

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*

SEX AND GENDER PERSPECTIVES
FOR WOMEN'S HEALTH RESEARCH

NATIONAL INSTITUTES
OF HEALTH
Office of the Director

*Scientific Meeting and Public Hearing
New Orleans, Louisiana
June 1997*

5

VOLUME

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Hosted by:

Tulane University Medical Center

Xavier University

Meharry Medical College

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P R E F A C E

In September 1991, the Office of Research on Women's Health (ORWH) of the National Institutes of Health convened a meeting in Hunt Valley, Maryland, to assess the state of the science of women's health and to develop an agenda to guide women's health research in the coming decade. The report generated by that meeting, *Report of the National Institutes of Health: Opportunities for Research on Women's Health*, set forth the research recommendations developed by working groups focused on the major divisions of a woman's life span and on scientific issues, diseases, and conditions that affect women's health. That report has served as the broad blueprint for women's health research at the National Institutes of Health.

Now, several years later, science has continued to expand the parameters of knowledge, generating additional questions and pursuits. New public health issues and challenges emerging in the field of women's health have demonstrated a need to re-examine and update the national agenda for women's health research. To advance this concept, ORWH began a process to identify continuing or emerging gaps in knowledge and to develop research-based strategies that will result in improved health status for all women. This process included holding a series of public hearings and scientific workshops.

The first regional conference was hosted by the University of Pennsylvania School of Medicine and Allegheny University of the Health Sciences in Philadelphia in September 1996. It focused on sex and gender issues and their impact on research in women's health; gaps in knowledge about women's health; and successful models for the recruitment, retention, re-entry, and advancement of women in biomedical careers. The second regional meeting — hosted by Tulane University Medical Center, Xavier University of Louisiana, and Meharry Medical College — was held in New Orleans in June 1997. The New Orleans meeting focused on sex and gender perspectives for women's health research. The third in the series was held in Santa Fe, New Mexico, in July 1997, and was hosted by the University of New Mexico School of Medicine and the University of Iowa College of Pharmacy. The Santa Fe meeting focused on differences among populations of women, factors that contribute to differences in their health status and health outcomes, and career issues for special populations of women. The final, national meeting, convened in Bethesda, Maryland, in November 1997, and subtitled, *Putting It All Together, The Agenda for Research on Women's Health for the 21st Century*, reviewed the deliberations and recommendations

from the three regional public hearings and scientific workshops and developed the recommendations and priorities for updating the women's health research agenda. All the meetings included an opportunity for public testimony as well as formal scientific sessions. Practitioners interested in women's health; representatives from scientific, professional, and women's health organizations; and women's health advocates participated in the process and continue to provide guidance and expertise to ORWH.

The information presented in this volume represents the outcome of the New Orleans regional meeting — the scientific workshops, the plenary presentations, and the public testimony by individuals representing themselves or organizations with an interest in biomedical and behavioral research on women's health, within the mandate of the National Institutes of Health.

Additional volumes in this series consist of scientific workshop reports, presentations by distinguished scientists, and public testimony presented at the regional meetings in Philadelphia and Santa Fe and at the national meeting in Bethesda.

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

The Office of Research on Women's Health wishes to acknowledge the contributions of the following individuals in planning this regional public hearing and scientific workshop held in New Orleans, and for their assistance in bringing this meeting to fruition.

Our regional cochairs for this meeting included Dr. Judith H. LaRosa, Professor and Chair of the Department of Applied Health Sciences at the Tulane University School of Public Health and Tropical Medicine. Dr. LaRosa also served as the first Deputy Director of the Office of Research on Women's Health at NIH. Second is Dr. John J. Estrada, who is a member of the national Advisory Committee on Research on Women's Health at NIH and an Assistant Professor of Pediatrics and Microbiology at Meharry Medical College, where he also serves as Director for Pediatric Education and Chair of the Faculty Senate. We are pleased to have with us Mrs. Sybil Haydel Morial, Associate Vice President for Public Affairs and Communications at Xavier University of Louisiana, also a valued cosponsor of this meeting. Additional people who were instrumental in planning this public hearing and scientific workshop were Dr. Anne Anderson, Melinda Epperson, and Roz Lewy of the Tulane University Medical Center.

