Although the rates of mastectomy as a percentage of breast surgeries has decreased in all regions of the country since then, the regional differences have been maintained. There are several possible explanations for these differences: the advice given by physicians, the attitudes of patients, and such practical factors as the difficulty of traveling long distances for repeated radiation treatment in some parts of the country. Despite the NIH consensus conference in 1990, there is clear evidence that many patients are not receiving the information they need to make the choices that are best for them.

Breast Cancer Genes and Preventive Mastectomy. Perhaps the most controversial issue is the use of mastectomy to prevent breast cancer in women whose family history of breast cancer has convinced them that mastectomy is the best strategy to save their lives. Certainly, women have the right to make this choice, but we are concerned that the choice is being made on the basis of very preliminary estimates of the likelihood of breast cancer associated with the breast cancer genes (BRCA1 and BRCA2); these estimates could prove to be quite inaccurate. We turn to NIH to do more to inform physicians and potential patients about these issues, such as holding a consensus conference, and supporting desperately needed research and public education efforts.

Ductal Carcinoma in Situ of the Breast. The diagnosis of ductal carcinoma in situ (DCIS) has been increasing in recent years, but the diagnosis remains poorly understood. Many women report that their doctors advised them to have a mastectomy "to be safe" even though there was no sign that the cancer would spread. Other physicians tell their patients that DCIS is a precancerous condition or a very early form of cancer which can best be treated with a lumpectomy, with or without radiation treatment. Differences in suggested treatment choices may be based on differences in diagnostic findings, but it appears that differences in physicians' attitudes and knowledge also greatly influence the advice a patient is given. We believe that NIH can do more to study the extent to which mastectomies may be unnecessarily performed for DCIS, and to inform the public and the medical community about the options that are most appropriate under various circumstances.

Lobular Carcinoma in Situ of the Breast. The diagnosis of lobular carcinoma in situ (LCIS) of the breast is less common, but the suggested treatment also varies from "watchful waiting" to double mastectomies. Since LCIS is not a strong predictor of invasive breast cancer, we strongly believe that women should be fully informed before making a irreversible decision to have a mastectomy. Again, we turn to NIH to do more to support research and inform the medical community and the public through a consensus conference or other means.

In conclusion, we are concerned that women patients who are at risk for breast cancer, have been diagnosed with DCIS or LCIS, or Stage I or Stage II breast cancer do not always receive the most accurate, up-to-date information about their treatment options. Although NIH's major focus is on basic research, NIH has played an important role in improving medical treatment through a wide range of research projects, and through various public education strategies. These efforts are essential in helping to make more accurate, understandable information available to patients and consumers.

SUMMARIES OF
PUBLIC TESTIMONY
BETHESDA, MARYLAND
NOVEMBER 17, 1997

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National Athletic Trainers Association

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Reproductive Health Technologies Project

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Marjorie J. Albohm, M.S., A.T.C. *National Athletic Trainers Association*

Physically active females are a rapidly expanding population. The positive benefits of physical activity are well documented. These benefits have been, and continue to be, realized by large numbers of females of all ages, throughout their life span.

Physical activity, by its inherent nature, increases exposure to injury. Injury can be a limiting factor in relation to exercise compliance and a major source of health care dollar expenditures.

To prevent activity-related injuries, minimize their effect, and ensure a safe participation environment for physically active females, a nationwide injury surveillance system designed to document, track, and monitor the injury/illness patterns of this population, must be established immediately. Only when injury/illness patterns are identified can appropriate preventative interventions be developed and implemented.

Injury documentation and the subsequent adoption of preventative intervention strategies will encourage females to participate in physical activities, ensuring a safer environment, and potentially reducing the need for the utilization of health care services.

Amy Allina *Reproductive Health Technologies Project*

Microbicide Research

My testimony focuses on the critically important task of making microbicide research an integral part of the women's health research agenda. Little attention has been given until recently to the need for prevention products women can use to protect themselves against AIDS and other sexually transmitted diseases (STDs), if necessary without their partners' knowledge or consent.

Seventeen years into the AIDS crisis and at a time when the incidence of STDs is reaching epidemic proportions, the single public health message to women about prevention of STDs is, "Use condoms." For many women, this advice is inadequate or unrealistic at best. At worst, it is life-threatening. It is only within the last few years that the need for woman-controlled prevention products has begun to receive the serious attention it deserves. Scientists are now conducting research on a variety of substances which kill or inactivate the bacteria and viruses that cause STDs. Such products known as microbicides would allow a woman to protect herself against disease without being forced to negotiate with her partner, as she must to ensure condom use.

There are a number of reasons why the need for microbicides is only now beginning to be recognized. First of all, microbicide development is not an appealing investment for pharmaceutical companies. Another barrier to microbicide development is that sexually transmitted diseases have only recently been recognized as a widespread problem affecting large numbers of women, and AIDS has not been considered a woman's problem.

Researchers working on the development of new products are pursuing some encouraging leads, and it is absolutely critical that resources be made available so that they can continue their efforts to develop microbicidal products. While the Reproductive Health Technologies Project commends NIH for its support of some such research, the resources available for microbicide development are still desperately inadequate. Federal funding is limited, few foundations fund in this area, few pharmaceutical companies have demonstrated an interest, and the small companies that are currently conducting research may lack the capital to market a new product successfully. Because large pharmaceutical companies have expressed little interest in pursuing microbicide research, public sector collaboration is essential both for developing new product leads and for supporting the increasing numbers of small biotech companies that are entering the field of microbicide research.

As microbicide advocates, we will continue to expand advocacy and public education efforts to build support for the research that is going on and to demonstrate the potential market for these products in hopes of increasing the investment in research aimed at developing microbicides. We believe that this research should be a priority of women's health research because it has the potential to save and improve millions of women's lives. Microbicidal products will give women all over the world one more tool to protect themselves against the ravage of sexually transmitted diseases, including HIV/AIDS.

Chief Nursing Officer
Cedars-Sinai Health System and Research Institute
Linda Burnes Bolton, Dr. P.H., R.N., F.A.A.N.
National Black Nurses Association, Inc.

The National Black Nurses Association, Inc., advocates increased research funding on issues disproportionately affecting black women and other women of color including premature labor and its sequelae of premature birth; low-birthweight infants and infant mortality; cardiovascular disease including stroke; breast and cervical cancer; physical and psychological trauma resulting from crime, battery, and other acts of violence; diabetes and kidney disease; osteoporosis and other debilitative disorders; systematic lupus and arthritis; infertility; infectious diseases including tuberculosis, AIDS/HIV; clinical depression and other mental health disorders; barriers to preventive health care utilization and practices; and the impact of poverty, lack of access to education, and economic viability on women's health and well being.

Education and Career Issues. The Association urges NIH to provide funding to increase the number of black health professional research scientists in all fields. The number of black nurses with earned doctorates represents less than 1 percent of all professional nurses in the United States.

Obstetrical Care. Delayed entry into prenatal care continues to be a major predictor of low birth weight and poor perinatal outcome. Research on stress and social support as mediating factors affecting prenatal care utilization behavior has been funded by NIH. We require additional funding to test interventions among diverse populations which would improve prenatal care utilization; and decrease the adverse effects of stress. Research on reduction of stress and the provision of community based social support services has been limited. NIH has funded research to identify biochemical markers of stress in pregnancy (Hobel, NICHD 1994). Preliminary data indicates a correlation between behavior in pregnancy and birth outcome. Funding is required to test interventions during pregnancy which will decrease the incidence of poor perinatal outcome. This research has a potential significant cost savings.

Research Across the Life Span. NIH should maintain the Office of Research on Women's Health as a center for sponsoring a comprehensive research enterprise. Additional funding should be allocated to support research initiatives on a comprehensive matrix of research across the life span of women including: prenatal and perinatal, childhood and preconceptual, puberty, reproductive adults, climacteric and menopausal, and postmenopausal stages.

Research Agenda Topics. Research funding to promote the women's health must include basic science research, epidemiological and health outcomes research, human studies and clinical trials, nutritional and non-nutritional dietary research, behavioral research (historical and ecological research of the effects of this factor on the risk of disease occurrence), organ systems and disease pathophysiology, lifestyle and health beliefs research including social isolation, disability, chronic disease management using self care and alternative care intervention.

In summary, the National Black Nurses Association, Inc., urges NIH to increase its funding for women's health research on issues affecting women's health across the life span. These include: coronary heart disease and vascular disease, diabetes, urologic, kidney and connective tissue diseases, breast, cervical and ovarian cancer, osteoporosis, functional disability, preterm labor and its sequelae, physical, psychological and emotional abuse, alcohol and substance abuse, infectious diseases, obesity and eating disorders, depression and mental disorders, poverty, violence, and crime and their effects on human potentiation.

Establish an effective recruitment and retention strategy to increase the number of women from diverse cultures included in NIH-sponsored clinical research trials; increase community access to NIH-sponsored clinical treatment centers; encourage partnerships between professional societies, community agencies, and NIH principal investigators to assure inclusion of culturally diverse human subjects; increase funding for NIH training grants for master, doctorate and post doctoral research scientists, provide funding for ORWH technical assistance workshops to be held at national conferences; and develop a public-private partnership to fund an integrated, comprehensive research agenda which addresses the breadth of social, environmental, physical, pathological, psychological, and behavioral issues which impact the health of women.

Lori A. Boyajian, D.O.

University of Health Sciences
College of Osteopathic Medicine

The University of Health Sciences College of Osteopathic Medicine supports the advancement of women's health through research. This includes, but is not limited to research into all aspects of women in biomedical careers, medical school curricula, establishment of postdoctoral training in women's health and the continuing medical education of professionals about women's health. We recognize the difficulties establishing norms for education and research but we also understand that we can help establish changes that will affect the health of women for generations.

We believe that some basic concerns be addressed in order for effective changes to be implemented. These are all interrelated and interdependent. The main points of the testimony are:

1. The development of medical school curricula to address women's health.
2. The encouragement of women to enter academic medicine.
3. The establishment of postgraduate training programs in the form of residencies and fellowships.
4. The continued education of practicing clinicians about women's health.
5. The establishment of departments of women's health in all medical schools.
6. The establishment of a speaker's bureau to disseminate information to schools and professional societies and associations about women's health.

Joel O. Brende, M.D.

Departments of Psychiatry and Internal Medicine
Mercer University School of Medicine

Psychological Trauma in Women Seeking Help for Emotional and Medical Problems

The literature as well as my personal experience points to the fact that many patients, particularly medical patients who have moderate levels of anxiety and depression, suffer from unresolved traumatic experiences. These problems remain undetected and untreated, in part because physicians tend not to ask their patients questions pertaining to prior stressors, violent traumatic experiences, or related posttraumatic symptoms.

Recognizing the need to integrate psychosocial and medical diagnosis and treatment, the Departments of Internal Medicine and Psychiatry at Mercer University School of Medicine have initiated a training program for internal medicine residents to improve their interviewing and listening skills. They are being taught that it is important to learn how to ask the right questions empathically, listen with sensitivity, and assess their patients' histories of trauma and stress so that appropriate treatment and/or referral may be forthcoming. We have now added a Behavioral Medicine Clinic wherein medical patients with depression, anxiety, and chronic pain are being evaluated more thoroughly by residents who are also learning the use of a trauma assessment. The results have been very positive and patients appear to be responding with more rapid recoveries in some cases, reduced need for pain medication in other cases, and less frequent medical visits in many. As a result of this success, a collaborative research project is planned in order to evaluate this diagnostic and treatment process more thoroughly.

We are hoping that this new program and proposed research will provide information that will help to improve training programs for medical personnel and also provide data about the effectiveness of improved diagnosis and treatment of medical patients with emotional problems.

Evelyn J. Bromet, Ph.D. *Sjögren's Syndrome Foundation Inc.*

Sjögren's syndrome has been described as the most prevalent of the autoimmune disorders, afflicting 2 to 4 million patients, primarily women. Yet, most scientists and lay people have never heard of Sjögren's syndrome, and physicians often misdiagnose it even when the symptoms, clinical history, and laboratory tests point to this disorder. This presentation, on behalf of the Sjögren's Syndrome Foundation, suggests that we redress the general ignorance about the etiology, clinical detection, and treatment of this disorder with the Sjögren's Medical Awareness Research and Treatment Program, or S/MART program. The "S" stands for Sjögren's syndrome, a chronic, potentially debilitating, progressive, incurable disorder with characteristic features of severe dry eyes and dry mouth, along with extreme fatigue, frequent low-grade fever, joint and muscle pain, irritable bowel, sleep problems, and weakness. It can occur alone (noted as primary Sjögren's syndrome) or comorbidly with other autoimmune diseases (or secondary Sjögren's syndrome). In the worst case scenario, it can lead to lymphoid malignancy. The "M" and "A" stand for medical awareness. Although no formal studies have documented the extent of the underdetection by primary care physicians, anecdotal evidence combined with an average 5 to 10 year period of help-seeking before obtaining a diagnosis suggest that the medical community is very poor at detecting Sjögren's syndrome. Changes in the medical and dental school curricula, inclusion of chapters on Sjögren's syndrome in new books on women's health, and educational programs at local and national conferences for dentists and physicians emphasizing the symptoms and medical management of this disease should be implemented. The "R" stands for research: basic, clinical, epidemiologic, and behavioral. Sjögren's syndrome has been as underresearched by biomedical researchers as it has been underdetected by medical professionals in part because it cuts across a number of NIH institutes, and thereby falls between the cracks. The paucity of epidemiologic research is particularly egregious. Disagreement on diagnostic criteria has been one excuse for the lack of clinical research. In reality, the different criteria sets overlap considerably, and biological markers exist for this disease. Thus, the research aim of the S/MART program has as its fundamental goal the promotion of active, interdisciplinary basic and clinical research aimed at understanding the etiology and course of this disease. The last letter, "T," stands for both treatment and team, because Sjögren's syndrome requires a team approach to treatment. We need both interdisciplinary and innovative treatments for the symptoms we endure, and most of all, we desire a cure. Currently, we can only treat symptoms as they arise because there is no treatment for the disease. We need to bring attention to the treatment of this disease through NIH-sponsored conferences, requests for grant applications, adding experts on Sjögren's syndrome to study sections, and working with pharmaceutical companies. Thus, we emphatically urge NIH to be the leader in the development of the S/MART program.

Director, Division of Gynecologic Oncology
University of Maryland Medical School
The Society of Gynecologic Oncologists

Sandra E. Brooks, M.D.

The Society of Gynecologic Oncologists (SGO) is the only national medical specialty devoted to the study and treatment of women with reproductive organ cancers. There are three main gynecologic cancers: (1) cervical, (2) uterine, and (3) ovarian. The incidence of each of these cancers and the women developing these diseases are different, reflecting the unique biologic characteristics of these diseases.

Both the incidence and mortality for invasive cervical cancer have declined steadily in this country over the last three decades. Although only 14,500 women will develop cervical cancer in 1997, a third of them will die from this preventable disease. African-American women continue to experience an incidence rate that is nearly two times higher than the incidence rate for white women, and African-American women have a 56 percent 5-year survival rate as compared with a 70 percent survival rate for white women.

Cancer of the uterine corpus or endometrium is the fourth most common cancer among U.S. women and is the most common invasive gynecologic cancer. An estimated 34,900 women will be diagnosed with uterine cancer in 1997. Fortunately, this cancer causes a limited number of deaths, as evidenced by a 5-year survival rate of 83 percent.

In 1997, the American Cancer Society estimates 26,800 new cases of ovarian cancer will be diagnosed in this country and 14,100 women will die from ovarian cancer this year. A relative survival rate of 90 percent can be achieved if ovarian cancer is diagnosed early, but unfortunately, 70 percent of women with ovarian cancer are not detected until the cancer has reached an advanced stage, which has an 80 percent fatality rate. The risk of a woman developing ovarian cancer is three to five times greater if her mother or her sisters had or have ovarian cancer. Women who have been diagnosed with breast cancer are 70 percent more likely to develop ovarian cancer than the general population.

Given these statistics, the SGO would like to share with the Office of Research on Women's Health some areas that need attention and hold great scientific promise if appropriate funding and research efforts are directed towards these issues.

The SGO urges ORWH to work with Dr. Klausner to ensure the creation of a Division of Gynecologic Oncology within the surgery branch of the intramural program at NCI. At a minimum, this division should include three independent labs, where the primary investigators are fully trained gynecologic oncologists.

The SGO is advocating that additional federal resources be directed towards increasing clinical trials for ovarian cancer prevention and detection.

The SGO asks ORWH to take a greater role in encouraging research directed at cancers of the reproductive system. One way to do this is to have ORWH dedicate a small portion of their budget, to partner with NCI to administer a young investigator program in gynecologic oncology research.

Ross C. Brownson, Ph.D.
Prevention Research Center
St. Louis University School of Public Health

Increasing Physical Activity Among Minority Women in the United States

Decades of research indicate that physical activity is an important health promoting and disease preventing behavior. Physical activity has been shown to lower risks of heart disease, hypertension, diabetes mellitus, some types of cancer, and osteoporosis.

One population that appears to be particularly vulnerable to hypokinetic-based risks is minority women. Limited information available indicates that minority women are less likely to be involved in physical activity than their white counterparts. In order to increase the prevalence of physical activity in this population, several research areas need urgent attention.

1. *Assessments:* Most of the assessments used to measure physical activity were developed and tested on white men. Extrapolating male test results to their female counterparts may result in serious limitations in data analysis. Research is needed to develop appropriate assessment tools and implementation plans.
2. *Identifying Barriers and Determinants:* Women, particularly minority women, have very different life situations than men. Research is needed to identify specific barriers and determinants of physical activity if interventions with this population are to be successful.
3. *Community Interventions:* Community interventions addressing the specific needs of women are necessary. Policy changes that promote physical activity in communities may also help increase the prevalence of physical activity in women.

There is a shortage of well-known strategies for increasing physical activity in minority women. Development and implementation of these strategies will greatly benefit the health of our nation.

Alan P. Brownstein
President and Chief Executive Officer
American Liver Foundation

Women's Health and Liver Disease

The American Liver Foundation (ALF) is a national voluntary health organization dedicated to the prevention, treatment and cure for all liver diseases through research and education. Certain liver diseases have a disproportionate impact on women. The most significant diseases in terms of mortality and morbidity are primary biliary cirrhosis (PBC), autoimmune hepatitis, and hepatitis B.

Primary biliary cirrhosis (PBC) is a chronic liver disease that causes slow, progressive destruction of bile ducts in the liver. Women are affected ten times more frequently than men. It is estimated that as many as 100,000 women are living with PBC, most of whom are undiagnosed. This disease advances slowly, is chronic and often leads to life-threatening complications. Once cirrhosis develops the only viable treatment is liver transplantation.

Autoimmune hepatitis is a progressive inflammation of the liver. It was first described in 1950 as a disease of young women, associated with increased gamma globulin in the blood and chronic hepatitis on liver biopsy. Seventy percent of all cases of autoimmune hepatitis are women. This disease is chronic and usually increases in severity over time resulting in possible liver failure. Liver transplantation is the only treatment of choice at the later stages of the illness.

Hepatitis B is a virus that causes the liver to become inflamed. It is estimated that 125,000 people contract this serious disease each year. Hepatitis B is responsible for 5,000 deaths annually, including approximately 1,500 from primary liver cancer and between 350 and 450 from fulminant hepatitis. Both men and women are at risk for contracting hepatitis B, however, women have the added risk of passing the virus on to their newborn children. It is estimated that 22,000 pregnant women in the USA each year are infected with the hepatitis B virus, an increase from the estimated 17,000 in 1991. Up to 90 percent of neonates of women who are carriers of hepatitis B become infected with the virus. Of the infants who develop chronic hepatitis B, one out of 12 will die prematurely of cirrhosis or liver cancer before they are 40 years old.

The Future for Women's Liver Diseases

The ALF is dedicated to preventing, treating, and curing liver diseases through research and education.

The significant liver diseases that disproportionately affect women are problematical in that they are difficult to diagnose, often go untreated for long periods of time because there are no signs of illness and result in life threatening outcomes. For a majority of the women infected with any of these liver diseases the prognosis is poor. They look forward to debilitating symptoms as the diseases progress, resulting in liver transplantation or death.

The ALF recommends that a research strategy be developed that includes basic science and clinical trials so that we may gain a better understanding of PBC and autoimmune hepatitis. This includes:

- Research in the areas of drug trials, involving a large number of patients around the world, exploring the potential use of several medications to lessen the symptoms produced by these diseases and the control of liver damage.