It was a great pleasure to have with us Dr. John LaRosa, Chancellor of the Tulane University Medical Center. In addition to his current esteemed position, Dr. LaRosa has long been in the forefront of research on women's health and health care, being an internationally recognized expert on cholesterol, coronary disease, and cardiovascular disease in women. He is also the former Dean for Clinical Affairs and Dean for Research at The George Washington University School of Medicine and Health Sciences in Washington, D.C.

This meeting was planned with the assistance of a great number of other individuals. Of our ORWH office staff, let me first acknowledge Ms. Joyce Rudick, who is the Acting Deputy Director of our Office, and who has tirelessly devoted her leadership to the development and implementation of these meetings to revise our research agenda. She has provided the heart and soul, as well as the elbow grease, to make these meetings occur, and to her we owe a special appreciation.

Our efforts to revisit our research agenda were led by our Task Force on the NIH Women's Health Research Agenda for the 21st Century. We were 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.

Our Task Force, which oversaw this workshop and the report generated from it, was cochaired by Dr. Donna Dean and Dr. Marianne Legato; we are so grateful for their dedicated leadership. Dr. Donna Dean, Acting Chief of the Referral and Review Branch, Division of Research Grants at NIH, is a member of the Coordinating Committee for Research on Women's Health, the advisory body to our office, which is composed of the Directors or their designee of the institutes, centers, and divisions of NIH. Dr. Dean is also Chair of the Research Subcommittee, which provides guidance to our office about our priorities and funding programs. Dr. Marianne Legato, who is a member of our Advisory Committee on Research on Women's Health and a noted expert on cardiovascular diseases of women, has recently established a center for women's health at Columbia University College of Physicians and Surgeons.

I would also like to acknowledge the participation in this meeting of Dr. Loretta Finnegan, Director of the Women's Health Initiative, one of the largest prevention studies ever conducted, which is examining the role of hormone replacement therapy, dietary modification, Vitamin D and calcium supplementation, and behavioral modification in the prevention of the major causes of death and frailty in postmenopausal women (i.e., cardiovascular disease, cancer, and osteoporotic fractures).

We also acknowledge and thank the individuals serving in the following groups:

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INTRODUCTION

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This was the second of a series of regional workshops and scientific meetings during which the Office of Research on Women's Health of the National Institutes of Health had an opportunity to learn about the public's and scientific community's visions of the Women's Health Research Agenda for the 21st Century.

The public testimony and the recommendations developed by the working groups assisted us in re-examining the existing NIH agenda for women's health research. Utilizing scientific directives in a science-driven agenda, we assessed our current priorities, with the assistance of our Task Force on the NIH Women's Health Research Agenda for the 21st Century and the Advisory Committee on Research on Women's Health, which are composed of non-federal scientists, health care providers, educators, and women's health advocates.

Recommendations from the scientific workshops allowed us to direct, or redirect, our future endeavors in such a way that the knowledge that we have gained through biomedical and behavioral research, and the momentum our collective efforts have generated, can be used to protect and improve the health and well being of girls and women.

It was a wonderful opportunity for us from NIH to meet with people in New Orleans. This would not have been possible without the leadership and efforts of our regional hosts, the Tulane University Medical Center, Xavier University of Louisiana, and Meharry Medical College. We are grateful to them for their efforts on our behalf to facilitate the participation of so many people in this process.

The major charge during this workshop was to help determine future directions for women's health research and its related issues. There is no question that research is central to providing the scientific foundation for change, and that new knowledge resulting from research can provide the basis for the improved health of girls and women.