- Research into the causes and treatment for liver diseases affecting women.

The ALF recommends education be conducted with both the public and professionals, education to improve women's awareness of the physiological functioning of the liver and the role it plays in many of the functions of the body. This is of particular importance for women of childbearing age who may have been exposed to hepatitis B virus, because a highly effective treatment is available for newborns.

- Educate women as to the risks they face as women when their livers are threatened with any one of these diseases. Through increased awareness women may be able to help advise their primary physicians as to signs and symptoms that could lead to earlier diagnoses and possibly preventative treatments to forestall the complications of sever liver damage and mortality.
- Educate primary care physicians about the signs of these diseases so as to lead to earlier diagnosis and improved outcomes for women.

The ALF recommends that more research into the causes and treatment of these diseases be conducted. Further, more education into the prevention of liver disease and awareness of the signs and symptoms be done with the general public and in the professional medical community. These diseases produce debilitating symptoms and the outcome is usually death or liver transplantation. Hopefully, more can be done to alleviate the suffering endured by women affected by these diseases.

Jacquelyn Campbell, Ph.D., R.N., F.A.A.N. *The Johns Hopkins University School of Nursing*

The Effects of Intimate Partner Battering on Women's Physical and Mental Health

Battering is defined here as repeated physical and/or sexual assault by an intimate partner within a context of coercive control. The emotional abuse that is almost always part of the coercive control also has serious psychological consequences according to women themselves, but the actual effects on women's health have seldom been measured separately. In the most recent national population-based *prevalence* study of battering, 8 percent of women said they were currently being physically abused.

The forced sex aspect of battering is directly associated with significant health problems with approximately 40 to 45 percent of all battered women forced into sex by their male partners. Relationship sexual abuse probably results in the increased pelvic inflammatory disease, heightened risk of sexually transmitted diseases, including HIV/AIDS, vaginal and anal tearing, bladder infections, sexual dysfunction, pelvic pain, urinary tract infections, unexplained bleeding, unintended pregnancy, and other genital-urinary-related health problems documented for battered women in several population-based, shelter, and health care setting studies.

Pregnancy can be a direct result of forced relationship sex, and abuse during pregnancy a continuation of the general battering. Health-related correlates of abuse during pregnancy included substance abuse, smoking, less than optimal weight gain and eating an unhealthy diet. In terms of pregnancy outcomes, at least three studies have documented an association of low birthweight (LBW) with abuse during pregnancy, even controlling for other risk factors, although other studies do not show the same association.

Other physical health problems and health care seeking of physically battered nonpregnant women are also well documented. In two population-based national surveys, women physically abused by a spouse or live-in partner were significantly more likely than other women to define their health as fair or poor. Abused women were also more likely to say they had needed medical care but did not get it, and severely battered women had almost twice the number of days in bed due to illness than other women. In the Bowker survey of self-identified battered women who had successfully ended the violence, the majority of women had sought help from medical professionals, a higher proportion than from other sources of help.

Injury is the most obvious health effect of battering. Other symptoms and conditions shown in controlled investigations to be associated with physical violence from intimate partners may be stress, including chronic irritable bowel syndrome, digestive problems, eating disorders, and other stress-related physical symptoms. Other physical conditions such as hypertension may also be related to abuse. Although suppression of the immune system from chronic stress has been investigated in other populations, the role of stress in the etiology of the frequent communicable diseases of battered women and their children has not been investigated.

Mental health sequalae to abuse are significant and prompt women to seek health care services as frequently as for physical health problems. In controlled studies from a variety of settings, battered women are consistently found to have more depressive symptoms and significantly higher diagnoses of major depression than other women. Higher rates of post traumatic stress disorder (PTSD) have also been documented in battered women in shelters than in other women. The prevalence of PTSD in battered women in the general population is also higher than for nonabused women. Battered women would generally not complain of PTSO per se to a health care provider, but rather of sleep disorders or stress. Thus, there is substantial probability of misdiagnosis or lack of diagnosis of PTSD by mental health providers.

Substance abuse is frequently seen as part of a trauma response and abuse of both alcohol and illicit drugs has been found as a substantiated correlate of abuse during pregnancy. Clearly substance abuse treatment programs for women need to address domestic violence, as are shelter programs becoming more inclusive of substance abusing battered women in their interventions.

Clearly, intimate partner violence is a significant health problem that interfaces with many of the other most important women's health problems. Funding for violence against women research is currently concentrated within CDC and NIH, but neither of those agencies investigate systematically the interface of intimate partner abuse and other major women's health problems. Therefore, the institutes of NIH need to have this area of investigation considered as a significant issue for research.

Molly S. Chatterjee, M.D. *Meharry Medical College*

American Women of East Indian Origin in Academic Medicine

American society has become diverse. Academic medicine has faced the challenge of this diverse society. The purpose of this testimony is to voice the concern of American women, particularly of East Indian origin. Under-representation of this ethnic group is reflected in the advisory panels of ORWH, NIH, AAMC, and the nation's 125 medical schools. These women are discriminated against and harassed in academic medicine. The process is usually adopted by male middle managers who are unfair, egoistic, unprofessional, and self-centered. Harassment is encountered by these women from secretarial and administrative staff with support of these middle managers. The legal field does not encourage these women to fight legal battles. They are advised that discrimination and harassment are hard to prove. As such, the "chairs" of these departments have taken a ploy for "genocide." Statistics clearly show the unequal distribution of women in hierarchy in general. This is glaring when it comes to women of East Indian origin. A list of multiple problems involving these women have been collected and analysis shows that history is being repeated throughout the nation. The solutions put together by different role models and organizations are to be applauded; their implementation remains problematic.

In conclusion, as academic medicine moves to the next millennium, the only choice this country has is to make the leadership diverse. This can only be achieved by recognition, reward, and ethical, professional, and fair treatment of all under-represented minority women faculty. Time has come to understand the need to include American women of East Indian origin in leadership positions of academic medicine. I hope this public testimony will challenge the stereotype and improve the environment in academic medicine for years to come.

Bente E. Cooney, M.S.W. *National Osteoporosis Foundation*

I am Director of Public Policy at the National Osteoporosis Foundation (NOF), the only national nonprofit health organization devoted to reducing the incidence of osteoporosis. New studies estimate that (1) medical expenditures for the treatment of osteoporotic fractures is $13.8 billion, which is considerably higher than the previous estimate of $10 billion; and (2) that 23 million women over the age of 50 either have osteoporosis or are at risk of developing the disease due to low bone mass. This report includes all U.S. women, whereas earlier reports were limited to white postmenopausal women. Another report further estimates that by the year 2015, the number of women affected will increase to 35 million — largely due to the aging of the population. We must join forces to prevent this frightening statistic from becoming a reality.

NOF asked the Research Committee of our Scientific Advisory Board to identify key areas for osteoporosis research. The committee has not yet finalized its report, but the initial results of the committee's work is outlined in the full testimony.

Human Research. The first priority is an overarching recommendation to increase clinical research. We have major gaps in patient-oriented research. We are not making the necessary translation from basic research to benefits available to patients. Figuring out the mechanisms of disease is very important, but once we solve the puzzle, we tend to move on to new challenges. The solution is rarely transmitted to help the patient. This is partly because of lack of support for this type of work, and partly because it is difficult to do. For example, there is concern that human gene research, which mistakenly has been labeled as "clinical research," may produce answers to questions, but not solutions to real patient problems. Finding the gene responsible for a disease is simply not enough.

Basic Research. The number one priority should be to investigate the biology of bone adaptation to mechanical loading. The most important research in this area is on the set point mechanism which senses loading and responds appropriately to control the skeletal adaptive response.

In summary, the full testimony presents a partial listing of gaps in our knowledge about osteoporosis. Because osteoporosis is such a young disease in terms of research focus and public attention, the research needs are great on multiple fronts. Sufficient methods for prevention, diagnosis, and treatment of osteoporosis still have not been identified. A comprehensive national strategy to address osteoporosis including a coordinated program of basic, clinical, psychosocial, behavioral, and epidemiologic research is urgently needed before the baby boom generation reaches the age of osteoporotic fractures. If we fail to do so, this disease will not only bankrupt our health care system, but the lives of millions of women and men.

Zara Cooper, B.S.
Student
Mount Sinai School of Medicine

Prenatal genetic testing is becoming an increasingly routine part of prenatal care. This trend is largely due to greater numbers of women having children after age 35, and rapid technological advances that have made testing more widely available. Additionally, current initiatives by a number of government agencies will continue to accelerate the general use of such testing. However, because of the inextricable link to reproductive choice and abortion, prenatal genetic testing has not received the same amount of attention that other areas of genetic testing have from politicians and policy makers. Consequently, our basic understanding of the complexities of prenatal genetic testing and counseling is full of gaps. The purpose of my testimony is to describe some of the key issues in prenatal genetic testing, highlight areas deserving further exploration, and make a place for this issue on the Women's Health Research Agenda for the 21st Century.

Brenda Crabbs *Arthritis Foundation*

Arthritis is the most prevalent chronic condition affecting women. Currently 23 million women have arthritis and the number is expected to grow to 36 million by the year 2020. The cost of arthritis to our nation in lost wages, disability payments, hospitalizations, physician visits, and medications is close to $65 billion annually which represents over 1 percent of our Gross National Product.

Arthritis is a serious disabling condition which discriminates against women in overall prevalence. Women with rheumatoid arthritis outnumber men 2 to 1. In the case of systemic lupus erythematosus and fibromyalgia, nine women have the disease compared to one male. Given its enormous impact on women and its projected rate of growth in the future, arthritis must have a prominent place in the women's health agenda of the 21st century.

The economic, social, and psychological impact of arthritis on women is staggering. Arthritis is the leading cause of disability and the second leading cause of disability payments. Studies indicate that approximately half of patients working when diagnosed with rheumatoid arthritis become disabled within 10 years, suffering substantial earnings loss. Arthritis is the condition reported by women as the leading cause of physical limitations in activities of daily living. The impact of arthritis on psychological status has been noted in terms of depression, coping strategies, anxiety, cognitive changes, self-efficacy, and learned helplessness.

Several research advances within the last 10 years stand out for arthritis patients. The use of methotrexate as a safe and effective long-term treatment for rheumatoid arthritis has successfully controlled symptoms and reduced the need for steroids in adults and children. Advances in genetic research, Lyme disease recognition and treatment, and joint replacement technology are considered among the most important in improving the lives of arthritis patients.

Perhaps the most significant gap for women in arthritis research is the role of genetic makeup and hormones. Most researchers believe that the triggers for arthritis are in a woman's physiologic makeup. Could a woman's body structure designed to bear children be a contributing factor to the cause of osteoarthritis? Even more significantly, are hormones responsible for the autoimmune forms of arthritis such as lupus and rheumatoid arthritis that so predominately attack women? Is there a single arthritis gene or are a combination of genes involved? Finding the answers to these questions will provide critical clues to finding a cure for arthritis.

Of critical importance to the Arthritis Foundation is the use of comprehensive measurements to evaluate research outcomes in the lives of women. 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. These outcomes must be realistic and relevant to women's lives. They must be developed to apply for a period of decades rather than months and they must place value in slowing the rate of decline in functional levels rather than maintaining functional status. It is imperative that good outcome measures in women's health research in the 21st century are quantifiable, include the patient and consider health status in terms of a woman's ability to function within roles of critical importance to her over the extended term of her life.

Frances Cuomo, M.D.

Chief, Shoulder Service
Hospital for Joint Diseases
American Shoulder and Elbow Surgeons

American shoulder and elbow surgeons are confronted with a vast and varied number of pathologies relating to the shoulder that are quite specific to females. These disorders are responsible for significant economic loss, medical cost, and emotional and physical burden that profoundly affect not only women but the population as a whole. The three most common disorders related to the shoulder which primarily affect females include osteoporosis-related proximal humerus fractures, frozen shoulder syndrome, and instability of the glenohumeral joint in teenage females.

Proximal humerus fractures comprise approximately 5 to 7 percent of all fractures reported. The rise in fracture incidence with age and the higher incidence among females are characteristic epidemiologic features of fractures associated with osteoporosis, which should be considered an important etiology in these injuries. Increasingly, osteoporosis-related fractures are linked to impaired vision, altered balance, decreased muscle trophism, overall poor health, and predisposition to falls in the elderly.

Elderly patients sustain proximal humerus fractures as a result of indirect and direct mechanisms of injury. Whatever the mechanism of injury, treatment is based upon the degree of displacement of the fracture. Regardless of the method of treatment deemed appropriate, problems of obtaining healing, loss of fixation in soft osteoporotic bone, and stiffness plague the management of these difficult injuries. Rehabilitation of these injuries is prolonged, requiring at least 12 to 18 months, even in the most minimally displaced fractures. The prolonged post injury rehabilitation including physical therapy is a great strain for all involved.

We feel this is a very important area for focusing research. Specific areas to concentrate upon include prevention be it pharmacologic, educational, or physical rehabilitation; bone reconstitution methods once obvious loss has already occurred; and fracture management including improved methods of fixation and healing enhancement techniques in bone with poor osteogenic potential.

Frozen shoulder syndrome is a disorder that has been described as a condition difficult to define, difficult to treat, and difficult to explain from the point of view of pathology. Adhesive capsulitis has continued to be one of the most poorly understood disorders of shoulder motion, posing significant challenges to the clinician. Much of the problem has stemmed from the fact that it has not been easy to define or clearly differentiate frozen shoulder from conditions with similar symptoms and findings but with distinctly different causes.

Frozen shoulder is a condition of uncertain cause characterized by significant restriction of active and passive shoulder motion that occurs in the absence of a known intrinsic shoulder disorder. Most studies report the cumulative risk for at least one episode to be approximately 2 percent. It is much more common in women than men.

The precise cause for the development of frozen shoulder remains largely unknown. The condition probably results from the combination of host factors (i.e., predisposition) and extrinsic factors (for e.g., trauma, hormonal changes, collagen-vascular disease, diabetes mellitus). In general the natural history of frozen shoulder is uncertain, and additional randomized, prospective studies are needed. Other main areas of research for frozen shoulder syndrome include its pathogenesis and efficacy of treatment options.

Last, a large group of patients suffer from what is known as *atraumatic multidirectional instability of the glenohumeral joint*, defined as instability that is insidious or spontaneous in onset with no history of significant trauma inducing the first episode of instability. This is very common in the teenage female. Patients often experience their first episode of instability before the age of 16 years. Why the female teenager is so much more frequently subjected to this disorder around the time of menarche and early thereafter, raises the question of a hormonally related phenomenon.

Management of this difficult problem is complex and quite time consuming. Some patients respond to rehabilitation and others do not. Treatment programs are quite costly and time consuming as well as being responsible for a significant amount of time lost from school and daily activities.

Research is sorely needed in the area of shoulder instability in teenage females. The possibility of a genetic predisposition versus a process which is activated during menarche and possibly hormonally related need to be investigated. Rehabilitation is a very important area for research as well as basic science studies on the glenohumeral ligaments of the female shoulder.

Leilani Doty, Ph.D. *Department of Neurology, University of Florida*

Problems in Health Promotion and Disease Prevention. Most symptoms are evaluated and treated outside the formal medical care delivery system by the family health gatekeeper who synthesizes lay medical knowledge from multiple sources — personal experience with illness, vicarious experiences of morbidity in nuclear, peripheral and public networks, and information gleaned from professionals and the media. A major gap in knowledge exists in the area of women and family health. In particular, there is a gap in the health needs perceived by the woman who typically is the health gatekeeper of the family unit, for it is the woman who treats the symptoms, monitors the trajectories of chronic disease, transmits health information, teaches health practices, secures appointments, and administers medication. Further, there is difficulty in providing health education and services in ways that reverse the upward spiral in health costs, prevent life span disease, and promote healthy lifestyles.

Community Partners' Study. A creative solution to this problem lies in a model project under development in Gainesville, Florida through the leadership of Community Partners. Community Partners links the University of Florida faculty and students, especially from the Health Science Center, with people of diverse age and cultural backgrounds from the public school system, community health services; civic, philanthropic, and volunteer organizations; and city and county governments.

Community Partners has combined a variety of resources to study the health needs of the most underserved, local citizens. The study examines health needs, health behavior decision-making, household and environmental risks and self-perceptions of health. Students from the University of Florida health professions schools teamed with local high school students to interview household heads and to photograph neighborhood settings to evaluate subjective and visual-objective health. In assessing the health promotion needs of the community, the researchers identified key members of the underserved communities to train as health messengers. After training in the Health Promotion School, Health Messengers share their health messages with peer groups and neighbors to foster health promotion behaviors in the community health gatekeepers, typically the woman of the family. The Health Promotion School will train the volunteer Health Messengers to address strategies, in culturally sensitive ways, that promote health and prevent disease over the life span.

Evaluation of Outcomes. Outcomes of the Health Promotion School will be measured through pre- and post-course tests of changed health professional student competence in community health promotion and disease prevention, through community patterns showing use of health facilities, changes in health issues awareness, and changes in numbers of prospective students from the community seeking entry to health-training programs.

Research support is needed for projects that partner academic health centers with community groups in a collaboration to identify and address the cultural diversity of the community and the self-perceived health needs of the citizens, especially the family health gatekeeper. Empowering key members of the underserved community to serve as Health Messengers for peers should result in appropriate, acceptable, accessible, cost-effective ways to promote healthy lifestyles over the life span of women and their family members.

Carolyn M. Dresler, M.D.

Thoracic Surgical Oncologist
American College of Chest Physicians

Lung cancer is the number one cause of cancer death in women, exceeding deaths from breast cancer by 22,000 per year. Between 1950 and the present there has been a 550 percent increase in the numbers of deaths in women due to lung cancer. In 1991, 36 percent of all lung cancer deaths were in women and by 1996, this had risen to 41 percent. Thus, the lung cancer death rate is decreasing in men, but continues to climb in women.

Approximately 48 million people currently smoke in the United States — 25.3 million men and 22.7 million women. Although data suggested that smoking prevalence appeared to be decreasing as of 1991, more recent surveys have demonstrated that the percentage of smokers has increased from 27.5 percent of students in grades 9 to 12 in 1991 to 34.8 percent in 1995. In addition, these 1995 data demonstrate that girls and boys are now smoking at equivalent rates: 34.3 percent and 35.4 percent, respectively. This increase in the prevalence of smoking is likely to reflect an increase in the incidence of lung cancers in the near future, particularly in women.

Epidemiologic studies have demonstrated that women have a 1.4 to 2.9 times higher risk of developing lung cancer than men, when the amount of tobacco exposure is controlled. In large case-controlled studies, the odds risk ratios for women have been consistently higher in women than in men. Authors of these studies have hypothesized that women may be more susceptible to tobacco-related carcinogens for a given level of cigarette consumption, particularly when examined for the prevalence of the histological subtype of lung cancer — adenocarcinoma.

In addition to the risk factor of tobacco exposure, women may also be affected by their exposure to estrogens and/or progesterones. Studies have demonstrated increased risk of lung carcinomas, particularly adenocarcinomas in women with increased exposures to estrogens. Estrogen is a known “growth hormone,” and has been identified as a risk factor in the development of adenocarcinomas in the breast, endometrium, and ovary.

According to the NIH Accounting Office, approximately 100 million dollars was spent in 1996 for lung cancer research; 600 million dollars was spent for breast cancer research (300 million from NCI and 300 million from the Department of Defense) and over 1 billion dollars for AIDS research. This allocation is inappropriately distributed for the health and societal costs resulting from the respective diseases.

The growing epidemic of lung cancer in women is an exceedingly important health problem, not only in our society, but of grave concern in the rest of the world. Women in exploding numbers are taking up smoking around the world. The particular risk of women, smoking, and lung cancer is not at all understood. It is imperative that serious, in-depth and well-funded research is directed to the multidimensional health problem of women and lung cancer.

Laura Flawn, M.D. *The Scoliosis Research Society*

The Scoliosis Research Society is a research-oriented society dedicated to the pursuit of knowledge about the causes, cures, and prevention of scoliosis and related spine deformities. As a representative of this Society, I would like to draw your attention to certain particular gender-specific spinal problems. Eighty percent of adult symptomatic scoliosis occurs in women. Progressive curvatures cause mechanical arthritic back pain, radicular or nerve root pain, loss of standing or sitting balance with trunk decompensation, and possibly even neurologic deficits.

Other spine disorders affecting primarily women are spondylolisthesis (both developmental and degenerative) and postmenopausal osteoporotic compression fractures and related deformities. These are very disabling problems adversely affecting both quality of life and function. We would like to draw your attention to these potentially devastating health problems and ask your involvement in directing research and promoting education into both treatment as well as prevention.