There must be a multidisciplinary collaboration, with multiple partners sharing the responsibility to establish and disseminate new information resulting from increased and enhanced research on women's health, to implement its findings into standards of health care delivery, and to influence the behavior and health practices of not only the scientific and medical communities but also of individual women and their families.

If research on and about women is to change with the times and respond to continuing and emerging gaps in knowledge, there must be a coalition of effort involving all segments of the scientific and health care communities, federal agencies, women's health advocacy groups, and, most importantly, women and their families and communities. And, history has demonstrated that the efforts of these groups, in harmony and concerted effort, have brought about a change.

We owe much change to the many individuals, groups, and organizations dedicated to improving the health of women, such as 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, among many others. They have been working in the "trenches," so to speak, to call attention to the need to focus our attention on women's health.

It is only recently that the efforts of the Federal Government have recognized women's health as a real issue requiring a real remedy, and today, because of the efforts of advocates and scientists, we are beginning to make progress.

PHS TASK FORCE AND ESTABLISHMENT OF ORWH

In 1983, the Assistant Secretary for Health, Dr. Edward N. Brandt, 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. This Task Force made a number of recommendations on a broad array of women's health issues across the entire life span of women in a report published in 1985.

Among the most pertinent recommendations of the Task Force report was one that stated:

*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

Dr. Brandt stated that, as Assistant Secretary for Health, "I am committed to seeing that this report results in action that is beneficial to the women of America..." Thus began the federal initiatives that continue to address women's health.

HISTORY OF INCLUSION POLICIES AT NIH

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by NIH has its origins in the women's health movement, but also received its initial impetus from the recommendations of the Task Force appointed by Dr. Brandt, of which Dr. Ruth Kirschstein, currently the Deputy Director of NIH, served as cochair for more than 10 years. Following the issuance 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.

This policy, which urged the inclusion of women, was first published in the *NIH Guide to Grants and Contracts* in 1987. In a later 1987 version of the NIH Guide, a policy encouraging the inclusion of minorities in clinical studies was first published.

The Congressional Caucus for Women's Issues requested a General Accounting Office (GAO) investigation of the implementation by NIH of the guidelines for the inclusion of women. In 1990, this GAO report stated that implementation of the policy for the inclusion of women was lacking, that implementation was slow and not well communicated, that gender analysis was not implemented, and that the impact of policy could not be determined.²

In September 1990, just 3 months after the release of the GAO report, the subsequent media coverage and public reaction catalyzed the establishment of the Office of Research on Women's Health (ORWH) at NIH. The Office was established to serve as the focal point for women's health research at NIH in a collaborative partnership with the institutes and centers. ORWH was given a threefold mandate:

- First, 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 research agenda for NIH for future directions in women's health research.
- Second, to ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially clinical trials, that are supported by NIH; and
- Third, to create direct initiatives to increase the number of women in biomedical careers and to facilitate their advancement and promotion.

In 1993, ORWH was legislatively mandated in the NIH Revitalization Act. It was this congressional language that also mandated that we establish a Coordinating Committee on Research on Women's

Health, to be composed of the Directors of the NIH institutes, divisions, and centers, and an Advisory Committee on Research on Women's Health, to be composed of non-federal employees who are experts on women's health.

Since the establishment of ORWH, our responsibilities and major program efforts have increased and, although there is still much to be accomplished, we have made some progress.

NIH MANDATE FOR THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

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, 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:

- that NIH ensure that women and minorities and their subpopulations be included in all human subject research;
- that women and minorities and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect;
- that cost is not allowed as an acceptable reason for excluding these groups; and
- that NIH 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 1994,³ and they have been fully implemented. We have established a tracking system to monitor inclusion. For the first time, we are able to determine the numbers of women and minorities in clinical trials, and, as we begin to analyze data from studies active in FY 1995, establish trends in inclusion and determine better ways to examine this data.