The Center to Improve Care of the Dying
George Washington University

Janet Heald Forlini, J.D.

As the representative for both The Center to Improve Care of the Dying and the Institute of Medicine, my testimony covers not only the policy implications of directed research on this issue, but also the recommendations and findings of the IOM's Committee on Care at the End of Life. The main points of my testimony are as follows:

- A discussion of why improving end-of-life care is especially important to women, given that women generally live longer than men and often act as care givers to ill family members and friends.
- Examples of questions that need to be asked and answered by NIH ORWH.
- A discussion of other groups, such as business owners and insurers, who could learn from research and data, thereby improving the chances that caregiving will not bankrupt families.
- A directive to change the emphasis of health care at the end of life to that of *caring* rather than *curing*.
- A summary of the most relevant conclusions and themes of the Institute of Medicine's Committee on Care at the End of Life.
- A recommendation by the Committee, directed specifically at NIH and the research establishment in general.

Julie Fleming Graham, M.Ed. *Oglethorpe County Primary School*

I am the mother of John Mark Fite, Jr., who at the age of 7 years old, died from cancer. I am also a public school principal in a primary school of 530 students. During the past 24 years, I have taught in eight different public schools and have found in each of these a common bond: children with diverse medical and special needs. What is so alarming to me is the increase in numbers of children who need to be served by a special education teacher for either a segment of the day or for the entire day. I am not sure if the numbers have actually increased or we are more educated as to the specific needs of children.

As an administrator for the past 10 years, I have had a lot of direct contact with other administrators, teachers, students, and their families to validate that there is a growing need in our schools to provide more financial, educational, and counseling support. The most important health issues impacting our children's learning in our small school alone are: attention deficit disorder, fetal alcohol syndrome, learning disabilities, diabetes, autism, cancer, behavior and emotional behavior disorders, asthma, allergies, mildly and moderately handicapped, OT/PT/OHI (orthopaedically handicapped or other health impaired), conjunctivitis (pink eye), impetigo, and pediculosis (head lice).

Although the school did not create these illnesses, I think it indirectly contributed to some of the problem. We face an oppositional group who do not want the building sprayed for bugs. We face another group who want the building sprayed. We face a group who want carpeted classrooms and another group who, like me, believe carpet is a haven for germs. How can we effectively sanitize a carpeted classroom where pediculosis exists? These are problems we face daily.

Phyllis Greenberger, M.S.W.
Executive Director
Society for the Advancement of Women's Health Research

The Society for the Advancement of Women's Health Research strongly supports the work of ORWH and believes these efforts will play a pivotal role in translating this research agenda into action across NIH.

The Society is a nonprofit advocacy group that was formed 7 years ago in response to mounting concern about gender biases and inequities in biomedical research. The Society has played a vital role as a catalyst for advances in women's health, including strengthening policies ensuring women's inclusion in federally funded clinical research and advancing the study of gender differences, which we call gender-based biology. Gender-based biology examines the differences between the genders in a cell, an organ, or an individual to discover what these differences tell us about the system in which they function. The Society strongly endorses the inclusion of gender-based biology research as an integral part of an updated NIH research agenda on women's health.

Gender-based biology is a concept that could potentially revolutionize the practice of clinical medicine. Evidence is already accumulating to show that resources spent in investigating biological gender differences will be rewarded by advances in medical knowledge and practice. For example, men and women's immune systems function differently in a manner that leaves women more prone to autoimmune disorders, women who smoke at the same levels as men are more susceptible to lung cancer, and several drugs such as a certain class of pain killers and an experimental drug to treat unstable angina have been found to have different effects in men and women.

These examples hint at the power of gender-based biology as a research approach and the wealth of clinically significant gender differences which might be uncovered by gender-based biology research. As this field of study is explored, we will enhance our understanding of how gender differences affect the manifestations of health and disease and convert this knowledge into new and effective therapies which address the uniqueness of both women and men. Because of the potential significance of gender-based biology research, serious attention by the scientific and medical establishment is necessary. As the nation's premiere biomedical establishment, NIH should play a pivotal role in advancing gender-based biology at all levels of research across all institutes beginning with its updated research agenda on women's health.

Letha Y. Griffin, M.D. *American Orthopaedic Society for Sports Medicine*

Over the past two decades there has been a marked rise in the number of women participating in recreational and competitive sports. For example, only 96 women competed in the 1972 Olympics for the United States, whereas in 1996, 280 women competed with the United States women's teams making an extremely strong showing in multiple sports. Colleges are seeking to provide women with scholarship opportunities equal to men, and the number of women athletes in our high schools rose from approximately 300,000 in 1971 to almost 2 million in 1990 — nearly a sevenfold increase. As the number of women athletes has grown, injuries that occur more commonly in our female athletes have received increasing recognition. These include ligament injuries of the knee, kneecap tracking problems, subluxation of the shoulder, stress fractures of various long bones as well as the pelvis and lumbar spine, and forefoot overuse problems (corns, bunions, callouses, etc.).

Unfortunately the cause or causes of many of these musculoskeletal problems are not well understood. Until they are, it is difficult to design adequate preventive programs. More money allocated to musculoskeletal research would give us the financial ability to determine injury mechanisms and hence to begin to prevent these muscular skeletal injuries which occur all too frequently in our young women resulting in significant consequences.

Andrew A. Guccione, Ph.D., P.T. *American Physical Therapy Association*

The American Physical Therapy Association believes that research is especially needed in the following areas:

Prevention of Chronic Conditions. (1) A continuing research emphasis is needed on the prevention of osteoporosis and hip fractures; (2) the influence of exercise and physical activity on balance activities, including the prevention of falls should be studied more extensively; (3) additional research is needed on the benefits of exercise for the prevention of disease and disability; and (4) research is needed to identify strategies that can be employed during childhood, adolescence, and adulthood to encourage women to develop good health habits.

Chronic Conditions. (1) Increased research is needed on chronic conditions and diseases that impact the quality of life of older women in the U.S.; (2) research is needed to identify the most effective way to reduce musculoskeletal impairment and improve function; (3) research on intervention for osteoporosis, including studies on the clinical effectiveness of weight bearing is indicated; (4) research on rehabilitation interventions which improve functional status following stroke is indicated; (5) additional research is needed on quality of life in individuals with diabetes; (6) research on the prevention and treatment of cardiovascular disease through cardiac rehabilitation for women is needed; and (7) additional research is needed to improve urinary incontinence treatments, including therapeutic exercises, electrotherapeutic modalities, and biofeedback.

Recreational and Sports-related Injuries. Investigations into the prevention, causes, and treatment of athletically related musculoskeletal injuries, especially knee injuries, are needed.

Environment. Attention should be given to interventions which influence the outcome of women with carpal tunnel syndrome and other repetitive strain injuries. In particular, research is needed to identify practical, effective ways to protect workers from job-related musculoskeletal risks, including repetitive stress syndrome.

Additional Topics. (1) Biomedical research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women of all age groups; (2) research is needed to investigate the effect of interventions, including surgery, on female anatomy as well as the impact of these interventions on women's health; (3) research is needed to study the etiology and treatment of the high incidence of musculoskeletal problems in menopausal and postmenopausal women; (4) studies that investigate how exercise can promote healthy aging in women are especially indicated; and (5) investigations targeting the identification of domestic violence by health care professionals are necessary.

Recommendations to Promote Research on Women's Health. (1) Promote efforts to include women in clinical trials, including choosing study site locations and hours that are conducive to participation by women; (2) promote funding for programs that foster women's health research; and (3) expand the mission of the Office of Research on Women's Health to monitor funding for women researchers and career opportunities.

Betty B. Hambleton *Health Resources and Services Administration*

The proportion of total AIDS cases attributable to women is increasing, rising from 7 percent in 1985 to 20 percent in 1996. HIV infection is the third leading cause of death among women ages 25 to 44, and the leading cause of death among black women in this age group. Black and Hispanic women are disproportionately affected, accounting for 59 percent and 19 percent respectively of cases reported for women in 1996 — rates that are 17 and 6 times higher than for white women. In 1994, transmission via heterosexual contact surpassed transition via drug use; however, sexual contact with a drug injecting male accounts for the majority of heterosexually acquired AIDS cases among women.

As the federal agency that provides health care to underserved and vulnerable Americans, HRSA focuses many initiatives on addressing the health needs for improving the health status of women. In addition to the community-based health centers offering primary care clinical and screening services, and support for the education and training of the health professional workforce, special services are funded through the Ryan White CARE Act (RWCA) of 1990, administered by HRSA's new HIV/AIDS Bureau, to assist HIV-positive substance abusing women, better integrate comprehensive primary care and HIV-related care, and to prevent perinatal transmission of HIV.

Title I of RWCA funds eligible metropolitan areas most severely affected by the HIV/AIDS epidemics. About 30 percent of clients are women, many of whom participate on planning councils established to assess needs, gaps in care and to set priorities. Title II provides formula funding to States and territories to improve quality, availability and accessibility of health care and support services for people living with HIV disease; nearly 28 percent of these clients are women. Under Title III, public and private nonprofit entities are funded for outpatient primary care and early intervention services. Of 83,000 HIV patients receiving health services, 794 were pregnant women. An assessment is underway of current HIV counseling and testing services delivered to women of childbearing age and pregnant women in the Community and Migrant Health Center, Health Care for the Homeless, Health Care for Residents of Public Housing, and other programs administered by HRSA's Bureau of Primary Health Care. Title IV funds public and nonprofit entities to increase access to research and comprehensive, community-based systems of care for children, youth, women and their families. About 53 percent of the clients are adolescent or adult women, and more than 25 percent of newly enrolled clients are pregnant women and mothers. The Women's Initiative for HIV Care and Reduction of Perinatal HIV Transmission develops models of care that enhance outreach, counseling and testing services for women. In 1996, the network of projects provided counseling to more than 12,000 women.

The education of primary health care providers about HIV-related issues is carried out through HRSA's National AIDS Education and Training Centers Program. More than 400,000 providers have been trained under this program since 1991.

HRSA will continue to monitor changes in health needs of women with HIV/AIDS. Research will be carried out to better understand the utilization and effectiveness of its programs and services on the behavior and health status of these women.

Jo A. Hannafin, M.D., Ph.D. *Orthopaedic Research Society*

The Orthopaedic Research Society is an organization of close to 2,000 individuals (M.D.s and Ph.D.s) who conduct research on the musculoskeletal system. Dr. Hannafin, an orthopaedic surgeon specializing in sports medicine, as well as a researcher studying tendon and ligament healing, provided information on the role of women in the Research Society and in the Orthopaedic Research Community, and presented data on the advances and unanswered questions pertinent to the Women's Health Initiative. Specific areas for which additional research is needed are:

- Osteoporosis, especially in the younger woman, a field in which there are numerous questions.
- Injuries in the female athlete, with emphasis on increasing numbers of women in sports and recent data on the types of injuries, and the questions that must be addressed in the future.
- Musculoskeletal consequences of breast cancer therapy, with insights into the advances that have been made in the treatment of breast cancer, and the established effects of some of these therapies on bone.

Susan Hendrix, D.O.

Wayne State University
Detroit Medical Center

I am an Obstetrician/Gynecologist representing Wayne State University and the Detroit Medical Center. I am the Principal Investigator of the Women's Health Initiative, Detroit Clinical Center, and Director of the Medical Center's Center of Excellence in Women's Health. I would like to add three areas to the future research agenda in women's health.

Ectopic Pregnancy. Ectopic pregnancy, the implantation of the fertilized egg outside the uterine cavity, is the most common cause of maternal death in the first 12 weeks of pregnancy. Ectopic pregnancies have increased nearly approximately threefold from the 1970s to the 1990s. The increase is attributed to many factors, including an increasing incidence of pelvic inflammatory disease, use of tubal reconstructive surgery and assisted reproductive technologies for infertility, use of tubal ligation for sterilization, and use of intrauterine devices. The annual cost of ectopic pregnancy in the United States exceeds $1 billion.

Highly sensitive blood tests for detecting pregnancy hormone have allowed clinicians to identify and treat this condition earlier in its course. Surgery is a major treatment for patients desiring future fertility. Ultrasound combined with blood tests allows patients to avoid surgery and its complications, reduces health care costs by reducing the need for hospitalization, and possibly improves long-term fertility. Studies are needed to determine the most effective and safest treatment of ectopic pregnancy, as well to determine which treatment affords optimum potential for future pregnancies.

Pelvic Prolapse. Genital prolapse (the detachment of the uterus, vagina, rectum, and bladder from their normal support) is a common condition in women. It is not clear who will develop pelvic prolapse or why, but the condition progressively worsens with age, and prevention measures at an early age are impeded by difficulties in identifying patients at risk. Little is known about the risk factors. Surgical management of this condition is the gold standard. However, more research is needed to better understand the causes of this condition and ways to prevent it.

Alternative Menopausal Treatments. Because physicians cannot answer their health questions, menopausal women are taking matters into their own hands. They want coordinated, comprehensive and preventative health care that is based on cutting-edge research. For many women traditional approaches to the treatment of menopause are unacceptable. They are turning to alternative treatments, including phyto-estrogens and herbal remedies, for symptom relief or disease prevention. However, "natural" does not necessarily mean safer or better treatment. The strength of plant products can vary and there is no quality oversight to the production of these products. Only clinical trials on the safety and efficacy of these products will answer that question.

Mary Hepburn, B.S. *Self*

Many obstacles in health affect how any disabled woman reacts during her life, as I described during my testimony about research on women's health for the 21st century. My experiences with multiple sclerosis presented me with daily challenges and many obstacles along the way. There are many obvious and not-so-obvious changes — physical, emotional, and spiritual that occur. Not only did I have to deal with physical limitations of multiple sclerosis, but the mental transition couldn't be avoided. These created a lot of turmoil for the individual and the family, caused chaos, and sometimes total frustration. With MS, a person's coping skills become a major challenge.

Nicolette Horbach, M.D. *American Urogynecologic Society*

The American Urogynecologic Society (AUGS) is a medical specialty society composed of over 700 members who specialize in providing the continuum of care to women with disorders of the pelvic organs including the diagnosis and treatment of urinary and fecal incontinence, pelvic organ prolapse, infections, and voiding disorders.

- Prevalence statistics regarding the number of women suffering from disorders of the pelvic floor are difficult to ascertain because of significant under-reporting of these conditions.
- It is estimated that 50 percent of parous women lose pelvic floor support, resulting in prolapse. Of these women only 10 to 20 percent seek medical care for their symptoms. The overall prevalence of all causes of urinary incontinence is reported to be approximately 40 percent less. Less than one half of women with incontinence report their symptoms to their health provider, and most wait at least 5 years before seeking care.
- The National Center for Health Statistics reports that nearly 400,000 operations are performed annually for these conditions. Recent research suggests that women have a 11.1 percent lifetime risk of undergoing a single operation for pelvic organ prolapse and/or urinary incontinence.
- The estimates regarding the direct costs of urinary incontinence have increased from $10 billion in 1987 to $16 billion in 1994. Only 4 percent of these dollars is used for the diagnosis and treatment of urinary incontinence. The remainder was spent on management of the problem.

I would now like to share with the Task Force three activities that the American Urogynecologic Society feels will help to uncover new knowledge that will improve the health of women with pelvic floor disorders.

- The first is to convene an inter-Institute working group in the area of pelvic floor dysfunction research.
- The second is to work with NIH to find a mechanism and funding source to support training and career development awards for new and young investigators interested in careers in incontinence and pelvic dysfunction research.

- The third objective is to assist NIH in developing an RFA in FY 1998 with the intent of funding three to five small pilot grants in the area of incontinence and pelvic floor research.

Mary Lloyd Ireland, M.D.

Ruth Jackson Orthopaedic Society
Kentucky Sports Medicine Clinic

Mobility: A Key Ingredient for Enhancing the Quality and Length of Women's Lives

Women must adopt an active lifestyle if they are to maintain good physical and mental health. Yet there are many threats to a woman's mobility. Societal biases still hamper women's opportunities to participate in and enjoy athletic activities. Women's physical and anatomical differences from men have not been fully appreciated by coaches and trainers, placing girls at unnecessary risk of pain and injury. As women age, they undergo the special stresses of mineral-depleting osteoporosis and become vulnerable to many kinds of fractures. Hip fracture represents an especially important risk to women since it has such a serious impact on independence and quality of life.

Women's tendency to become less active with age exacerbates their susceptibility to a myriad of health problems including obesity, heart disease, depression, and diabetes. Inactive women often become trapped in a downward spiral of poor health and immobility. The loss of a woman's mobility often results, directly or indirectly, in her premature death.

Physical activity is a critical element of a healthy and satisfying lifestyle. We must learn more about how to promote movement among women, and how to circumvent the social and biological processes which threaten their mobility.

Anne Kasper, Ph.D.

Boston Women's Health Collective

Our definition of women's health includes women's experiences with their bodies and their sexuality, and their interactions with the health and medical care system, as well as specific biologic conditions or diseases mostly affecting women. Our work, in the public interest, is to empower women by providing them with the best information available. We support them with providers who respect and encourage their participation and responsibility. We have focused on the normal in each life stage and reproductive transition because so much medical information has focused on diseases, or defines normal life transitions as inherently deficient, and unmanageable without medical intervention and surveillance. We research and describe nonmedical, self-help approaches as well as medical treatments, believing that true informed consent includes both. From the start of our work we have named race and class, along with gender and sexual preference, as key determinants of health, and important human rights concerns. We are advocates for women who use the system, and work with professionals and consumers who organize to change it. We call for greater roles for women in governance of a system which impacts them so profoundly, since that system depends on women's unpaid caregiving on behalf of ill family members. We bring a critical lens to the conduct of research and the practice of medicine, and actively pursue evidence of treatment effectiveness as essential to rational decisionmaking. Our scrutiny of the doctor-patient or practitioner-patient relationship has intensified under managed care since providers working under these plans may no longer be able to give the best advice and information. As we work with the media, we bring feminist, gender analysis to health issues whose impact is often distorted by gender-neutral or color-blind approaches, or biased by special interest.

We call on ORWH and NIH to research methods for dissemination of information about determinants of health, normal processes of development across the life span, and the importance of evidence-based perspectives in health and medical decisionmaking. This research includes finding methods to disseminate the ineffectiveness or potential harm and abuse, and to illuminate ethical issues, as well as reporting the effectiveness of biological research or treatment approaches. We cite examples from maternity care, gene research, development, and use of medical technology (especially in normal women), diet and exercise benefits, smoking in girls, the impact of poverty and social class on mortality, women's overwork in the workplace and home, barrier method contraception, and nonmedical approaches to HIV/AIDS care, in order to illustrate how additional research is needed to examine the impact of research and the implementation of research, on the lives of women from a variety of backgrounds. We also call for greater utilization of methodologies already in use, or piloted recently, such as Consensus Development Conferences and the Urban Women's Health regional "Report Cards" to provide research issues with greater community perspective and input.

Marlene Keeling *Chemically Associated Neurological Disorders (CANDO)*

Exposure to chemical toxins has become an urgent global problem. Much of our knowledge regarding neurotoxicity of specific chemicals has not been found in the laboratory but rather has come from outbreaks of human neurotoxicological disease due to excessive environmental and industrial overexposures resulting from both accident or ignorance. With methyl mercury and PCBs, neurotoxicological illness was not restricted to the adult population; children born to exposed mothers also suffered lasting neurological and behavioral effects.

It is now commonly accepted that the developing nervous systems in the unborn child are especially sensitive to chemical toxicity. Research on lead, alcohol, methyl mercury, and PCBs indicate that infants and children may be at an increased risk of exposure in the womb and during breast feeding.

As we approach the 21st century, I urge ORWH to focus research on one source of probable chemical toxicity that has not been adequately researched — silicone implants — which includes toxic chemicals known to have neurologic, carcinogenic, and teratogenic effects in exposed mothers and their unborn children. This issue affects so many women and their unborn children. Silicone, silica, and its components have not only been used in implantable devices but are used in cosmetics, medicine, food, needle tips, and hundreds of other products. Research now clearly shows that it is not inert in the body, as previously purported by the chemical industry.