We have found a high compliance with the inclusion policy. Analysis of FY 1994 NIH enrollment data showed that substantial numbers of both women and minorities have been recruited as research subjects. The goal of NIH policy is not to satisfy quotas for proportional representation, but rather to conduct biomedical and behavioral research in such a manner that the scientific knowledge acquired will be generalizable to the entire population.

We also funded the Institute of Medicine study, *Women in Health Research*, an excellent report on the legal and ethical issues related to women, especially women of childbearing age, in human subject research. However, as we have moved from being cognizant of regulations established to protect women and minorities and other populations from being exploited in research, and to respond to the tragedies witnessed in the Tuskegee syphilis study and on the effects of those exposed to DES and thalidomide in utero, we still must grapple with the very important issues of women of childbearing age in clinical research and the issues of protection of women and their potential offspring as the risks versus benefits are weighed.

We firmly believe that 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.

W O M E N I N B I O M E D I C A L C A R E E R S

To determine best directions to increase opportunities for women in biomedical research careers, we held a public hearing and workshop on the recruitment, retention, advancement, and re-entry of women in biomedical careers to determine barriers to women's success and how to overcome these barriers. A number of barriers were identified in the report from our Task Force on Women in Biomedical Careers, for which the cochairs were Drs. Carola Eisenberg and Shirley Malcolm. Following the recommendations of this report, we have established a number of programs, including our re-entry program to address the loss of women whose dual roles as care givers led to an interruption of their research careers. We also put into place a number of other initiatives to develop the careers of women and men scientists in research on women's health, including workshops on how to speak and write about science.

Under the leadership of Joyce Rudick, Dr. Anne Sassaman, and Dr. Julia Freeman, cochairs of the Career Development Subcommittee of our Coordinating Committee on Research on Women's Health, we have evaluated the re-entry program, and we are now looking for ways to best expand our other initiatives. As an integral part of our regional meetings, we focused on recommendations to assist us with future program planning.

N I H N A T I O N A L R E S E A R C H A G E N D A O N W O M E N ' S H E A L T H

While much remains to be done to address the many pressing issues in women's health, it is all too easy to focus only on the gaps in knowledge that remain, forgetting where we started and how far we have traveled. The NIH Office of Research on Women's Health convened this meeting, "Beyond Hunt Valley: Research on Women's Health for the 21st Century," to look ahead, but also to pause for a moment to see how far we have come.

Since 1991, the national agenda on women's health research has been shaped by certain underlying principles that must continue to inform our directions for the future. The basis for our current agenda began with the Hunt Valley report, *National Institutes of Health: Opportunities for Research on Women's Health*.

This agenda was formulated from a public hearing and workshop held in September 1991 in Hunt Valley, Maryland, from which the parameters of women's health have been redefined, and research has been redirected to provide better information on sex and gender differences between women and men in development, health and disease, and to focus on populations of women that have been underrepresented in clinical research.

Our 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 the expanded concepts of women's health and research to address the health of girls and women across the life span. We are recognizing that women's health encompasses more than the reproductive system, and that research does involve the entire spectrum and not just human subject research. We also expanded our boundaries of the life span to take into account the health of women from the prenatal stage to that of the frail elderly — the divisions of the working groups that convened during this meeting.

The research agenda includes biomedical as well as behavioral and psychosocial research. We have incorporated as an integral part of our research priorities that we must reach out to populations of women and girls who have been previously excluded from scientific investigation, such as minorities, women of differing socioeconomic status and geographic locations, lesbians, and women with disabilities. In all our efforts to implement our research agenda, we are in an active and beneficial partnership with all NIH institutes, divisions, and centers. We constantly review our research priorities to determine where the major gaps in knowledge exist.

As a part of our efforts to address implementation of women's health research and its incorporation into the standards of health care practice, and promoting 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 the extent of women's health in their curricula. This report also contains examples of model women's health curricula. We are now working with dental, nursing, and pharmacy school representatives to initiate a similar study of their educational curricula.