With more than 100,000 implanted women having been diagnosed with severe illness, this is the time to do the critical research that should have begun thirty years ago. Some of the serious problems seen in many implanted women include peripheral neuropathy, demyelinating neuropathy, atypical neurological disorders, cognitive dysfunction, organic brain disorders, and immune dysfunction. Silicone has the ability to produce human hypersensitivity in as high as 26 percent of implanted patients. The following questions should be answered:

1. Is silicone or silica a soluble neurotoxin?
2. What part does silicone or silica play in the incidence of chronic illness?
3. Does silicone, silica, or its components pass through the placenta and breast milk with harmful consequences?
4. Does silicone, silica, D4, or other components act as a synthetic estrogen or estrogen blocker as industry research has reported?
5. Do the reports of increasing cases of multiple myeloma in young women with breast implants indicate a cancer latency factor?

Gwendolyn Puryear Keita, Ph.D. *American Psychological Association*

On behalf of the American Psychological Association (APA), I would like to convey our deep appreciation for recognition of the importance of psychosocial and behavioral and social scientists in the development of the new women's health research agenda.

Despite increased focus on medical and epidemiological aspects of women's health, research has not adequately addressed psychosocial and behavioral factors that contribute to health status. In May 1994, APA in collaboration with a number of federal agencies and professional organizations sponsored an interdisciplinary conference titled "Psychosocial and Behavioral Factors in Women's Health."

The "Research Agenda for Psychosocial and Behavioral Factors in Women's Health," which evolved out of the conference, was developed by experts from across disciplines, institutes, and federal agencies. It defines research priorities pertaining to specific diseases and health practices that greatly affect women. The diseases included are those that show high mortality or morbidity rates for women and that may cause great physical disability, lowered financial resources, and poorer quality of life.

APA believes that consideration of future research and funding needs for women should be made (1) with full awareness of the issues of concern to women's health, (2) with knowledge of what research has already shown, (3) with knowledge of what questions remain unanswered, and (4) with a full appreciation of the behavioral and psychosocial factors that impact each health issue. Our research agenda was developed with these factors in mind. We, therefore, propose that ORWH use our research agenda as a foundation upon which ORWH builds its new research agenda. This would avoid duplication of efforts and enable women's health researchers, federal agency personnel, and policy makers to most effectively address women's health research and would go a long way in furthering the much-needed federal commitment to improving the health of America's girls and women. Copies of the research agenda are readily available for your use.

Ann Kolker *Ovarian Cancer National Alliance: Ovar'coming Together*

The Ovarian Cancer National Alliance, formed last spring, is the creation of leaders from the growing number of ovarian cancer groups across the country. These groups united to establish an umbrella group, the Alliance, because they believe that it is essential to have a coordinated effort that will put ovarian cancer policy, education, and research issues squarely on the agenda of national policy makers and leaders in women's health. This conference is our public debut.

I have a straightforward message. It is urgent that researchers, clinicians and policy makers dramatically expand awareness of and resources devoted to ovarian cancer with the goal of significantly improving early detection. The tragedy of ovarian cancer is that more than 50 percent of the women who have it *die within 5 years of diagnosis*, because the vast majority of women are not diagnosed until the cancer has reached late stage, when it is too late to cure.

There are several reasons for this serious state of affairs. One is that awareness of ovarian cancer in the medical community is limited. Because it is not a common disease — affecting only 1 in 55 women — it is not "on the screen" of many primary care doctors who first see women who report abdominal discomfort, bloating, bleeding or some of the other common symptoms. Gaining the attention of the medical community about ovarian cancer is a top priority of the Alliance. Another concern is that many at-risk women are unaware of symptoms, which are often subtle and not unique to ovarian cancer. Thus, another Alliance priority is to educate women about this disease, so that when symptoms occur, women request appropriate testing. The third problem that dooms so many women to late-stage diagnosis is the imperfect status of diagnostic tools and the absence of a simple, cost-effective, and reliable screening mechanism for ovarian cancer. An immediate Alliance priority is the development of a screening mechanism, as simple and accessible as the Pap smear or mammogram. We urge those of you here today to make this a top priority, and to urge colleagues to do the same. Until such a screening device is available, early stage ovarian cancer will continue to be missed too often and many thousands of women will needlessly continue to die.

Despite the many new life saving therapies developed in recent years and the infusion of new funds designated for ovarian cancer research, much more research must be done to gain a better understanding of key aspects of this disease, to improve dramatically the survival rate. We urge that as the women's health research agenda is set, the compelling needs of ovarian cancer be given top priority.

Virginia T. Ladd, R.T.

Executive Director
American Autoimmune Related Diseases Association

Autoimmunity is a women's health issue. Women with an autoimmune disease frequently experience physical and emotional problems as a result of delay in correctly diagnosing an autoimmune disease. Additionally, autoimmunity must be understood as a category of diseases, like cancer. A powerful need exists to conduct collaborative research on autoimmunity, the common link to many chronic diseases which are currently treated, and studied, independently.

Autoimmunity is a Major Health Problem. Autoimmunity is a debilitating condition in which the immune system attacks the body's own tissues or cells. Autoimmunity is the root cause of over 80 serious, chronic diseases, including lupus, rheumatoid arthritis, multiple sclerosis, Graves' disease/hyperthyroidism and Type I diabetes. Autoimmune diseases afflict an estimated 50 million Americans at an annual cost of $86 billion.

Autoimmunity is a Major Women's Health Problem. Autoimmune diseases represent the fourth largest cause of disability among women in the U.S., striking three times as many women as men. The gender disparity is even greater for many autoimmune diseases.

Autoimmunity is known to have a genetic component, and tends to cluster in families as different diseases. People with autoimmunity often experience more than one autoimmune disease. Because confusing, sometimes intermittent symptoms of autoimmunity vary both among the different autoimmune diseases and within a particular disease, getting a proper diagnosis for an autoimmune disorder can prove as difficult for some women as living with the disease itself.

The physical and psychological toll of misdiagnosis and late diagnosis for sufferers of autoimmune diseases can be substantial. No early diagnosis means no early treatment, worsening the health burden that a patient must bear. Late diagnosis is also devastating, as a physician may not take the patient's complaints seriously, and the patient may have to endure a long series of unsuccessful tests and procedures from a range of specialists before receiving a successful diagnosis.

Need for Basic, Collaborative Research. Basic research on autoimmunity will yield information that benefits the treatment and diagnosis of all autoimmune diseases and represents the most promising approach to finding a cure. There has been no general focus on autoimmunity as the underlying cause of these related chronic conditions.

Some progress has been made. Exciting breakthroughs in research focused on new treatments for autoimmune diseases, such as with oral tolerization, have shown promise for several autoimmune diseases across clinical categories and underscore the common link among the different diseases.

Conclusion. ORWH has the capability to improve our country's approach to autoimmunity. Efforts to channel additional resources to basic biomedical research on autoimmunity will encourage the coordination of currently fractured research efforts. Such collaboration will also promote the increasingly supported view that autoimmune diseases are connected by common threads. And research will concurrently increase awareness and knowledge of autoimmunity among the medical community and the public, thereby aiding early diagnosis and treatment. AARDA urges ORWH to seize this timely opportunity to address one of the leading and most vexing health problems facing American women.

Mary Lamielle *National Center for Environmental Health Strategies, Inc.*

The National Center for Environmental Health Strategies, Inc., based in Voorhees, New Jersey, is a national, not-for-profit, membership organization fostering the development of creative solutions to environmental health problems with a focus on indoor pollution, chemical sensitivities, and environmental disabilities. The Center has become a preeminent source of public information, educational materials, technical support, and input on research and to the Government on environmental illnesses including sick building syndrome, chemical sensitivities, Gulf War Syndrome, and related disorders.

We have been the pathfinders in the area of multiple chemical sensitivities (MCS). Based on several government and university-based studies, the number of individuals reporting sensitivity to everyday chemical exposures is on the rise, with women reportedly outnumbering men. Little research has been done to help us understand the phenomenon, address the health issues for those who report chronic illness and disability, provide treatment protocol, or protect public health.

Patients most frequently report an initiating event such as a pesticide application, new carpet installation, remodeling activities, solvent exposures, inadequate ventilation, or poor air quality. Following this exposure event the patient will find, over time, that she reacts to more and more, different substances and products at lower and lower exposure levels. Clusters of symptoms will be triggered on a day-to-day basis upon exposure to a diverse array of common substances and products including pesticides, perfumes, auto and diesel exhaust, tobacco smoke, air fresheners, deodorizers, dry cleaning fluid, hair spray, and other personal products just to name a few. Those patients who cannot remove themselves from such exposures will generally find that their health declines rapidly, and that they experience significant levels of illness and disability.

In July 1987, the Board on Environmental Studies and Toxicology at the National Academy of Sciences held a workshop to examine indoor pollution and chemical sensitivity. Experts at this workshop issued an estimate that "approximately 15 percent of the U.S. population have an increased allergic sensitivity to chemicals commonly found in household products, such as detergents, solvents, pesticides, metals and rubber, thus placing them at increased risk to disease." The consensus from the meeting was that further research is needed to examine the extent of this public health problem and the role that indoor pollutants, particularly from consumer products, play in promoting chemical sensitivity. Despite this auspicious beginning, the first government-sponsored workshop on MCS was not held until 3 years later. It took directed Congressional funding and another 2 years until the Agency for Toxic Substances and Disease Registry created an expert panel and convened a neuroscience workshop in Baltimore. To date little research has taken place to illuminate this issue.

Meanwhile, industry, segments of the medical community, and insurance companies are among those groups who remain the tremendous obstacles to investigating and acting on MCS. A research agenda to investigate MCS and related disorders is long overdue. I would urge you to examine the compelling needs of those disabled by MCS, and to assign the highest priority to this significant and growing public health problem. If the apparent rise in MCS patients is accurate, progressive loss of tolerance for everyday chemical and environmental exposures may have profound consequences for the public health and society.

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

Coronary heart disease (CHD) is the leading cause of death in American women. While not comprehensively studied over previous decades, information now exists about risk factors, diagnosis, management and prognosis for women with CHD. Differences between men and women are evident in many aspects of the CHD spectrum of evaluation and outcomes. For some increases in mortality, differences have been shown to be related to increased levels of other features that impart higher risk, including older age, more advanced disease and more concomitant diseases, rather than gender-specific factors. Some reports suggest bias in decisionmaking when diagnosing or treating women. Much more information is needed to determine the sources of differences and the adjustments needed to improve the outcome of women with CHD.

Topics recommended for further research include: assessing risk factor intervention (particularly diabetes); primary prevention of CHD with cholesterol lowering agents with consideration of the potential interaction with hormone replacement therapy; programs to improve health behaviors, in general, and programs designed to reduce teenage smoking and increase physical activity, in particular; treatments for obesity and their impact on CHD; algorithms for diagnostic testing; studies to assess optimal therapy for men and women to eliminate biases and produce evidence-based guidelines; studies on survival of myocardial infarction; assessing appropriate dosing of new agents for women and men; and studies to assess the impact on aging vs. gender on diagnostic and therapeutic decisions and in assessing outcome.

Lisa Lindahl *Epilepsy Foundation of America*

The Epilepsy Foundation of America (EFA) is a national voluntary health agency representing the interests of the over 2 million Americans with epilepsy. Ms. Lindahl is a member of the EFA Board of Directors and chairs the Foundation's Women and Epilepsy Initiative. EFA has a long-standing commitment to basic and clinical research advocacy and has recently focused efforts on promoting more research on women's health issues.

Over 1 million women in the United States have epilepsy. Seizures and exposure to anti-epileptic drugs (AEDs) may alter female reproductive function and may have a negative effect on pregnancy and reproductive health. For instance, women with epilepsy are at greater risk for pregnancy complications, while fetal exposure to AEDs increases the risk of birth defects. Efficacy of hormonal contraceptives may be compromised by interactions with drugs to control seizures. Recent studies show that fertility is lowered and sexual dysfunction affects nearly one-third of women with seizure disorders.

Recommendations for further research:

- *Birth outcomes.* Issues around teratogenic drugs and pregnancy must be explored to address the serious problems of infant mortality and birth defects; we currently do not know enough about the association between folic acid and decreased risks of serious birth defects, or actual outcomes from folate use.
- *Reproductive health.* Incidence of reproductive endocrine disorders in women with epilepsy must be examined, including concerns about anovulatory cycles and polycystic ovarian disease; impact of this on general health, such as cardiac functioning and other metabolic issues are poorly elucidated or understood.
- *Family planning/contraception.* Increased risk of contraceptive failure needs examination; need to understand if contraceptives affect seizure control.
- *Hormone replacement therapy.* Need findings to establish relative risk-benefits of HRT for women with epilepsy.
- *Bone health.* Poorly understood in women with epilepsy, especially with regard to usage of anti-epileptic drugs.
- *Hormone-to-seizure/seizure-to-hormone relationships.* Need to understand reasons for changes in seizures and seizure control at puberty, during the menstrual phases, and at menopause.
- *Behavioral and psychosocial issues.* Impact of epilepsy on factors of neuropsychological functioning and independent living must be examined more thoroughly, including learning, memory, depression, employment, and parenting, among others.

Randall McCoy *CareTrends Health Education and Research Institute*

Osteoporosis is a major public health problem today and is certain to grow in the future. Osteoporosis occurs in 37 percent of the population of which one-third are men. In the 1990s, an estimated 2.5 million hip fractures, 5 million vertebral fractures, and 375,000 deaths occur annually due to osteoporosis. This will increase as the elderly population continues to grow. The risk of a 50-year-old white woman for a fracture related to osteoporosis is 30 to 40 percent.

In addition to being devastating to its victims' quality of life, osteoporosis has a profound, negative economic impact. The condition costs more than $20 billion per year, with projections of $60 billion by the year 2010. Costs include treatment for fractures, acute-care hospitalization, and rehabilitation. Complications following fractures further add to the costs. A large percentage of persons with osteoporosis-related hip fractures are discharged from the hospital to skilled long-term care facilities. Because many persons are being treated for osteoporosis, the majority of funding for treatment comes from publicly financed health care programs. The staggering economic and social cost of osteoporosis places a heavy burden on the health care system.

Osteoporosis can be detected early by a simple x-ray test known as a Dual Energy X-ray Absorptiometry (DEXA) scan that is extremely accurate. Evaluation of bone mass of the hip, spine, and wrist early in life can predict who will develop osteoporosis later in life with a high degree of reliability. Identified individuals at high risk for osteoporosis can receive interventions which will delay or prevent osteoporosis development. Screening of young adults must be done to identify those persons requiring intensive intervention to prevent osteoporosis complications in the future.

Nutrition and exercise are major factors in the prevention of osteoporosis. Adequate calcium and vitamin D intake in children and adolescents is necessary for increased bone mass. A significant body of research demonstrates that women who have received adequate nutrition, particularly calcium and vitamin D, have a lower rate of osteoporosis. Therefore, intensive nutrition education and intervention are mandatory and should contribute to osteoporosis prevention. Lifestyle is an additional factor in osteoporosis prevention. In children, a positive association exists between physical activity and bone mass affecting skeletal mass later in life. Weight bearing or strength and resistance training/exercise can also reduce bone loss in older women. Therefore, exercise education is essential to prevent osteoporosis.

In addition to behavioral modification, a number of effective pharmacologic agents are available to treat osteoporosis. The therapy of choice is hormone replacement therapy, specifically estrogen. At the menopause, estrogen has been proven successful in maintaining bone mass, for the majority of women, for the duration of the therapy. However, as soon as estrogen therapy is withdrawn, loss of bone mass will resume. In many patients, medications from the bisphosphonate class will increase bone mass by 5 to 7 percent. Compliance with medication treatment is not reliable. While estrogen therapy has been the treatment of choice for osteoporosis, only 15 percent of women who are prescribed estrogen continue to take the hormone 12 months after the initial prescription is filled. Very little data exists about the rate of compliance for other agents used for osteoporosis treatment. Further study is necessary to evaluate the compliance with medication regimens.

Currently, no ongoing, long-range program exists to determine bone mass in premenopausal women and, in particular, female teens. Studies are required to determine the need for therapies to stabilize bone mass in young women who may have seriously depleted skeletal mass. Dietary surveys in the U.S. report decreased calcium intake in adolescent females at a time when their need for calcium is high. These factors contribute to low bone density as women age, which leads to increased fractures. Similarly, little is known about the adolescent development of the male skeleton and to what extent risk factors such as poor diet, lack of exercise, and smoking have on skeletal mass in the general male population. Baseline data are needed on the prevalence of low bone mass in males between 20 and 50 years of age and from 51 and beyond.

Given the prevalence of the risk factors in the general population, osteoporosis is, and will continue to be, a greater public health problem than generally is recognized. We have been involved in a clinical trial of a drug thought to be effective in the treatment of women with osteoporosis and established vertebral compression fractures. Approximately 4,000 women have been screened since mid-October 1996 in the northern Plains states. At several of the screening sites, nearly 70 percent of the women receiving DEXA scans have qualifying bone mass. Approximately two-thirds of that number have qualifying fractures and osteoporosis.

In the earliest recruiting efforts for the clinical trials, bone scans were offered to women of any age in order to heighten awareness of the study and to encourage younger women to bring to their mothers, aunts, and grandmothers to the osteoporosis screening. Although the number of premenopausal women scanned was small, the results were alarming. We demonstrated that the number of women in the population with low bone density may be higher than originally thought, due to the prevalence of many risk factors such as excessive smoking, alcohol consumption, lack of regular exercise, and poor diet. Given the diversity in the population being scanned, there is great concern that the incidence of osteoporosis in the general population is much greater than current estimates.

The status of bone mass and skeletal health in the U.S. must be addressed more vigorously. Saving billions of dollars in health care costs is possible if a proactive approach to prevention and early treatment is taken. However, data are insufficient to determine the magnitude of the problem in the population. In addition, little is known about the impact of preventative measures taken by young adults which might drastically reduce the likelihood of developing osteoporosis and paying the high economic and human costs in their later years of life. Therefore, we propose a national, longitudinal osteoporosis project to identify persons at risk for the disease and provide health education to decrease the prevalence of osteoporosis. The overall, long-term goal of our program is to provide screening and health education to the general public to decrease the prevalence of osteoporosis. The specific aims are to:

- Develop accurate epidemiological information on the number of men and women of various ages in the United States who have clinically significant low bone mass.
- Determine to what degree behaviors can be modified and how behavior modification impacts on skeletal health.
- Determine if educational intervention in young women will change behaviors and improve skeletal health in late adolescence.

- Determine compliance rates in women who have been placed on bisphosphonates, calcitonin, and other therapeutic regimens.
- Evaluate the usefulness of biological markers in monitoring the study populations.
- Reduce costs to publicly funded health care programs.

Details of the Longitudinal Osteoporosis Research Project are presented in the full version of our testimony.

Nancy K. Mello, Ph.D.

Professor of Psychology (Neuroscience), Harvard Medical School
Director, Alcohol and Drug Abuse Research Center
McLean Hospital

Recommendations for Research on Drug Abuse and Alcoholism in Women

Drug and Alcohol Effects on Reproductive Function. Alcoholism and drug abuse are frequent problems among young women, early in their reproductive years. A number of neuroendocrine abnormalities are associated with chronic drug and alcohol abuse that may impair fertility and/or compromise neurobehavioral development of the offspring. Neuroendocrine abnormalities in women are expressed clinically as disorders of the menstrual cycle, i.e., annovulation, luteal phase dysfunction, and amenorrhea. Disorders of prolactin regulation, expressed as hyperprolactinemia, sometimes associated with galactorrhea, are also observed. The risk for spontaneous abortion is a frequent concomitant of alcohol and cocaine abuse. Alcoholism is also implicated in early menopause, but the cocaine epidemic is too recent to evaluate its effects on the menopause. Most drugs of abuse can disrupt the menstrual cycle. Polydrug abuse probably exacerbates the severity of these disorders as well as complicating interpretation of the role of cocaine, opiates or alcohol per se. However, many menstrual cycle disorders have been replicated in animal models of drug and alcohol self-administration under controlled conditions. The possible mechanisms by which cocaine, opiates, and alcohol disrupt the menstrual cycle are unknown and have important implications for women's health.

Interactions Between Menstrual Cycle Phases, Abused Drugs, and Treatment Medications. In addition to the adverse effects of abused drugs on the menstrual cycle, hormonal changes across the menstrual cycle also can influence the effects of abused drugs. Recent evidence suggests that the hormonal profile associated with the follicular, peri-ovulatory and mid-luteal phases of the menstrual cycle may influence the reinforcing as well as the toxic effects of abused drugs. These interactions are poorly understood and may affect initiation as well as perpetuation of drug abuse.

There is also increasing evidence that the efficacy of some therapeutic agents may vary as a function of menstrual cycle phase. It is important to evaluate the ways in which the hormonal milieu of each phase of the menstrual cycle may modify the effectiveness of medications as a function of hormone-related changes in the pharmacokinetics and pharmacodynamics of the medications. Finally, treatment medications may also disrupt the menstrual cycle. Opioid antagonists that are effective in treating opioid abuse also may stimulate gonadotropin release and enhance fertility. Preclinical and clinical studies should be conducted to address these important health issues.

Substance Use After Menopause. In view of the trend towards 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. Recent evidence that social drinking can increase estradiol levels by over 300 percent in postmenopausal women on estrogen replacement therapy suggests the importance of evaluating drug and alcohol effects in older women. Drug induced changes in estradiol could alter the complex risk-benefit ratio of hormone replacement therapy in postmenopausal women. Moderate alcohol use could contribute to protection from osteoporosis and premature cardiac disease often ascribed to estrogen replacement therapy and/or enhance the risk for adverse health consequences. Alcohol and drug effects on the health of older women is an understudied area.

Immune Function and Vulnerability to AIDS: The Role of Drug-related Hormonal Changes. Cocaine administration may enhance both risk for HIV infection and severity of progression of HIV as a function of needle-sharing, direct immunosuppressive effects and hormonal factors. Cocaine stimulates the hypothalamic-pituitary-adrenal axis, and pharmacokinetic analyses have revealed a very close temporal concordance between increases in plasma cocaine levels and plasma ACTH levels in humans. In addition, cocaine administration causes a significant increase in plasma cortisol levels following an antecedent increment in the pulsatile release of ACTH. Recent studies have revealed the importance of glucocorticoids in modulating immune function in HIV infection. Development of medications for the treatment of cocaine abuse and dependence should involve evaluation of medication effects upon the hypothalamic-pituitary-adrenal axis to determine the hormonal consequences of treatment.

Virginia Miller, Ph.D. *Women's Health Care Council, Mayo Clinic*

The Women's Health Care Council is a group of 20 physicians and scientists appointed by the Board of Governors of the Mayo Clinic to address mechanisms to improve women's health care through clinical practice, education and research. The Mayo Clinic and Foundation is a private, multidisciplinary, integrative practice with three primary locations in Rochester, MN, Scottsdale, AZ, and Jacksonville, FL and regional practices in the upper Midwest.

Priorities for women's health through the 21st century should encompass the entire scope of a woman's health experience including prevention, early detection, intervention, and rehabilitation programs. Several areas are identified in which the resources available at the Mayo Clinic could be used to advance women's health. These are:

1. Translating outcomes from clinical trials to the community setting.
2. Applying innovative prognostic, predictive and early detection diagnostic procedures to appropriate populations for women at risk for cardiovascular disease, cancer, and osteoporosis.

3. Translating knowledge from basic sciences to relevant populations of women through integrative, multidisciplinary approaches.

4. Understanding basic mechanisms of disease processes with an emphasis on cardiovascular disease, ovarian cancer, and anabolic therapies for bone.

5. Establishing smoking cessation and other rehabilitation programs tailored to meet the unique needs of women.

Ann Mulligan *DES Cancer Network*

The DES Cancer Network is a national nonprofit consumer advocacy organization that addresses the special needs of women who have had clear cell adenocarcinoma of the vagina or cervix — a cancer linked to prenatal exposure to the synthetic estrogen diethylstilbestrol or DES. The DES Cancer Network provides surviving clear cell cancer patients with ways to contact and support one another; to offer assistance and information to newly diagnosed patients who are undergoing treatment; and, to support those women whose clear cell cancer is terminal.

DES daughters are at increased risk for a rare cancer of the vagina or cervix, called clear cell cancer. So far, clear cell adenocarcinoma has been found in DES daughters between the ages of 7 and 42. Clear cell vaginal or cervical cancer, the “signature” cancer of DES, is linked to in utero exposure to DES. Typical treatment includes radical hysterectomy, vaginectomy, lymphadenectomy, and vaginal reconstruction. Radiation is often used with surgery. The current estimate is that one in 1,000 DES daughters are at risk for developing clear cell cancer. It is important that DES daughters and their physicians be aware that there is no specific age after which the risk for clear cell cancer is over. At this time the upper age limit for the development of the cancer is unknown.

Several issues related to DES exposure and clear cell cancer should be made a priority for research at NIH.

- What are the risks for DES daughters as they enter menopause?

- What are the benefits and risks of estrogen/hormone replacement therapy for women who were prenatally exposed to the synthetic estrogen diethylstilbestrol?

- Are DES daughters at increased risk of developing clear cell adenocarcinoma at perimenopause? Is there another incidence peak of clear cell cancer at menopause?

- Clear cell adenocarcinoma was known before DES in postmenopausal women. What might the experience of DES daughters be when they reach the age when clear cell had previously been diagnosed? Are we headed for an explosion of clear cell cancer cases?

- What are the best treatments for clear cell adenocarcinoma? Is surgery, chemotherapy, or radiation most successful?

- What is the an effective treatment for recurrences of clear cell cancer?

Mary Lynn Newport, M.D. *American Society for Surgery of the Hand*

The American Society for Surgery of the Hand identified three areas in women's musculoskeletal health that need further investigation. These include the study of distal radius fractures (Colles' fracture), carpal tunnel syndrome, and osteoarthritis of the basilar joint of the thumb.

Colles' fractures comprise approximately 10 percent of all adult fractures. Women are affected seven times more often than men. After fracture of the distal radius, the risk for fracture of the hip increases threefold, which has a nearly 25 percent mortality rate within 1 year of injury. Colles' fractures clearly are not a benign entity when considering the patient's overall health and there is significant upper extremity and lifestyle morbidity after sustaining such a fracture. There has been significant interest in treatment of the distal radius fracture itself, but almost no research in preventing these injuries or using them as a catalyst for treatment of the underlying osteoporosis and prevention of hip fracture.

Carpal tunnel syndrome, or compression of the median nerve in the wrist, is another upper extremity condition which preferentially affects women, with nearly 11 percent of all women living to age 70 suffering from this condition. There has been a great deal of research into treatment of the condition itself, especially the surgical decompression of the carpal canal, but almost no research into the underlying pathophysiology of the condition in an effort to prevent its occurrence.

Osteoarthritis of the basilar joint of the thumb in effect compromises the function of the entire hand. Nearly 50 percent of postmenopausal Caucasian women will suffer near complete destruction of the cartilage of this joint. A number of surgical treatments have developed for this condition but no research is currently being conducted to discern the cause of this condition or how this condition might be prevented.

These are all areas that significantly impact women's health, their family, and the economy. All deserve greater attention as we work to help prevent many of the conditions that today we can only incompletely treat.

Gloria J. Nichols, B.S.P., M.Ed., Ph.D. and
Catherine A. White, B.S.P., Ph.D. *College of Pharmacy, The University of Georgia*

New Priorities for Research on Women's Health in the Pharmaceutical Sciences

1. Gender-related analysis of medications; specifically the pharmacokinetic differences in the absorption, distribution, metabolism, and elimination of drugs and changes that occur during pregnancy and different phases of a women's life span.

2. Research on the considerations of the sociodemographic factors such as gender, age, race, socioeconomic status, ethnicity, and cultural background affecting quality-of-life measures and pharmacoeconomic studies in women and minorities.

3. Epidemiological research on disease patterns, health risk assessment profiles, and methodological developments in gender-related outcomes measurement. Health risk assessment focuses on the characteristics of the targeted population that are linked to behavioral and environmental risks, and the health consequences of exposure to those risks. Research is particularly needed to explore factors that lead to and result from exposure to adverse effects of drug entities as potential risks in women.

4. Research on the influence of hormonal factors on the course of specific diseases and disorders affecting women, along with the utility of using hormonal strategies as potential hormonal agents in treatment and patient management.

5. Outcomes research studies that relate to the clinical manifestations, risk factors, disease course and response in such disorders as osteoporosis, osteoarthritis, and fragility. Studies are needed on the markers of prognosis and followup on recent progress on biologic and genetic markers along with therapeutic management decisions to the disease potential.

6. Ongoing research for new developments in AIDS research and drug development. This will include an overview of the epidemiology of the disease state and the outcomes research for evaluating effective drug therapy protocols; successful medical interventions, and optimal economic and therapeutic options for the practice setting.

7. Research studies on the risk and benefits of hormone replacement therapy and new developments in terms of humanistic, economic, and quality-of-life parameters. Cross sectional, longitudinal, retrospective and prospective studies are needed. Different populations at risk, compliance, and followup, and the presence of concomitant risk factors and duration of HRT should be considered.

8. Cardiovascular disease research in women should include more demonstration projects on management strategies, including the use of group and educational programs for risk factor reduction, as well as indications for drug therapy and practice guidelines for hormone replacement therapy. Factors defining the high-risk patient (utilization of standardized guidelines), assessing and identifying women at high risk, and guidelines for utilization of therapeutic options need to be clarified.

9. Research that examines the physiologic and pathophysiological differences that are responsible for cardiovascular disease and altered drug responses that occur in minority populations and women.

10. Patient decisionmaking models and information systems, and computerized systems of on-line information services should be further developed, tested, and evaluated, for accuracy of information; their impact on knowledge and confidence; and their usefulness in patient education and compliance in the management of drug therapy.

Nancy J. Norton, B.S. *International Foundation for Functional Gastrointestinal Disorders*

Functional Gastrointestinal Disorders have not been adequately addressed in the research and patient care communities. Irritable bowel syndrome (IBS) is the most predominant of the functional gastrointestinal disorders.

Approximately 35 million Americans suffer from IBS. The symptoms of abdominal pain, bloating, constipation, diarrhea, and fecal soiling affect people from all walks of life. The fact that 75 percent of sufferers are female makes IBS a major issue in women's health.

IBS accounts for 20 to 50 percent of referrals to gastroenterology clinics. An IBS sufferer will miss an average of 13.4 days of work annually. It is a multibillion dollar problem.

Because of the risk of unnecessary surgery, the potential for misdiagnosis, and the use of unneeded diagnostic procedures, there is a pressing need to support education and research that will benefit both the public and the medical community.

IBS is a chronic disorder and continued scientific investigation is needed to understand the precise mechanism. In addition, it is necessary to study the patient to find the proper treatment that reduces symptoms and improves quality of life. A biopsychosocial understanding must be developed in order to advance behavioral and pharmacologic treatments.

Nancy L. Parsley, D.P.M. *American Podiatric Medical Association*

Podiatrists are keenly aware of the need for more research directed at foot ailments. Foot disorders represent a tremendous cost to the health care system. Foot pain and foot disorders not only drain vital health care dollars in a direct way, but their wider socioeconomic impact includes lost productivity as well as potential compromises to one's quality of life. This presentation addresses a variety of issues related to foot health and the substantial need for further research.

First, diabetes is a chronic disease afflicting approximately 16 million people in the United States, half of whom are unaware they have the disease. It is the fourth leading cause of death by disease in the United States. An estimated 15 percent of those with diabetes will develop an ulceration on the foot during their lifetime, and 20 percent of those ulcerations will lead to amputations. Existing data suggests that amputation rates are higher in males than females, but anyone with the disease faces potentially devastating consequences.

Women with a history of diabetes, especially those who developed it at a young age, undergo menopause early, which increases their risk of cardiovascular disease. One suggestion for counteracting the effects of early menopause is the development of a regular exercise program. The importance of proper foot care in adhering to a physical fitness program cannot be underestimated. We must study and understand better what the long-term effects of exercise on the feet are, especially in the presence of complicating illnesses such as diabetes. Diabetes foot pathology exists as the most common diabetic complication requiring hospitalization with approximately 70 percent of all diabetics experiencing some form of neuropathy. Greater concentration in the area of diabetes, specifically involving the prevention of foot deformities and complications must be a research priority.

Another area for focus involves the proper choice of footwear. The 1990 National Health Interview Survey concluded that foot problems were more commonly reported by females than males, and by Caucasians than blacks. The survey results demonstrate just how prevalent foot disorders are. A prevalence-to-incidence ratio of 83 percent was reported for corns and calluses; for bunions and arthritis of the toes, the ratio was in the vicinity of 90 percent. Bunions were found to be five times as common among females as males and arthritis of the toes was reported twice as often by females versus males. Other deformities of the toes or joint were also found to be twice as common among females as males. We need to explore how we account for these findings and how we address them.

In 1992, the APMA commissioned a survey on public attitudes towards foot care. The results of the survey revealed some disturbing trends. For instance, over half of the women interviewed admit to experiencing foot pain. Nearly one-third reported wearing shoes that are uncomfortable but look good. One-third of the women in the survey wore high heels despite the pain and the potential damage to their feet.

What are the long-term effects of these attitudes and trends? Does the society in which we live and function create unrealistic demands on women in their selection of appropriate footwear? To what degree does foot pain due to inappropriate shoe selection contribute to lost productivity on the job? Is foot pain compromising one's quality of life by preventing an individual from participating in a physical fitness program or desired social activities? To what extent might foot pain create undue stress that affects one's mental health? We recognize a connection between foot health and overall health status, but to what degree can improved foot health improve physical as well as mental health? These questions deserve consideration in assessing research needs and priorities. More research would allow us to treat foot disorders more effectively while enhancing preventive efforts.

Another area specific to women's health that deserves further investigation involves the effects of pregnancy on the feet. A study by Vullo, et al. found that lower extremity pain is more likely to be developed by pregnant and postpartum women compared to nulliparous women. Another study by Alvarez, et al. found that the mean volume of the feet increases by 57.2 milliliters between early and late pregnancy and decreases by only 8.42 milliliters between late pregnancy and 8 weeks postpartum. These changes were attributed to retention of fluid or to an increase in soft tissues. A better understanding of and appreciation for the effects of pregnancy on one's feet requires further study.

Consider also the role of women in sports. Women have consistently expanded their participation in sports at every level, not only at the collegiate and professional levels. As young children and adolescents, girls are encouraged to be participate in sports-related activities. Women are demonstrating athletic prowess in areas previously considered to be the sole domain of men. The long-term effects of these changes in attitudes and patterns of physical fitness are yet to be sufficiently explored.

Available evidence indicates an inverse association between physical activity and chronic diseases. The feet factor prominently in many forms of exercise and maintaining healthy feet is imperative to maintaining good health. But while the benefits of exercise are obvious, more research is needed to determine the effects of a variety of factors on the risks of exercise-related injuries as well as how to make more judicious choices on how best to achieve the benefits of exercise while preventing injuries.

Rheumatoid arthritis (RA) exists as another important area for investigation and research. Not only is the disease not well understood, but the prevalence in females is between 2:1 and 4:1 over males, depending upon the source. RA is incurable and its progression can lead to debilitating deformities which substantially affect a patient's quality of life. When the feet are involved, the presentation is most often in a symmetrical pattern. Additional research is needed to better understand the effects of RA in general and on the feet, in particular.

Considerations with an aging population deserve attention. Mobility is a vital ingredient of the independence that older people, in particular, cherish. Therefore, dedication of research dollars and research efforts in maintaining foot health should be a priority.

The APMA believes ORWH can offer important leadership in the research arena. Between 1994 and 1996, only 10 percent of the total dollars dedicated to podiatric medical research came from the Federal Government. The APMA and the podiatric medical colleges contributed a combined amount of almost 50 percent of the total research dollars. The wide disparity in research funding cannot continue if we are to address the specific needs of women in today's health care environment. If we are to fulfill our role in keeping America walking and maintaining foot health, we need to see noticeable increases in research dollars dedicated to these purposes. An investment of this type is guaranteed to have far-reaching and long-lasting benefits far into the future.

Kenneth A. Perkins, Ph.D. *University of Pittsburgh School of Medicine*

Need for New Directions in Research on Smoking Cessation in Women

The prevalence of tobacco smoking has declined gradually in the U.S. since publication of the first Surgeon General's Report on Smoking in 1964. However, this decline in smoking has not been equal across all smokers but has been attenuated in women compared with men. There has been evidence for several decades that women are less likely than men to successfully quit smoking. Some large-scale smoking cessation trials, especially those involving nicotine replacement therapy, suggest that women are less likely than men to initiate quitting and more likely to relapse if they do quit. Various explanations for the poorer success of smoking cessation efforts in women have been offered, including reinforcement in women of the influence of smoking on body weight or food intake control, reduced availability of social support for cessation in women, and greater impact of advertising on promoting smoking in women.

One possible explanation that has not received attention is that men and women may differ in the extent to which they smoke for nicotine reinforcement, as opposed to smoking for other, non-nicotine factors (e.g., other sensory effects of smoke inhalation, conditioned responses to smoke stimuli, secondary social reinforcement). Recent research suggests that: nicotine self-administration (i.e., reinforcement) is less robust in women; women may reduce their smoking to a lesser degree following nicotine pre-loading, and women may be less sensitive to subjective/mood effects of nicotine. In contrast, women may be more responsive to non-nicotine stimuli of smoking. These findings are consistent with other research indicating that women are less able than men to detect interoceptive stimuli (physiological changes) as well as some findings that women may be less sensitive to other drugs, such as cocaine.

Since many current smoking cessation efforts focus on nicotine replacement therapy (gum, patch, etc.), smokers who smoke less for nicotine reinforcement would be less likely to obtain therapeutic benefits from nicotine replacement strategies. Perhaps not surprising, a review of clinical research studies indicates that women are less likely than men to be successful in quitting smoking as a result of receiving nicotine replacement. Therefore, the most widely-used strategies for aiding smokers to quit are less effective in women, and new interventions that adequately address the consequences of quitting in women are needed.

In summary, based on current research, it appears that, relative to men, smoking behavior of women is reinforced less by nicotine intake and more by other, non-nicotine factors. These sex differences have important clinical implications; nicotine replacement may warrant a less important role in smoking cessation while interventions to counter non-nicotine aspects of smoking may need to be emphasized. Greater research on sex differences in nicotine effects and in new directions for smoking cessation treatment in women is warranted.

Jann Primus, Ph.D. *Associate Professor of Biology, Spelman College*

It is no secret that the U.S. educational enterprise is seriously underperforming. Distressing indicators include an alarmingly low level of scientific and technological literacy in the general population; a projected shortage of well-equipped scientists, mathematicians, and engineers; and severe inequities in the access of minorities and women to science and medical professional fields.

Data reveal that in 1973, minorities comprised only 8.3 percent of employed scientists and engineers. Two decades later, this figure had increased to only 17.5 percent. Analyses of rates of participation of blacks and Hispanics confirm a picture of severe underrepresentation in science and mathematics at all levels of our system of education as well as in the health professions.

In contrast to national trends, historically black, minority, and women's institutions have been the forerunner in recruiting, retaining, and successfully graduating women and minorities in the sciences at the baccalaureate level and have been successful in encouraging these underrepresented populations to enter professional schools and Ph.D. programs. These schools have in common a strong tradition of community. Community is what propels many minority graduates and graduates of women's colleges to successful careers. These settings warm the chilly climate for women and minorities so often noted at all levels of education in this country. Private liberal arts women colleges have been especially productive of women science and mathematics graduates and of women graduates who subsequently earn a doctorate in science or mathematics. Indeed, these colleges produce a higher percentage of women science graduates than any other nonspecialized category of institution.

The high concentration of black science and mathematics graduates in the historically black colleges and universities stands in sharp contrast to the almost complete absence of black graduates in science and mathematics at the vast majority of the nation's colleges and universities — this despite the fact that nearly all colleges and universities have black students.

The existence of effective learning communities in HBCUs is an important factor in the success of students in science, but it is not the only factor. In HBCUs, professors demand serious study and hard work, and they believe that deficiencies in background can be overcome. Promising students are encouraged to engage in research projects. As a result of high expectations by the faculty, students see success in science and mathematics as attainable, and therefore they can achieve.

The success of HBCUs and women's institutions in successfully nurturing, preparing, and graduating skilled scientists and health professionals is especially evident at Spelman College. Spelman's success in producing dynamic African-American women is most profoundly represented in the sciences. Before it was an issue of national concern, Spelman was building a strong science program with the goal of answering the needs of our nation and its business and educational communities.

Research and research training are an integral part of the Spelman College science program. Faculty at HBCUs are active researchers. We attempt to instill in our students a love and respect for research and investigation. As Spelman prepares for the new millennium, we do so with a strong appreciation of the role science and technology will play in determining our nations ability to compete and our responsibility to educate students who are equipped with the skills to meet these challenges. If Spelman College typifies the atmosphere of excellence that resonates on the campuses of our nation's HBCUs, then we can not underestimate the critical role HBCUs, minority and women's institutions will continue to play in providing our nation with dynamic future leaders in science and the health professions.