In 1991, the Hunt Valley meeting led to our current working research document. We believe that it is time to look "beyond Hunt Valley" and to update our agenda. We found that the model of broad participation in this process through public hearings and workshops with representative and voluntary participation worked well and have thus turned again to this model to help us in the current process. This mechanism provides an opportunity for continued collaboration among individuals, groups of women, advocates, scientists, health care practitioners, and public health policymakers with NIH to establish our research agenda as we move forward into the 21st century.

Our research agenda currently 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 different populations of women.

Beginning in September 1996, at our first regional meeting in Philadelphia, we began the process of re-examining our research agenda to ensure that it is relevant as we move towards the next century. At the Philadelphia meeting we directed attention to some of the major areas of concern for women's health.

At this meeting in New Orleans, we looked at two of the ways to examine knowledge about women's health: sex and gender factors *and* differences among populations of women. Therefore, during the scientific workshop, we examined aspects of the research agenda based upon sex and gender perspectives. Our plenary presentations examined whether sex and gender differences are due only to hormones, and we looked at the impact of environmental factors and genetic information on the health and well being of women. The specific objectives of this 2-day meeting were to:

- Assess the current status of research on women's health and identify gaps in knowledge.
- Identify factors that may influence health status, including physiological, psychosocial, and pharmacologic differences that exist between women and men.
- Address emerging issues across the research spectrum from basic studies to clinical and applied research, with special focus on the effects of environmental hazards and toxins across the life span.
- Develop strategies based on research that can result in an improved health status for all women, regardless of race, ethnicity, or age.

At the third and last regional meeting held in Santa Fe, New Mexico, in July 1997, and hosted by the University of New Mexico Medical Center and the University of Iowa School of Pharmacy, we focused on factors that contribute to differences in health status and health outcome among different populations of women, including biology, genetics, 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.

Finally, in November 1997, we brought together the results of all three regional meetings in a national workshop in Bethesda, Maryland, to provide an opportunity for our participants to guide our Task Force in developing recommendations for the NIH research

agenda for the beginning of the 21st century. We asked the working groups to develop their reports within the following parameters.

- Identify scientific progress since the establishment of ORWH.
- Highlight successes in the advances of scientific knowledge about women's health and gender and sex information.
- Highlight programs that have advanced women's health research.
- Develop strategies for identifying continuing or emerging gaps in knowledge and how to address them.
- Generate recommendations for future research priorities and necessary consideration of the biomedical and behavioral research community.
- Provide pathways for networking and collaboration among researchers.
- Consider effective implementation of research outcomes in public policy and health care of women, with consideration of changing parameters (e.g., advances in biotechnology, managed care, etc.).
- Consider how, where, and in what manner to best assure implementation of the results of our advances in knowledge from research.

All of our programs and initiatives should be science driven. Our updated agenda must reaffirm the commitment to integrate scientific disciplines and medical specialties with advocacy and forward thinking optimism.

With the creation of new laws, policies, and programs, we have made tangible progress toward improving women's health, and we have gained a sure sense of our power to effect real change. With assistance, as we enter the 21st century, ORWH can build on that power and maximize its power to improve the health of women and their families. That is the vision for women's health in the United States and beyond. No single individual or group can do the job alone. The challenge — and the responsibility — must be shared by all of us.

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WORKING GROUP REPORTS

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

NEW ORLEANS, LOUISIANA
JUNE 12–13, 1997

*SEX AND GENDER PERSPECTIVES FOR
WOMEN'S HEALTH RESEARCH*

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BACKGROUND

The breadth of the prenatal through early puberty stage of the life cycle is the first challenge in addressing women's health concerns. Throughout these stages, development occurs rapidly and not necessarily according to a preordained time table.