In sum, minorities and women increasingly emerge as a vital part of the human resources that our country depends upon to ensure its continued growth and well being. The AAMC has established a goal of enrolling 3,000 underrepresented minority students in U.S. medical schools by the year 2000. Current trends indicate that we will fail to achieve that goal. NIH, however, with a $12.7 billion annual budget, can lead the way in the federal sector to reverse this trend. We need additional programs targeted toward enhancing the capacity of HBCUs, minority, and women's institutions. We want to branch out into RO1 level research. We want to become meaningful partners, principal investigators, in the more than $12 billion in research that NIH funds each year through its 21 institutes. And we want to be in earnest conversation with NIH and other federal agencies to help set the nation's scientific research policy agenda.

In this way, we can be assured that populations who can most benefit — African Americans, minorities and women — are included in clinical trials, have options for experimental drugs, and that faculty from minority institutions are significantly involved in performing the investigations. We can also be assured that diseases and ailments that so disproportionately affect minorities and women — diabetes, hypertension, teenage pregnancy, low-birthweight babies, heart attacks, strokes, sickle cell anemia, kidney failure — are given adequate attention and funding.

Bette A. Rank and **Thomas M. Bruckman**

Bladder Health Council of the
American Foundation for Urologic Disease

The mission of the Bladder Health Council (BHC) of the American Foundation for Urologic Disease (AFUD) is to provide research, education, and awareness to the general public, patients, and health care providers nationally about bladder diseases and conditions. These include urinary incontinence, urinary tract infections, interstitial cystitis, and bladder cancer.

Urinary incontinence afflicts approximately 13 million Americans over 65, of whom 80 percent are women. The condition affects people of all ages and social and economic levels. Approximately 800,000 elder Americans living at home are beset severely enough to limit daily activities and become socially isolated. Urinary incontinence is one of the three major reasons for admittance to nursing homes. The economic impact of urinary incontinence among persons over the age of 65, including direct costs attributable to routine care and adverse consequences, and indirect costs incurred by the patient, spouse, or caregiver who loses the potential to earn wages elsewhere, totals $27.8 billion, or $3,941 per person.

A study on "Women and Incontinence" by Yankelovich Partners published in *Bladder Health Week* found that:

- A majority of women wait at least 1 year before discussing their condition with relatives, friends, or their physician.
- Most are hesitant to talk about incontinence, they are too embarrassed.
- Many curtail daily activities such as going to the store, taking walks, going on trips, and visiting friends.
- Generally urinary incontinence is accepted as a part of growing older.
- Numerous women surveyed stated that they were unhappy with their current treatment and were willing to try other options.
- Women were not satisfied with the care provided by their physician and would be willing to change physicians.

Better education for, research on, and treatment of women with urinary incontinence, especially at an earlier age, could lead to improved quality of life and ultimately lower health care costs.

Urinary tract infections (UTIs) are the number one urologic condition requiring approximately 1.6 million hospitalizations and 10 million physician visits each year, for a total cost of $4.4 billion. UTIs are an annoying problem. One in five women will visit their doctor at least once each year for relief from a UTI. Twenty-five percent of women who experience one infection will develop recurrent UTIs and 5 percent of these are infections caused by the same organism that caused the first infection. Young girls around 5 years of age may get a UTI; girls as they become sexually active may develop UTIs; and pregnant women can develop pyelonephritis during their third trimester. More than 20 percent of women over the age of 65 will experience asymptomatic bacteriuria and need to be carefully monitored. Bacteria in the urine can cause infection and inflammation of the bladder. If the bacteria travel upward from the bladder and reach the kidneys, a kidney infection may develop. Kidney infections are less common, but often more serious than bladder infections.

As many as one-half million people in the United States may suffer from interstitial cystitis (IC). Ninety percent of IC sufferers are women and the average age of onset is 40, with 25 percent of the cases under 30 years of age.

IC is a chronic inflammation of the bladder. The symptoms are pain and pressure in the bladder, urethra, and pelvic areas, as well as increased urinary urgency and frequency. People with IC experience urgency and frequency of urination. They suffer with immense pain in the bladder, lower abdomen, and urethra. The pain experienced has been described as feeling like paper cuts, razor blades, or acid in the bladder.

Cigarette smokers have an increased risk of developing bladder cancer. Exposure to certain chemicals in the workplace has also been associated with an increased risk. When found and treated in the early stages, even cancerous bladder tumors are not likely to spread and are not likely to be life threatening.

We encourage and support research and education of bladder diseases for women. Together we can make a difference toward improving quality of life for millions of women.

Vicki Ratner, M.D. *Interstitial Cystitis Association*

Interstitial cystitis (IC) is a chronic inflammatory bladder condition that affects approximately 450,000 people in the U.S., 90 percent of whom are women. Its cause is unknown and, at present, no treatments are uniformly effective. The symptoms are similar to an acute urinary tract infection, but urine cultures are negative and the symptoms do not respond to antibiotics. IC symptoms can vary from mild to severe and unrelenting pain, urgency and frequency of urination — up to 60 or more times in 24 hours. Although IC is not a fatal disease, suicides occur every year because of inadequate pain management.

Although IC was first described early in the 20th century, virtually nothing was done before 1994 to adequately address IC in terms of diagnosis, treatment or research. Only in the last ten years has IC been removed from the psychosomatic chapter in *Campbell's Urology*, the standard urologic textbook. 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 4½ years to get a correct diagnosis and often having to see an average of five physicians before IC is diagnosed.

IC symptoms are varied and not uniformly present in all IC sufferers. The severity of the pain, frequency, and urgency associated with IC can vary from reasonably manageable to unbearable, making it hard to classify as well as diagnose. No specific marker or test has been developed for IC, and it is considered largely a diagnosis of exclusion.

Because of its relentless demands on the body, IC can cause dramatic changes in the lives of people who suffer from it, making it difficult to maintain a job, making travel impossible, severely disrupting sleep, and making sexual intercourse extremely painful (many women abstain).

Since the founding of the Interstitial Cystitis Association (ICA) in 1984, much progress has been made in helping to create public awareness for the disease but much remains to be done.

1. Epidemiologic studies must be continued.
2. Basic science research, including identifying inflammatory mediators; etiology of IC; neuroinflammatory pathways in IC; pathology; endocrinological, hormonal and immunological aspects of IC.
3. Clinical trials of promising drugs.

4. Further analysis of the IC database, a 6-year project which will be completed in spring, 1998.
5. Developing better educational resources and outreach programs to educate patients and members of the medical community. Encouraging researchers to work in this area and establishing research fellowships in this area.

The American Academy of Orthopaedic Surgeons
The American Orthopaedic Foot and Ankle Society

Sally A. Rudicel, M.D.

The Orthopaedic Health of Women: Foot and Ankle Issues

Foot and ankle complaints are a common source of pain and disability in the United States. It is estimated that 43 million people in this country have foot complaints yearly. Fifteen million of these people will eventually seek medical help, and the majority of these people will be women.

Forefoot pain is a very common complaint in all age groups. In this country, however, problems of the forefoot occur in women seven to eight times more commonly than men. In a study of 356 healthy women between the ages of 20 to 60, a stunning 80 percent complained of foot pain. This same study found that 88 percent of these women were wearing shoes too small for their feet, and that 76 percent of these women had some foot deformity. The most common forefoot problems are bunions, bunionettes, hammer toes and neuromas, all of which occur disproportionately in women. These forefoot problems are a cause of pain and disability. As the deformities progress, surgery is often necessary. An estimated 75 percent of forefoot surgery in this country is necessary because of constrictive shoe wear. In 1995, approximately 285,000 bunionectomies, 300,000 hammertoes, 80,000 neuromas and 130,000 bunionettes were surgically corrected in the United States. If 75 percent of these procedures were caused by constricting shoewear, the estimated surgical cost for forefoot problems is $2 billion dollars. If time off from work is included, another 1.5 billion dollars in expenses is added. These figures are staggering and do not even address the morbidity to the patients suffering from these problems. All of this for high fashion footwear.

The American Orthopaedic Foot and Ankle Society and its Council on Women's Footwear has made major efforts to publicize this information and educate the public, the shoe retailers, and the shoe manufacturers. Consumers must be educated about this debilitating health problem. We also need to investigate more vigorous early preventative measures and look more critically at the benefits of surgery.

Education of appropriate shoe wear needs to begin in childhood, since we know that shoes have an effect on foot health. Education of parents as well as children about shoes is necessary. We also need further studies about changing shoe trends and the effects on the feet in the long term. In addition, some businesses have dress codes and requirements for women's shoes. We need to stress the health risk this imposes and work toward a change of such policies.

At the opposite end of the age spectrum, Carol Frey, M.D. has done some investigative work on the relationship of shoe wear to falls in the elderly. While a tie shoe is a safer shoe, Dr. Frey has found that even some athletic shoes may be a cause of falls because of large lugs which wrap around the toe area of running shoes. Also, outer soles which are wearing down, even on appropriate tie shoes, may cause a problem. More effort in exploring this source of injury in the rapidly expanding elderly population may bring huge benefits both in the health of the elderly and in better use of financial resources.

Rheumatoid arthritis is another entity with a predilection toward women. Women are affected three times more often than men. About 17 percent of cases of rheumatoid arthritis begin in the foot and the majority of patients will have foot problems during the course of their disease. Again, education and earlier intervention may prevent or lessen the formation of these severe deformities. More investigative work on the primary treatment of the disease may also prove helpful.

When the foot hurts, the entire body hurts, and activity is severely restricted. Foot pains and deformities are a common finding in all age groups as our studies show. Forefoot problems in particular, affect women seven to eight times more frequently than men. We need to look further into the causes of these problems, search for prevention and educate our population at an earlier age. The Office of Research on Women's Health can help us in the AAOS and AOFAS to play a leadership role in this important aspect of health.

Rosalie Sagraves, Pharm.D., F.C.C.P. *American Pharmaceutical Association*

APhA submits the following recommendations for specific areas in which the Office of Research on Women's Health can have a major impact.

Gender Differences in Drug Delivery. ORWH should work with (1) the FDA in implementing the latter's guidelines to ensure that women are included proportionately in future clinical studies, and that gender analysis be as complete as possible for labeling of commercially available products; (2) NIH to ensure that basic and clinical pharmacokinetic/pharmacodynamic studies are carried out. Regarding vitamins, pharmacokinetic/pharmacodynamic proposals should examine possible gender differences.

Women as Care Givers. Women are the primary care givers for their families. The workshop should end with recommendations to provide the tools women need to fulfill this function adequately. I applaud the FDA for identifying prescription medication use as an important women's health issue, and for taking the initiative to involve pharmacists and pharmacy students in educating women about their medicines and how to use them.

"Real-world" Research. Research recommended by ORWH could provide solid evidence that the cost to society of noncompliance and drug misadventure can be sharply decreased if pharmacy services are property structured and supported. APhA has created a Practice-Based Research Network (PBRN) of pharmacy practitioners who have the skills and interest to perform research studies at their practice site under the aegis of Principal Investigators

who may be either physicians or pharmaceutical scientists. Pharmaceutical manufacturers are exploring with APhA the possibility of using the PBRN in a variety of Phase IV studies. Recommendations from this workshop should take note that health professionals other than physicians are able to provide effective care in their respective areas of knowledge, while continuing to recognize that the physician leads the team of well-trained health care professionals. The issue of information exchange between professionals to smooth the continuum of care, particularly in light of emerging technologies, is an excellent example of an area for additional research.

Population-based Care. Recommendations should focus on the usefulness of population-based studies for reasons other than reducing costs. Managed care organizations in particular must be encouraged to share their databases with researchers to make these studies possible.

Self Care. The development of guidelines to help the consumer judge the quality and reliability of available information should be one outcome of your work.

Cost-effectiveness. Research on the fastest growing group of health care users — the oldest old, who use the most resources on a per capita basis as they near the end of their lives — should be emphasized. Focusing research on pharmacoeconomic issues clearly would do much more than merely cut costs. Outcomes and quality of life would be enhanced as well.

Charlotte (Barney) Sanborne, Ph.D. *Texas Woman's University*

Although wellness has been emphasized during the past 10 years, statistics show that women are choosing not to participate in a wellness lifestyle. ORWH postulates that inactivity and harmful behaviors lead females to be more vulnerable to diseases, to experience more severe maladies than men, and to be impacted by health problems that are unique to women. In fact, women can significantly reduce the risk of both cardiovascular disease and osteoporosis with regular physical activity and proper nutrition. Despite this information, approximately 40 percent of American adults lead a sedentary lifestyle. These patterns begin in childhood and are especially prevalent in females. Early onset of obesity (by age 6) relates to an increased chance of obesity as an adult. Furthermore, the psychosocial ramifications, such as being ostracized by peers, may contribute to an overweight child's low self esteem and poor body image.

Although principles for a wellness lifestyle have been established, involving people in the process of participating in healthy lifestyles is a completely different concern. Early detection and prevention health strategies are the keys to avoiding a lifetime of medical treatments and financial burdens. For success, this process must focus on prevention and be multifaceted, ongoing, include all ages, and remove significant barriers to health care resources.

Historically, the medical model emphasizes diagnosis and treatment over the larger picture of health maintenance throughout the life span. While this attitude is presently in a state of transition, it is still apparent in the health care policies and systems in the United States. Such a narrow perspective of health, coupled with the financial rewards and career advancement that may be associated with successful solutions to medical problems, invariably leads to lack of multidisciplinary collaboration.

We propose an interdisciplinary approach integrating primary and specialty care as the best way for medicine to focus on women as whole people. An interdisciplinary focus includes psychosocial factors as well as physical and biological factors. Research related to the health of women should encompass a more comprehensive design which includes a broad, carefully planned assessment of the influence of culture, other psychosocial factors, and the environment in which that community functions. Such designs should focus upon the community's potential (i.e., capacity-building factors). Further investigation should explore the mechanisms and realities of truly crossing disciplines, not simply collaborating across subspecialties within a discipline. True multidisciplinary research will bring together professionals involved in all levels of care, from prevention to diagnosis to treatment to education, to insure a whole person exploration of women's health.

Another specific research area that needs to be addressed is the impact of public policy on women's health. An example is the Welfare Reform Act of 1996 in which resources have been limited in an effort to decrease unwanted pregnancy. Research is needed to examine the impact of public policy on the health of not only the mother but also the far reaching implications on the fetus, baby, and child.

Barbara Seaman *National Women's Health Network*

Consumer Participation in Government-funded Research

There is a worldwide movement, gaining momentum, to include greater consumer participation in the concept, design, execution, and (perhaps) analysis of medical research, especially where taxpayer funding is involved. As an editorial by Alessanda Liberati (Mario Negri Institute, Milan, Italy) in the *British Medical Journal*, August 31, 1997 observes:

> *"The quality and relevance of much clinical research falls short of patients' needs....Even among progressive scientists and health professionals, a paternalistic attitude still prevails. They do not believe that patients and consumers can improve the decisionmaking process.....But successful efforts to shift the balance are becoming a reality, even in difficult areas such as oncology."*

I will briefly review the philosophies, ethics, and practical issues brought forward by advocates in these discussions, and provide the case history of a dispute between the National Women's Health Network and a past Director of NIH, where, as it turned out, our consumer perspective was the more accurate.

Diane K. Seay

National Association for the Advancement of Women in Science (NAAWS)
Girls and Mentors Manifesting Achievement (GAMMA) Project

The National Association for the Advancement of Women in Science (NAAWS) is a student organization chartered at the University of New Mexico (UNM). The organization provides an arena for scientists to share their work and the dynamics of career, school and family. Gloria Sarto, M.D., Ph.D., Professor, Department of Obstetrics and Gynecology, and Andrea Allan, Ph.D., Assistant Professor, Department of Neuroscience, UNM, and Ellen Goldberg, Ph.D., President, the Santa Fe Institute, are our advisors.

A review of the literature substantiated our realization that confidence and an interest in science is best fostered at an early age. Consequently, in spring 1995, the Girls and Mentors Manifesting Achievement (GAMMA) project was initiated. UNM women science students volunteered to mentor 5th and 7th grade rural school girls in small groups, generating and answering questions which follow the steps of scientific inquiry. Girls were selected from Los Lunas, New Mexico, a district that reflects the state of New Mexico in ethnicity. Intervention and control groups were set up. Initially no female 5th graders agreed to participate stating that science was "boring" and "for boys." At that point, it was determined that intervention should include younger girls, and a tiered mentoring system for 3rd, 5th and 7th graders was devised. At the conclusion of each year, students visit research laboratories of women scientists at UNM. A closing ceremony gives girls the opportunity to discuss their projects in front of peers, mentors, and supporters from UNM.

The GAMMA project would like to make the following observations:

1. Rural school girls need to be instructed in science by individuals who themselves have an interest in math and science. All students should be encouraged to think about scientific ideas and concepts in a manner which facilitates their teaching someone else.

2. Rural school girls need not only access to improved electronic methods for learning, but also, training in the use of these methods by individuals who are themselves comfortable with their capabilities.

3. Overall, awareness is heightened by such intervention methods regardless of whether the girls eventually take more science and math classes or choose math or science careers. Better methods to measure effectiveness of mentoring interventions need to be developed.

4. Rural school girls need increased exposure to women in science. We must continue to increase public awareness of women in science.

5. To generate an active rather than a passive interest in science and health issues for their future, rural school girls must be challenged to think and ask questions, to develop critical thought processes and perspective.

NAAWS would like to propose that women Ph.D. graduates in science be given the opportunity to teach science in elementary, middle, and high schools in rural areas and to receive credit toward student loans just as physicians and nurses who choose to work in rural areas do. Additionally, course credit could be given for graduate students to teach science in rural schools. In these ways an excitement for scientific inquiry would be fostered and maintained in the rural school setting. Finally, we would like to challenge every woman scientist to acknowledge the influential part she plays in the lives of girls and women she encounters. Your example and encouragement make a difference.

Wesley Segawa *Emory University School of Nursing*

The Malama Community Prenatal Care program, in Hilo, Hawaii, was developed as the focus of an NIH-NINR-funded research demonstration project (1990-1995) with Dr. Dyanne Affonso from Emory University in Atlanta, Georgia as principal investigator. The program aim was to deliver prenatal care to rural Hawaiian women living in the Hilo-Puna district on the Island of Hawaii and was expanded to two additional sites on Oahu in 1995. Originally titled "Malama Na Wahine Hapai," or Caring for Pregnant Women, this program was designed to be complementary to standard obstetrical care already available in each community and targeted Native Hawaiian, Filipino, and Japanese women who were identified as being at higher risk for delivering low-birthweight infants. Program mechanisms included: the establishment of a Neighborhood Women's Health Watch involving ethnic and cultural healers or elders; use of "mobile health stations"; organization of prenatal and postpartum services in collaboration with State of Hawaii, Department of Health public health nurses; and multiple community partnerships with local businesses, men's service organizations, and ethnic organizations such as the Ke Ola Mamo-Native Hawaiian agency. Mr. Segawa has been an active member of the Hilo community advisory board associated with the Malama program for the past 7 years.

Amanda Sherman *DES Action USA*

DES Action USA is a national nonprofit organization representing an estimated 10 million mothers, daughters, and sons exposed to the drug, diethylstilbestrol (DES). DES Action USA provides education and support to those exposed to DES, to increase public awareness about DES so that individuals can discover if they are exposed, and to educate medical professionals so they can provide knowledgeable services to DES-exposed people. We also seek to keep public attention on the story of DES as a reminder of the need for vigilance in regard to health care practices.

Eight years ago we at DES Action were alarmed to hear about the impending cutoff of funding for DES research at the National Cancer Institute. Some of the comments which circulated included the sentiment that DES-related cancer affects a very small number of women, a finite population. We also heard that while cancer of the vagina or cervix is certainly a tragic diagnosis, the DES experience represented an anomaly of history, with few applications for the larger society.

We were disheartened, though not entirely surprised, to hear this line of reasoning. We realized that DES Action had to accelerate our work and include a campaign to raise awareness about the following points. One, that DES exposure has resulted in many disastrous health outcomes, some still under investigation, in addition to cancer. These outcomes have affected many more women and men than DES-related cancer. And two, that the DES experience contains essential lessons relevant to the entire population in terms of the particular hazards of fetal exposure to estrogen and the powerful potential of endocrine disrupting chemicals. After all, those who have been exposed to DES have been the "canaries in the coal mine" for a number of very important health problems now coming to the fore.

With this in mind, DES Action launched a campaign that eventually not only restored and increased NCI funding, but also expanded research to include for the first time DES mothers and DES sons. In addition, the NCI has also broadened the scope of their inquiry to look at many other adverse health effects besides DES-related cancer. We now seek to answer many outstanding questions, such as the possible effect of DES on such bodily systems as the skeletal and immune system, and on the grandchildren of the women who were exposed to DES.

Eleanor G. Shore, M.D., M.P.H.

Dean for Faculty Affairs
Harvard Medical School

Program to Increase Representation of Women at all Ranks in Academic Medicine

One year ago, as Dean for Faculty Affairs at Harvard Medical School, I submitted public testimony about a new program to provide fellowship support for junior faculty at the most vulnerable point in their academic careers, i.e., when professional and personal responsibilities conflict. I documented the lack of adequate representation of women at the higher academic ranks both at Harvard Medical School and nationally. Today I would like to give you a 1-year followup regarding the early effects of this program on the junior faculty who were recipients of these fellowships. Private funding from alumni/ae, friends, hospital departments, affiliated institutions, and women faculty was secured to provide partial support for ten junior faculty members each year for 5 years. The $25,000 awards are intended to buy protected time in which the recipients can do research, prepare grant proposals, write papers, or develop a new curriculum. Or, if they are laboratory scientists, they can purchase the time of a research assistant. Men as well as women, may apply if they can demonstrate similar levels of conflicting personal responsibilities and obstacles to their academic work.

As of this fall [1997], ten junior faculty have completed their fellowships, and 11 more have begun theirs. More than 136 applications were submitted this year for the second round of fellowships. Each recipient is asked to complete a report at the end of the year's work.

At a meeting in October 1997, three fellowship recipients appeared on a panel to discuss in more detail the effects of their fellowships on their academic careers. The most compelling feature of their individual accounts was their description of the leverage the fellowship awards had produced. Department heads regarded their academic aspirations more seriously, protected time for academic activities was extended beyond the year of the actual fellowship, new collaborations materialized, and more departmental support was forthcoming for their research.

We have been particularly pleased to see that there has been a spin-off effect from this effort. A separately funded set of fellowships for basic scientists in the Faculty of Medicine at Harvard was announced with a particular emphasis on women applicants. Of the seven $50,000 fellowships offered in June 1997, four were awarded to women. Similarly, at an affiliated hospital in Boston, three fellowships were awarded to women with academic promise and these same obstacles to their academic careers.

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.

While these fellowships have already had a leverage effect for the recipients, they touch only a small fraction of the women and men who need help at this particular phase of their careers. The same problem is certainly occurring in academic medical centers all over the country. A nationally funded, competitive fellowship program that acknowledges this time-limited but serious problem when promising academic careers may be stifled without temporary support for academic activities, would go a long way toward strengthening the talent pool for future medical research and teaching. It would also help to diversify the senior faculty ranks by preventing the loss of junior women faculty who are well trained and motivated but temporarily in need of assistance to overcome the very real pressures created by the need to teach, do research, prepare manuscripts, submit grant proposals, and take care of patients at the same time they are beginning to assume greater family and other personal responsibilities. The country can not afford to lose this talent.

Amanda Spitler *American College of Rheumatology*

The American College of Rheumatology is an organization of physicians, health professionals and scientists that serves its members through programs of education, research and advocacy that foster excellence in the care of people with arthritis, rheumatic and musculoskeletal diseases. Many of these diseases — including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and Sjörgen's syndrome, as well as osteoarthritis and osteoporosis, affect women disproportionately compared to men. The reasons for this disparity are not well understood, but there is evidence that the reasons are not just hormonal, but may reflect gender differences at the genome level via control of gene expression. Our statement outlines the state of knowledge and future priorities in these women's health areas.

Osteoarthritis and rheumatoid arthritis, the most prevalent forms of arthritis, range from mild to severe and can cause pain, stiffness and tenderness in and around the joint. Research on the effects of certain antibiotics, particularly doxycyline, on the progression of osteoarthritis is an area of continued focus. Advancements in research on rheumatoid arthritis have also been made through the identification of the genes involved in its onset.

Lupus, an inflammatory, autoimmune disease characterized by excessive production of antibodies directed against the body's own tissue, affects women approximately nine times more often than men and strikes during their reproductive years. Research into the cause of lupus has focused primarily on the genetic susceptibility of individuals. Recent studies indicate that more than one gene may be involved in conferring susceptibility to lupus, emphasizing the complexity inherent in identifying the genetic basis of the disease.

Scleroderma is characterized by inflammation and excessive accumulation of the structural protein collagen, which leads to thickening or hardening of tissue, affecting women four times more often than men. In animal models, researchers have discovered a new cleavage site on the collagen molecule which may be an avenue for further development.

Osteoporosis, characterized by low bone mass, has recently come to the forefront of women's health due to the disproportionate occurrence of the disease in women compared to men. Unlike the aforementioned diseases, osteoporosis is a disease which is entirely preventable. Adequate calcium consumption, weight-bearing exercise, and an overall healthy lifestyle are a few ways in which this disease can be prevented. Perhaps the most significant ally in the fight against this disease is estrogen replacement therapy. Significant cost savings due to the fracture-sparing effect of hormone replacement therapy have been documented.

The ACR continues to support the efforts of ORWH in contributing to the NIH women's health research agenda.

Donna E. Stewart, M.D., D.Psych. *The Toronto Hospital, Ontario Cancer Institute*

Women's Health Program at the University of Toronto

The Toronto Hospital, Ontario Cancer Institute, (TTH, OCI) Women's Health Program focuses on seven priority areas: women and cancer, cardiovascular disease, neurosciences, organ transplantation, mental health/ eating disorders, and reproductive health. The program emphasizes research, education, and health care delivery and policy to adult women. The Joint Oncology Program with the Ontario Cancer Institute and Princess Margaret Hospital has added special strength to programs in cancer prevention, screening, diagnosis, treatment, and survivorship in women.

In 1996 the Women's Health Program at the University of Toronto obtained over $9 million dollars in research grants supporting studies in women's health. Research projects range from basic biological sciences to clinical projects including the context of women's health, decisional science, psychosocial behaviour, and quality-of-life concerns.

Our Informed Medical Decision Group in Women's Health with a core team from clinical epidemiology, health psychology, neurosciences, women's health, pharmacology, health administration, sociology, nursing, bioethics, obstetrics and gynecology, surgery, family medicine, internal medicine, anaesthesia, and oncology is central to our work. This group participates in quality-of-life studies, cost-effectiveness studies, the effects of drugs in pregnancy and lactation, drug side effects, health psychology, information needs, decisional sciences, choice and compliance, education, and postmenopausal health studies.

Current research grants involve women and cardiovascular disease and study gender differences in symptoms, presentation time, treatments and outcomes in tertiary and community hospitals. Cancer research involves gender differences in cancer information, decisional preferences, and quality of life. Studies in transplantation look at equal access to transplantation by women and whether women choose organ transplantation for the same reasons and frequency as men. Our neurosciences research includes projects on epilepsy in women and differences in cognition and choice. Autoimmune disease research covers the accelerated pace of arteriosclerotic disease in women with lupus erythematosis. Mental health research includes studies of depression, anxiety, eating disorders, and psychotropic drugs in women. Reproductive sciences research includes post menopausal health and decisional determinants of prevention and treatment, advanced reproductive technology, and psychosocial screening for pregnant women at risk for adverse postpartum outcomes. The Women's Health Program's information needs and concerns surveys, and decision studies have resulted in consultations to a number of local, national, and international groups.

Equally important to the Women's Health Program is educating health care professionals and policy makers. The Women's Health Symposia Community Education Series was inaugurated to address identified needs of public health education and consumer motivated research projects in women's health. The symposia have resulted in ten currently ongoing research projects. Improved clinical care and teaching in women's health are additional outcomes.

We have also been active in health provider curriculum reform for women's health including participation in the National Academy for Women's Health Medical Education, the American Association for Medical Colleges initiative on professional development for women and numerous international, and national presentations on women's health to professional audiences.

It is our belief that through consumer and professional education about women's health, women and their health care providers will become more knowledgeable and responsive to women's special needs. Research in women's health will further inform us of women's gender differences, preferences, and best practices. Our informed decisionmaking group is central to the delivery of health information to women and advocacy for them to participate in their desired degree of informed medical decisionmaking.

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

The American Association of Dental Schools (AADS) has a strong interest in promoting the advancement of women in the field of dental research, and identifying and representing women's issues is a priority for the association. Unlike the training of medical doctors, whose research training is a post-residency endeavor, financial disincentives as well as current legislation limiting research award programs make it difficult for many dental school graduates to pursue doctoral programs. In addition, medical research training programs are funded by a variety of sources, whereas the National Institute of Dental Research is the only predominant funding source that supports training for oral health research.

These problems faced by all dentists in pursuing research training are compounded for female dentists, especially since universities are the prime area for dental research and training. Although an increase in female enrollment in advanced dental programs is occurring, there is still evidence that women who are involved in oral health research are underrepresented in dental school faculties. Compared to other professions such as law and medicine, dental schools have a noticeably smaller percentage of professors at various levels who are women.

The AADS recommends several initiatives to provide for qualified female researchers in academic dentistry. These initiatives include programs which:

1. establish mentoring programs linking high schools to universities;
2. expand fellowship programs beyond basic research to include more clinical areas of oral health research;
3. increase the number of positions in specific training and research programs to accommodate the increasing pool of women dental graduates;
4. expand short-term research opportunities to simulate interest in research careers;
5. develop research grants for other advanced dental education programs beyond oral and maxillofacial surgery and oral pathology; and
6. provide supplemental research opportunities to women who must often interrupt their careers for family care responsibilities, especially as these women re-enter dentistry and wish to continue their research careers.

These initiatives will not only help more women contribute to advances in dentistry through research, but will also contribute to better oral health for all Americans.

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

Nearly 39 million people visited physicians for musculoskeletal conditions in 1995, of which almost 21 million patients were women. Orthopaedic surgeons see a large number of these patients. It is the hope of the American Academy of Orthopaedic Surgeons that this testimony will help the Office of Research on Women's Health accomplish its mission of increasing awareness of the importance of women's health, the nature of women's health issues, and the need for more research.

This testimony addresses what is known, the gaps in knowledge, and suggested future research directions about four conditions (prominent both by virtue of their prevalence and cost to society) that occur predominantly in women. Among the conditions seen most frequently in women are arthritis, osteoporosis, and sports injuries. Although not as prevalent as these three, frozen shoulder syndrome remains one of the most common, yet least understood conditions affecting shoulder mobility. Much information is known about these conditions, nonetheless, even more remains to be uncovered.

Further research on etiology, pathogenesis, diagnostic techniques, and treatment regimens will assist musculoskeletal care providers in providing the best possible care for their patients, both female and male.

Charlene Waldman *The Paget Foundation for Paget's Disease of Bone and Related Disorders*

The Paget Foundation for Paget's Disease of Bone and Related Disorders is a voluntary health agency which provides information and programs for consumers and medical professionals for a number of bone disorders involving abnormal bone resorption. One of the disorders addressed by the foundation is primary hyperparathyroidism, a hormonal problem which occurs when one or more of the parathyroid glands produce too much parathyroid hormone. When this happens, the blood calcium becomes elevated. Bones may lose calcium, and too much calcium may be excreted by the kidneys.

In the U.S. population, 28 out of every 100,000 people can be expected to develop hyperparathyroidism each year. Women outnumber men by three to one, and the frequency of the condition increases with age. Among women over age 60, new cases can be as high as 2 out of every 1,000 women or 2,000 out of every 1,000,000 annually.

A major complication of primary hyperparathyroidism is the weakening of bones due to loss of calcium, sometimes causing osteoporosis. Other complications include depression and kidney stones.

At present, the only known cure for this condition is surgical removal of the affected gland(s). Estrogen therapy may reduce some of the effects of the disease in women who have gone through menopause, but this treatment will not directly control the glandular overactivity. There are also some experimental drugs to control the elevated calcium but these are not approved for routine use.

Clinical studies are needed to acquire information about the natural history of the disease, the incidence of fracture, and other complications including the neuropsychiatric manifestations. Also, greater insight into the relationship between the hyperparathyroid process and postmenopausal bone loss is essential. Information is also needed on the course of patients who undergo parathyroid surgery as well as those who are followed conservatively. Additional studies will help to refine more clearly currently accepted guidelines for surgery versus medical management for primary hyperparathyroidism. Also, research is needed to study possible medical therapies.

Joanne A.P. Wilson, M.D., F.A.C.P. *American Gastroentrological Association*

I represent the American Gastroenterological Association (AGA), a professional society of 8,900 clinicians, researchers, and educators specializing in digestive diseases, and the Gastroenterology Women's Coalition (GWC), which is composed of women gastroenterologists from the AGA, American Society for Gastrointestinal Endoscopy, American Society for the Study of Liver Disease, and the American College of Gastroenterology. The GWC's mission is to promote the awareness of the impact of digestive diseases on women and to enhance research funding into the causes, treatment, and cures of these disorders. The GWC also works to promote gender diversity in the fields of gastroenterology and hepatology.

Gender-based differences have been well documented in a number of digestive diseases which affect Americans. I wish to highlight the advances that have been made in the study of these disorders, and the areas that need further investigation and should be included in the women's health agenda for the 21st century.

Colorectal Cancer. Colorectal cancer is the second deadliest cancer in the United States. It is the third leading cause of cancer death in women. In the coming year over 130,000 Americans will be diagnosed with colorectal cancer and over 50,000 will die from this disease. The risk for 65-year-old women for colon cancer is approximately the same as that of breast cancer. However, research dollars for investigation of this preventable cancer pale in comparison to that allotted for breast cancer research.

The AGA and a consortium of GI societies and governmental agencies have developed national practice guidelines for the screening and surveillance of colorectal cancer. The expert panels concluded that screening and surveillance regimens beginning at age 50 for average risk individuals and at a younger age for persons at increased risk are effective in preventing and curing colon cancer. This year Congress passed important legislation providing for Medicare coverage of colon cancer screening in the elderly. Our next task is to educate the public, especially women, physicians, and health care providers on the benefits of screening and surveillance and to encourage further research into epidemiological, prevention, and intervention strategies, including dietary and hormone replacement therapy.

Irritable Bowel Syndrome and Functional Bowel Disorders. Irritable bowel syndrome is twice as common in women as in men and affects up to 15 percent of the U.S. population. These disorders, which are associated with abdominal pain and bowel dysfunction, result in increased health care utilization and decreased work productivity and are one of the leading causes of absenteeism. Recent research has improved our understanding of these disorders. Additional research is needed into the effects of:

- menstrual cycle,
- predictors of chronicity,
- other etiologic factors that may contribute to the development of this disorder, and
- effective treatment and development of more specific agents for the treatment of these disorders.

Helicobacter Pylori and the Upper GI Tract. Great strides have been made in the treatment of peptic ulcer disease with the discovery of Helicobacter pylori. However, further research is needed to fashion more effective treatment and to explore gender differences with respect to the role of this organism in the development of gastric cancer.

NSAIDs and Peptic Ulcer Disease. Non-steroidal antiinflammatory drugs (NSAIDs) are also important causes of peptic ulcer disease in women. Further education of both women and men to the potential of side effects of these medications is needed.

Gallstone Disease. Gallstone disease is a major problem affecting approximately 10 percent of the U.S. population and is twice as common in women as in men. This increased prevalence is attributable to estrogens and progesterones on the liver and gallbladder, especially during pregnancy. Little is known of a natural history of gallstones in women as most of the histologic studies done in this country were performed in men. We need further research into the development and prevention of gallstones in women and outcome of treatment with regard to incidence, mortality and health costs.

Liver Disease. Disorders of the liver, such as primary biliary cirrhosis and other liver diseases, require further research particularly on the effects of estrogens on the immune system and metabolic research.

Many research questions regarding GI disorders in women deserve further study. I have highlighted the ones which are most notable for increased incidence in women, high health cost utilization and expenditures, and high morbidity and mortality.

I wish to emphasize the need for enhancing biomedical career opportunities for women. The GI societies and the AGA have supported career-mentoring in women and minorities. We encourage NIH to expand its support for mentoring and to encourage special academic tracks for women. We encourage academic institutions to adjust tenure and promotion policies to accommodate leaves of absence that may be necessary for parenting. I encourage institutions to fund programs to prepare women for senior administrative positions which will be so necessary as we advance into the 21st century.

Association of Women's Health
Ruth York, Ph.D., R.N., F.A.A.N. *Obstetric and Neonatal Nurses*

The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), an organization of 22,000 nurses and others committed to excellence in nursing practice for the health and health care of women and newborns, has a long-standing commitment to women's health research and the use of that research in practice.

As an organization, we support and conduct research endeavors that strengthen the scientific basis of nursing practice. We believe that research which seeks to improve the health of women across their life span, such as prevention of adolescent pregnancy, improved reproductive health, and enhancement of postmenopausal well being, is necessary and vitally important.

Research in women's health does not provide information about how the health of women in today's society can be optimized. In addition, inadequate access to primary preventive services, underrepresentation of women in clinical research trials, underutilization of research findings to support clinical practice and lack of information on the economic ramifications of women's health outcomes research are critical issues for all research conducted in women's health. Within the context of these issues research on adolescent pregnancy, violence against women, substance abuse, breast cancer, menopause, cardiovascular disease, are but some of the health problems that remain vital concerns to women, their families, and society.

- Research has had little impact on providing solutions to reducing the incidence of adolescent pregnancy. Clearly, unique and innovative research approaches are needed to address the issues of adolescent pregnancy and its multiple, negative-associated sequela.
- In the area of violence against women, delineating the factors which impede or facilitate women to resolve the abuse situation is critical and may vary for women of different ages, races, and ethnic groups. In the area of substance abuse, research has shown that the effect is gender dependent. Therefore, comprehensive investigations are needed to develop and test appropriate, cost-effective management strategies for substance-abusing women and their families.
- For the women diagnosed with breast cancer, research on treatment, sociocultural and behavioral concerns is essential. With advent of genetic testing, new and important areas for research will expand.
- Insufficient research has been conducted on clinical management of women's postmenopausal health concerns, such as use of hormone replacement therapy and other potential health altering intervention modalities.
- It has generally been assumed that management of cardiovascular diseases is the same for men as it is for women. However, new evidence strongly suggests that interventions which are gender specific must be developed and tested.

AWHONN supports research that focuses on health promotion and maintenance, as well as disease prevention, throughout women's life span; adequate representation of women in future studies of health problems; research on health problems that primarily affect women; and research on diseases with social origins with emphasis on development of gender-specific interventions.

APPENDIX

BEYOND HUNT VALLEY:
RESEARCH ON WOMEN'S HEALTH
FOR THE 21st CENTURY

DoubleTree Hotel Philadelphia
Philadelphia, Pennsylvania

September 25-27, 1996

AGENDA

WEDNESDAY, SEPTEMBER 25, 1996

PREMEETING ACTIVITIES: A PUBLIC HEARING

1:00-6:00 p.m. ***Public Testimony: The Women's Health Research Agenda for the 21st Century***
Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, NIH, and Director, ORWH

1. Continuing or Emerging Gaps in Knowledge About Women's Health
Task Force

2. Successful Models for the Recruitment, Retention, Re-entry, and/or Advancement of Women in Biomedical Careers
Task Force

6:00-7:30 p.m. ***Meeting with Task Force/Ad Hoc Working Group and Workshop Cochairs***
Dr. Pinn

THURSDAY, SEPTEMBER 26, 1996

WORKSHOP DAY 1
Continuing and Emerging Scientific Issues for Women's Health Research: Influence of Sex and Gender on Health

8:30 a.m. ***Workshop Welcoming Remarks and Overall Charge for the Conference***
Dr. Pinn

Introduction of Conference Cochairs

Donna Dean, Ph.D.
Acting Chief, Referral and Review Branch, Division of Research Grants, NIH

Marianne Legato, M.D.
Associate Professor of Clinical Medicine, Columbia University
College of Physicians and Surgeons

Introduction of Host Institution Cochairs

Jeane Ann Grisso, M.D., M.Sc.
University of Pennsylvania, School of Medicine

Bonita Falkner, M.D.
Professor of Medicine and Pediatrics, Institute for Women's Health
Allegheny University of the Health Sciences

Overview: Beyond Hunt Valley: Research on Women's Health for the 21st Century
Charge to Working Groups

Dr. Pinn
Task Force Cochairs

Logistical Instructions

Local Cochairs
Dr. Grisso
Dr. Falkner

9:45 a.m. ***Break***

10:00 a.m. ***Concurrent Breakout Working Groups***

Consider overarching health and issues of aging, chronic disease, the molecular bases for male/female differences in disease, behavioral and prevention strategies, risk factors for major health issues, gender, diversity, and the environmental impact on women's health.