Devising a standard, applicable method of stratification with useful and meaningful categories, without using extensive testing, is essential. Because human development during these life stages is rapid and diverse, a method of stratification that uses chronology exclusively is not desirable; behavioral and psychological factors must be included. For research into this stage of women's life cycle, the following nondiscreet stratification is recommended as a guideline:

- *Preconception.* Includes the external and internal influences on the mother and the father, and the effects that these influences will have on the child.
- *Embryonic/fetal development.* Includes the substrata of gene expression, implantation, and more minute divisions of the current trimester partitions.
- *After birth.* Includes a chronological division tempered with behavioral and psychological development that extends the stratification to six subcategories: newborn, infant, toddler, preschool-aged child, early school-aged child, and preadolescent.

Within this stratification, research should be clarified according to gender and ethnic and cultural backgrounds whenever possible.

Gaps in knowledge about normal biological development processes constitute the second challenge facing the study of this stage of the life cycle. More information is needed about the early stages of prenatal development and of behavioral, social, and physical development throughout this period of life.

The third obstacle facing study of this area of women's health is the number of external and internal factors involved from preconception through early puberty. The influences and effects of these factors throughout a woman's life are monumental and difficult to single out. With these obstacles in mind, education and prevention must be emphasized to promote overall wellness, beginning with the preconception stage and extending through childhood.

RESEARCH RECOMMENDATIONS

Normative Development

The working group sessions repeatedly mentioned the lack of knowledge concerning normative development of the fetus and the child. Basic biological research is needed concerning the prenatal through early puberty

stages of life, because understanding normative development allows for a clearer understanding of pathological processes. Research into normative development needs to be stratified according to developmental stage, gender, and ethnicity. A multidisciplinary approach that includes the social, environmental, behavioral, and physical aspects of development is recommended as the best approach for research. Recommended research topics in this area include:

- Gene expression and the interaction of the environment with genes.
- Implantation and the first trimester development, including gender differences in development.
- Normative placental function and the function of the placenta as a protective barrier.
- Development of organ systems using a multidisciplinary approach. This research should include but not be limited to dentition, the cardiovascular system, the central nervous system, the endocrine system, and the impact of prenatal events on development.
- The impact of and the gender differences in response to stress and nutrition in this stage of the life cycle.
- Determination of the critical developmental periods and the critical periods of sensitivity to environmental factors during this stage of the life cycle.
- Regulation of normal labor and the mechanisms of preterm labor.
- Importance and effect of preconception health, plus how to disseminate this information effectively.

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

Gaps in knowledge exist about the effects of prescription and over-the-counter medications, xenobiotics, and herbal remedies on women and children. The effects of a drug on an adult male are not necessarily similar to those experienced by a child, a pregnant or lactating woman, a fetus, or a breast-feeding infant. In researching these areas of pharmacokinetics and pharmacodynamics, a stratification must be adopted that addresses the differences of age, gender, and ethnicity. Recommended topics for research include:

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

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

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

based on culture, gender, and age. Essential to any program before implementation is an understanding of the steps of prevention and intervention for specific diseases and behaviors. Education and prevention programs must have long- and short-term targets in order to produce lasting results.

Recommended research topics in this area include:

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

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

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

- Effects of environmental agents on gene expression.
- Impact of environmental agents on implantation and first trimester development.
- Effects of environmental agents on placental function.
- Effect of the environment on organ systems, including dentition, the cardiovascular system, the central

nervous system, the endocrine system, and the impact of prenatal events on development.

- Narrow windows of critical periods of exposure to environmental agents, plus the long- and short-term consequences of exposure during these windows.
- Critical pathways of exposure, such as nutrition, lactation, and formula.
- Community-based prevention and research pertaining to environmental exposure and effects.