GROUP 1. CARDIOVASCULAR DISEASE AND VASCULAR BIOLOGY
The role of gender in angiogenesis, vascular remodeling, cell structure/function, thrombosis. Linkage with sex hormones and cardiovascular disease, diabetes, stroke, obesity, and role of nutrition.

GROUP 2. NEUROSCIENCE AND BEHAVIOR
The role of sex/gender in neurodevelopment, CNS structure/function. Linkage with sex hormones and cognitive function, perimenopausal cognition, aging cognition, eating disorders, and the impact of environmental exposures in women.

GROUP 3. IMMUNOLOGY, GROWTH, AND DEVELOPMENT
The role of sex/gender in inflammation and immune response. Linkage with sex hormones, aging, arthritis, and lupus. Role of sex, gender, signaling, and growth factors.

GROUP 4. INFECTIOUS DISEASES AND EMERGING INFECTIONS
Role of sex/gender in the etiology, transmission, course, and outcomes of infectious diseases, including HIV, STDs, and others involving emerging pathogens, with a focus on improved prevention, diagnosis, and treatment for women.

GROUP 5. MENTAL AND ADDICTIVE DISORDERS
The role of sex/gender in the etiology, course, comorbidity, and outcomes of mental and addictive disorders, including sex hormones, genes, gene-environment interactions, gender-related risk behaviors, depression, and eating disorders.

GROUP 6. REPRODUCTIVE HEALTH
Research to address life-span issues including research on contraception (development, use, and post marketing evaluation), (IOM report), as well as the influence of contraceptive choice on infertility, STDs, (IOM report), acute and chronic conditions, and lifestyle. Consider particularly implantation, maternal issues, prevention, diagnosis, treatment of pregnancy complications and embryo or fetal loss and reducing morbidity from myoma, endometriosis, abnormal uterine bleeding, uterine prolapse, and other benign gynecologic diseases. Address hormone replacement therapy, menarche, menopause, postmenopausal issues, and cultural, ethnic, socioeconomic, and behavioral issues.

GROUP 7. CANCER
Address basic science, genetics, gender differences, and environmental factors contributing to mortality in breast, lung, colon, and gynecological cancers to understand the malignant processes and to lead to improved prevention, diagnosis, and treatment. Consider female populations that bear a disproportionate burden of cancer incidence and mortality. Ethical, legal, and social implications of new technologies including screening and genetic testing.

Noon ***Lunch Remarks***
Jo Ivey Boufford, M.D.
Principal Deputy Assistant Secretary for Health
U.S. Department of Health and Human Services

1:30 p.m. ***Working Groups (continued)***

3:30 p.m. ***Break***

3:45 p.m. ***Plenary Keynote Speaker***
Nancy Wexler, Ph.D.
Higgins Professor of Neuropsychology, Columbia University

4:15 p.m. ***Working Group Summary Reports***

5:30 p.m. ***Adjourn***

6:00 p.m. ***Reception***

FRIDAY, SEPTEMBER 27, 1996

WORKSHOP DAY 2

Continuing and Emerging Scientific Issues for Women's Health Research: Research Strategies

8:30 a.m. ***Kickoff Speaker***

Ruth L. Kirschstein, M.D.
Deputy Director, NIH

9:00 a.m. ***Plenary Session***

Models for the Conduct of Research on Women's Health: Research Strategies and Methods

9:30 a.m. ***Charge to the Working Groups: The Future for Women's Health Research***

9:45 a.m. ***Break***

10:00 a.m. ***Concurrent Breakout Working Groups***

Consider overarching issues of life span, aging, prevention, diversity, and collaborative and multidisciplinary approaches. The impact of managed care, informatics, and what is ready for testing and commercial application should be considered as well as socioeconomic, cultural, and sex/gender factors in the identification of unique barriers for:

A. RESEARCH DESIGNS

1. *Multidisciplinary Perspectives:* How can synergy between scientific disciplines be achieved through a multidisciplinary perspective that incorporates biomedical, psychosocial, and socioeconomic approaches to women's health research?

2. *Cultural Diversity:* How can diverse communities of women participate actively in helping set research priorities, participate in clinical studies, and, most importantly, benefit from the implementation of the outcomes. Communities refer to different levels of social organization, from families to neighborhoods, and to other forms of community. How can cultural and socioeconomic factors be differentiated from race and incorporated into the study of health and disease of women? Culture refers to shared values and beliefs about the world. Epidemiologic analyses of health outcomes in diverse populations should also be addressed.

3. *Gender:* What are the best ways of conceptualizing and studying similarities and differences between males and females? As examples, effects might be due to genetics, sex-related hormones, gender role socialization, and disparities in power and status in society between women and men.

B. HEALTH IMPACT AND HEALTH OUTCOMES

1. *Biotechnical Advances:* How can advances in biotechnology be incorporated into clinical care and health professional education programs for women's health, including prevention, screening, and treatment? The role of gender in access to care, diagnostic and therapeutic interventions, and patient-provider communication should be considered. What are the ethical, legal, and social issues? How can the diverse community of women benefit from state-of-the-art research?

2. *Gender Differences:* How can knowledge of gender differences across the life span be applied to preventative interventions? Consideration should be given to what constitutes successful life course transitions (entrance to school, adolescence, entrance to parenthood, widowhood).

C. WOMEN IN BIOMEDICAL CAREERS: ISSUES OF IMPORTANCE FOR YOUNG INVESTIGATORS

Positive ways to advance women's careers through training, leadership opportunities, and mentorship. What are successful examples of recruitment, retention, re-entry, and advancement?

12:15 p.m. ***Break***

12:30 p.m. ***Lunch***

Keynote Speaker

Karen Davis, Ph.D.
President, The Commonwealth Fund

1:45 p.m. ***Plenary (Working Group Reports)***

3:30 p.m. ***Closing Remarks and Adjournment***

Dr. Pinn

PHILADELPHIA, PENNSYLVANIA
SEPTEMBER 25-27, 1996

PARTICIPANTS

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BEYOND HUNT VALLEY:
RESEARCH ON WOMEN'S HEALTH
FOR THE 21st CENTURY

Sheraton New Orleans Hotel
New Orleans, Louisiana

June 11-13, 1997

AGENDA

WEDNESDAY, JUNE 11, 1997

PREMEETING ACTIVITIES: PUBLIC HEARING

11:00 a.m. ***Working Meeting/Lunch***

Task Force
Advisory Committee
Local Hosts
Planning Committee
Rapporteurs

1:00-5:00 p.m. ***Public Testimony: The Women's Health Research Agenda for the 21st Century***

Welcome and Introductory Remarks

Dr. Vivian W. Pinn
Dr. Ann Anderson

I. ***State of Knowledge in Women's Health Across the Life Span***
II. ***Sex and Gender Differences — Impact on Women's Health***
III. ***New Priorities for Research on Women's Health***
IV. ***Environmental, Genetic, Hormonal, Nonhormonal, and Other Factors that Impact on Women's Health***
V. ***Career Issues for Women Scientists and How To Overcome Barriers***

5:15-6:00 p.m. ***Meetings/Interviews with Testifiers, Participants, and Local Press***

6:00-7:30 p.m. ***Meeting with Task Force/Ad Hoc***
Working Group and Cochairs
Local Hosts
Working Dinner

Dr. Vivian W. Pinn

THURSDAY, JUNE 12, 1997

SCIENTIFIC WORKSHOP DAY 1

Physiological, Psychosocial, and Pharmacologic Differences Between Women and Men

8:30 a.m. ***Opening Plenary Session***

Dr. Vivian W. Pinn

Welcoming Remarks and Introductions

Dr. Judith LaRosa
Dr. John Estrada
Ms. Sybil Morial

Comments

Dr. John LaRosa
Chancellor, TUMC

9:00 a.m. ***Overview: Beyond Hunt Valley: Research on Women's Health for the 21st Century***

Dr. Vivian W. Pinn

9:30 a.m. ***Plenary Address — Is It All Steroidal Sex Hormones?***

Dr. Michael Lockshin

Moderator

Dr. John Estrada

10:00 a.m. ***Break***

10:30 a.m. ***Panel Discussion: Physiological, Psychosocial, and Pharmacologic Differences Between Women and Men***

Moderator

Dr. Shiriki Kumanyika

Physiological Differences Between Women and Men

Dr. Marianne Legato

Psychosocial Differences Between Women and Men

Dr. Vickie Mays

Pharmacologic Differences Between Women and Men

Dr. Raymond Woosley

Biological homogeneity exists. Similarly, differences exist, especially between the sexes. For too long these differences were not appreciated — from the most basic cellular level to the vast expanse of behavior. What's the same and what's different? How do the differences affect research design and execution; health status; health care?

12:00 p.m. ***Charge to the Working Groups***

Dr. Marianne Legato
Dr. Donna Dean

12:30 p.m. ***Lunch***

1:30 p.m. ***Breakout to Working Groups***
    Prenatal, Infancy, and Childhood Years (prenatal to puberty)
    Adolescent Years (puberty to 18 years)
    Reproductive and Middle Years
    Perimenopausal and Postmenopausal Years
    Elderly and Frail Elderly Years (65+)

3:30 p.m. ***Break***

4:15 p.m. ***Working Group Interim Reports***
    Dr. Marianne Legato
    Dr. Donna Dean

5:30 p.m. ***Adjourn***

6:00 p.m. ***Reception***
New Orleans Jazz Reception — Tulane/Xavier Center for Bioenvironmental Research

FRIDAY, JUNE 13, 1997

SCIENTIFIC WORKSHOP DAY 2

9:00 a.m. ***Comments***
    Dr. Vivian W. Pinn

9:15 a.m. ***Plenary Address: Emerging Issues in Research: Environment, Genetic/Genomic, and Hormones***
    Dr. John McLachlan

Moderator
    Dr. Terry Damstra

10:30 a.m. ***Break***

10:45 a.m. ***Concurrent Working Groups (continue)***

12:00 noon ***Break***

12:15 p.m. ***Lunch***
Introduction
    Dr. Judith LaRosa

Speaker
    The Honorable Lindy Boggs

1:30 p.m. ***Working Group Reports***
    Dr. Marianne Legato
    Dr. Donna Dean

3:00 p.m. ***Closing Remarks/Adjourn***
    Dr. Vivian W. Pinn

NEW ORLEANS, LOUISIANA
JUNE 11-13, 1997

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BEYOND HUNT VALLEY:
RESEARCH ON WOMEN'S HEALTH
FOR THE 21ST CENTURY

Santa Fe Hilton Hotel
Santa Fe, New Mexico

July 21-23, 1997

AGENDA

Sponsored by:	***Office of Research on Women's Health*** ***National Institutes of Health***
Hosted by:	***University of New Mexico*** ***School of Medicine*** ***University of Iowa*** ***College of Pharmacy***

MONDAY, JULY 21, 1997

PUBLIC HEARING DAY 1

9:00-11:00 a.m. ***Meeting***
  Task Force
  Working Group Cochairs
  Rapporteurs

1:00-2:40 p.m. ***Public Testimony: Women's Health Research for the 21st Century***
  I. Continuing or Emerging Gaps in Knowledge About Women's Health Across the Life Span
  II. Population Differences: Race, Culture, and Ethnicity and Their Impact on Women's Health
  III. Women with Special Health Concerns: Recommendations for Future Research
  IV. Career Issues for Women Scientists

2:40-3:00 p.m. ***Break***

3:00-5:00 p.m. ***Public Testimony continues***

TUESDAY, JULY 22, 1997

SCIENTIFIC WORKSHOP DAY 2

Special Populations of Women: Factors Impacting Health and the Scientific Research Agenda

7:00 a.m.-6:30 p.m.	***Conference Registration***
7:00-8:00 a.m.	***Continental Breakfast***
8:00 a.m.-12:00 p.m.	***Opening Plenary Session***
8:00-8:20 a.m.	***Opening Remarks*** Dr. Vivian W. Pinn ***Welcoming Remarks*** Dr. Gloria E. Sarto Dr. Mary J. Berg
8:20-8:50 a.m.	***Overview: Beyond Hunt Valley: Research on Women's Health for the 21st Century*** Dr. Vivian W. Pinn
8:50-9:10 a.m.	***The Health of Special Populations of Women: Implications for Research*** Dr. Gloria E. Sarto
9:10-10:15 a.m.	***Panel Discussion: Definitions of Race, Culture, and Ethnicity*** ***Moderator*** Dr. Vanessa Gamble ***OMB: Current Activities*** Ms. Katherine Wallman ***Anthropological Perspectives*** Dr. Louise Lamphere ***Comments: Implications for NIH-Funded Research*** Dr. Belinda Seto Dr. Otis Brawley ***Discussion***
10:15-10:30 a.m.	***Break***
10:30-11:30 a.m.	***Panel Discussion: Impact of Traditional and Cultural Health Practices*** ***Introduction*** Dr. Gloria Sarto ***Co-Moderators*** Dr. Linda Burhansstipanov Dr. Amelie Ramirez

Asian
Dr. Barbara Yee

Hispanic
Dr. Helen Rodriguez-Trias

Hawaiian
Dr. Carol Korenbrot

African American
Dr. Marcia Bayne-Smith

Doctor-Patient Relationships
Dr. Marianne Legato

11:30-11:55 a.m. ***Discussion***

11:55 a.m.-12:00 p.m. ***Charge to Working Groups***
Dr. Marianne Legato
Dr. Donna Dean

12:00-1:15 p.m. ***Lunch***
Introduction of Speaker
Dr. Amelie Ramirez

Traditional Mexican Folk Medicine and Folk Beliefs: Their Influence in the Southwest
Dr. Eliseo “Cheo” Torres

1:30-4:15 p.m. ***Convening of Working Groups by Life Span***
Prenatal Years
Infancy and Childhood Years
Adolescent Years
Reproductive and Middle Years
Perimenopausal Years
Postmenopausal Years
Elderly and Frail Elderly Years
Career Issues for Special Populations of Women Scientists

4:15-4:30 p.m. ***Break***

4:30-6:15 p.m. ***Plenary Session***

4:30-6:15 p.m. ***Panel Discussion: Cancer Genetics and Its Implications for Different Populations of Women***

Moderator
Dr. Karen Antman

Breast Cancer Genetics
Dr. Barbara Weber

	Breast Cancer Epidemiology Dr. Elizabeth Schubert
	Decision Analysis Dr. Deborah Shrag
	Ethics Dr. Joan Gibson
	Genetic Counseling Ms. Stephanie Smith
	Discussion
6:15 p.m.	***Adjourn***
6:30 p.m.	***Networking Reception — Native American Dance Program***

WEDNESDAY, JULY 23, 1997

SCIENTIFIC WORKSHOP DAY 3

7:00-8:00 a.m.	***Continental Breakfast***
8:15-9:30 a.m.	***Plenary Session***
8:00-8:15 a.m.	***Opening Comments*** Dr. Vivian W. Pinn
8:15-8:45 a.m.	***Introduction of Speaker*** Dr. Mary J. Berg ***Psychosocial, Behavioral, and Educational Factors that Affect Population Differences in Health Among Women*** Dr. Norman Anderson
8:45-9:00 a.m.	***Discussion***
9:00-9:15 a.m.	***Introduction of Speaker*** Dr. George Bryan ***Health Issues for Women with Disabilities*** Ms. Carol Howland
9:15-9:30 a.m.	***Discussion***

9:30-9:45 a.m. ***Break***

9:45 a.m.-12:00 p.m. ***Concurrent Working Groups (continue)***

12:15-1:15 p.m. ***Lunch***
Introduction of Native American Cultural Program
Dr. Linda Burhansstipanov

Where Tradition Meets Science: Traditional Practices in Conflict with Western Medicine
Dr. Tieraona Low Dog

1:15-2:30 p.m. ***Closing Plenary Session***

1:15-2:25 p.m. ***Plenary: Working Group Reports***
Working Group Cochairs

Discussion

2:25-2:30 p.m. ***Closing Remarks/Adjourn***
Dr. Vivian W. Pinn

SANTA FE, NEW MEXICO
JULY 21-23, 1997

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Putting It All Together: The Agenda for Research on Women's Health for the 21st Century

Bethesda Marriott
Bethesda, Maryland

November 17-19, 1997

AGENDA

MONDAY, NOVEMBER 17, 1997

11:00 a.m.-7:00 p.m. ***Conference Registration***

PUBLIC HEARING

1:00-6:00 p.m. ***Public Testimony: The Women's Health Task Force Research Agenda for the 21st Century***

TUESDAY, NOVEMBER 18, 1997

SCIENTIFIC WORKSHOP DAY 1

7:00 a.m.-6:30 p.m. ***Conference Registration***

7:00-8:00 a.m. ***Continental Breakfast***

8:00 a.m.-12:00 p.m. ***Opening Plenary Session***

8:00-9:00 a.m. ***Welcome and Opening Remarks***
Vivian W. Pinn, M.D.
Ruth L. Kirschstein, M.D.

Remarks
The Honorable Barbara A. Mikulski, U.S. Senate
The Honorable Constance A. Morella, U.S. House of Representatives

9:00-9:30 a.m. ***Overview: Beyond Hunt Valley: Research on Women's Health for the 21st Century***
Vivian W. Pinn, M.D.

9:45-10:00 a.m.	***Break***
10:00-11:00 a.m.	***Scientific Plenary Session I*** ***Genetics, Genomics, and Women's Health*** Francis Collins, M.D., Ph.D. Director, NHGRI ***Panel Discussion: Legal and Ethical Issues*** Karen Rothenberg, J.D. John Fletcher, Ph.D. Robert Murray, Ph.D.
11:00-11:45 a.m.	***Scientific Plenary Session II*** ***Heart Disease Research in Women: A Look Back and a View to the Future*** Claude Lenfant, M.D., Director, NHLBI ***Remarks: Research on Women: An Investigator's View*** Julie Buring, Sc.D. ***Charge to the Working Groups*** Donna Dean, Ph.D. Marianne Legato, M.D.
12:00-1:15 p.m.	***Lunch*** ***Speaker: The Cancer Program at the End of the 20th Century*** Richard Klausner, M.D., Director, NCI
1:30-4:15 p.m.	***Breakout to Working Groups*** ***Alcohol and Other Drug Use Disorders and Consequences*** ***Bone and Musculoskeletal Disorders*** ***Cancer*** ***Cardiovascular and Pulmonary Disease*** ***Career Issues for Women Scientists*** ***Digestive Diseases*** ***Immunity and Autoimmune Diseases*** ***Mental Disorders*** ***Neuroscience*** ***Oral Health*** ***Pharmacology*** ***Reproductive Issues*** ***Urologic and Kidney Conditions***
4:30-6:00 p.m.	***Scientific Plenary Session III*** ***Panel Discussion: Women's Health Research*** ***Women and Research: Quo Vadis?*** Antonia C. Novello, M.D., M.P.H.

Beyond Hunt Valley: Perspectives
Maureen Henderson, M.D., M.P.H.

Implications for Education and Public Policy
Barbara Ross-Lee, D.O.

Remarks
Audrey T. Haynes, Deputy Assistant to the President
White House Office for Women's Initiatives and Outreach

6:00-7:30 p.m. ***Networking Reception***
The Honorable Louise M. Slaughter, U.S. House of Representatives

WEDNESDAY, NOVEMBER 19, 1997

SCIENTIFIC WORKSHOP DAY 2

7:00-8:00 a.m. ***Continental Breakfast***
8:00-9:00 a.m. ***Scientific Plenary Session IV***
Speaker: Women in Biomedical Careers
Lydia Villa-Kamaroff, Ph.D.

Remarks: Women in Health — Towards a New Paradigm
Margaret Chesney, Ph.D.

9:00 a.m.-12:00 p.m. ***Concurrent Working Groups (continue)***

12:00 p.m. ***Lunch***
Remarks
The Honorable Louis Stokes, U.S. House of Representatives

Speaker: Putting It All Together
Byllye Avery, M.Ed.

1:15-3:00 p.m. ***Closing Plenary Session***
Working Group Reports
Working Group Cochairs
Task Force Cochairs

Discussion
Closing Remarks/Adjournment
Task Force Cochairs
Vivian W. Pinn, M.D.

3:15 p.m. ***Press Briefing***

BEYOND HUNT VALLEY:
RESEARCH ON WOMEN'S HEALTH FOR THE 21ST CENTURY

BETHESDA, MARYLAND
NOVEMBER 17-19, 1997

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