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

Major gaps exist in our knowledge of normative behavioral and psychological development. Even at early ages, the differences in behavior between the genders are noticeable, yet this area is lacking in research and study; studies of behavior often ignore developmental differences. Recommendations for research include:

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

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

Additional knowledge about the passage of disease from mother to child is needed. Children become predisposed to diseases in the early stages of their development. Topics for research include:

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

E T H I C A L C O N C E R N S

Because of the diversity of studies and research and because of the impact these studies can have on women, children, and society as a whole, ethical concerns must be studied and evaluated. The following categories are of concern: surrogate motherhood, embryo research, fetal research, cloning, genetic testing, genetic records, prenatal gene therapy, storing and discarding embryos, rights of the fetus and the woman, fetal surgery, and fetal and neonatal organ donation.

C O N C L U S I O N

The importance and delicacy of this stage of women’s life cycle cannot be emphasized enough. Sensitivity to the mother and the child is required in all endeavors that advance our understanding of these aspects of women’s health.

ADOLESCENT YEARS

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BACKGROUND

Adolescence is a time of explosive change. The body grows and develops faster from puberty to 18 years than at any other time of life except from birth to age 1. Physical growth is the most obvious change: children become taller and heavier, and their facial features become more adult-like. They also gain sexual maturity and become able to bear children. Less obvious, but just as important, are the intellectual and psychological changes that take place. Adolescents grow mentally, gaining new insight and understanding and the ability to comprehend increasingly complex issues. Psychological growth helps young people better understand the changes taking place and how these changes alter their overall being. Although physical, intellectual, and psychological growth are normal aspects of adolescent development, they occur unevenly — they are unsynchronized — and can often lead to insecurity, anxiety, conflict, risk-taking behavior, and other emotional challenges.

The rate of change varies not just between boys and girls (girls mature faster in all areas than boys do), but also from individual to individual, race to race, and culture to culture (Puerto Rican, Mexican, and South American girls develop at different rates and in different ways from each other in spite of the fact that they are all Hispanic). Great diversity exists among adolescents. This diversity dramatically affects developmental processes. One size does not fit all.

ADOLESCENT ISSUES

Maturation

Physical maturity begins at a much earlier age today than it did a century ago, probably due to improvements in nutrition, general health, and living conditions. In the United States, the age of menarche has decreased three to four months per decade during the past 100 years, but has now leveled off. Ironically, however, although puberty is beginning earlier, the completion of the transition from adolescence into adulthood and independence is occurring later. Drug use and sexual activity are beginning at an earlier age as well. The challenges of adolescence are far greater, more serious, more complex, and more life threatening than in the past.

Adolescent Pregnancy

Teenage pregnancy is higher in the United States than in any other industrialized country. More than 1 million teenaged girls in the United States become pregnant each year. More than one-third of U.S. girls become pregnant at least once during adolescence, and most of these girls complete their pregnancy. A third of these girls become pregnant a second time during their adolescent years. In many inner city communities, teenage pregnancy is considered epidemic.

In 1987, 472,623 infants were born to U.S. teenagers, an estimated 12 percent of all births. Sixty-four percent of these infants were born out of wedlock.

About 10,311 babies were born to mothers under 15 years of age. About 400,000 therapeutic abortions are performed on teenagers each year. The divorce rate for teenage marriages is 50 percent within 2 years and 80 percent by 5 years. Many teenaged mothers have not done well in school and have a history of psychological problems. Pregnancy and marriage, stressful enough for adults, add turmoil to adolescent years at a time when life is already in flux. Pregnant teens and their partners usually drop out of school, which increases economic difficulties, loss of self esteem, and strain on interpersonal relationships. Abortion does not resolve the situation because the psychological distress caused by the unwanted pregnancy still occurs. Trauma may result when the pregnancy is diagnosed, when the decision to have an abortion is made, during the post-abortion recovery period, on the date the baby would have been born, and on the anniversaries of that date.

Abuse and Neglect

The upheavals taking place during adolescence can be further confounded by neglect and abuse. Although neglect occurs 10 to 15 times more often than abuse, more than 12 million children are involved in abuse. Twenty percent of physically abused children are permanently injured, and 1,200 deaths occur each year in the United States as a result of abuse and neglect. Adolescents, who are in the process of trying to figure out who they are anyway, can experience very low self esteem if neglected and can be severely psychologically traumatized by sexual abuse.

Rape and incest are devastating. These hostile and dehumanizing events can have lasting effects on adolescents' self worth and identity. If rape is a teenager's first sexual experience, future sexual adjustment can be threatened. Twenty percent of women under 18 years who presented at an STD clinic had a violent sexual experience, 75 percent of girls 14 and under had a coercive sexual experience, and 62 percent of girls 16 and under had a violent sexual encounter. Rape victims have rapid mood swings; feel alternately degraded, angry, guilty, and helpless; and may have nightmares and trouble sleeping. Relationships with

peers and consenting sex partners may suffer. The victim, out of fear of the attacker, may withdraw and develop ritualistic behaviors as a defense. Incest victims often do not report the incest because of fear of disrupting family structure; therefore, the incest may occur repeatedly over a long period of time. Of growing concern is the fact that many perpetrators of rape and incest against adolescent girls are much older men.

Drug Use and Addiction

Use of illegal drugs by U.S. teenagers increased sharply during the 1960s and 1970s. The increased use has subsided somewhat; however, of greater concern is the decreasing age at which adolescents are beginning to experiment with drugs. Today, two-thirds of all teenagers have tried marijuana at least once before finishing high school, with some experimenting in grade school. Treatment for drug abuse and addiction has traditionally focused on adults, with few programs admitting anyone under the age of 18. Human developmental differences have rarely been identified and examined to determine how they might enhance or adversely affect the process or outcome of treatment.

Death

Three-quarters of all deaths among teenagers are the result of accidents, murder, and suicide; accidents, particularly car accidents, are the leading cause of adolescent deaths. The teen death rate is increasing due to violent deaths, although the death rate in other age groups is stable or declining. Factors that raise the risk of death in adolescents include drug abuse, poverty, stressful family situations, and risk-taking behavior.

Suicide is the third leading cause of death among teenagers. Approximately 500,000 teenagers survive suicide attempts each year. Most adolescents who attempt suicide are depressed, but many others attempt suicide because of a specific event such as the breakup of a relationship, the death of a friend or family member, psychological problems within the family, chronic physical illness, drug abuse, or physical or sexual abuse.

Dentition

The oral cavity is undergoing change during adolescence. During this time, the presence of caries and gingivitis is highest. Adolescents experiment with sex, smoking, and drugs, all of which have manifestations in the oral cavity, on the mucosa, and on the tongue.

PROGRESS SINCE ESTABLISHMENT OF ORWH

The 1991 Hunt Valley report contained a number of recommendations for research that should help provide understanding of the changes that take place during adolescence:

Hunt Valley 1991 Recommendations

Developmental Issues

- Parameters of optimal physical functioning — that is, exercise capacity — should be outlined to gain a better understanding of young women's full biologic potential. Optimal limits may vary by ethnicity, body habitus, pubertal staging, or other parameters.
- Studies should investigate the effects of pregnancy, childbirth, rearing of children, and abortions on subsequent development, since many adolescents have these experiences.

Wellness and Risk-taking Behavior

- Studies should look into strategies for teaching adolescent females responsible health behaviors that encourage beneficial decisionmaking.
- Research is needed to understand the interaction among biological, psychological, and social factors that lead to harmful behaviors, such as early and unprotected sexual activity, use of harmful substances (especially cigarette smoking and the use of alcohol), and risky behaviors such as reckless driving.
- Research is needed to find out whether there are developmental factors that play a role in whether

women will adopt a proper diet. There is evidence that cancer risks can be reduced twice as much in women as in men by adherence to a low-fat diet.

- Prospective longitudinal studies are needed to determine the short- and long-term consequences of sexually transmitted diseases, including infection with human immunodeficiency virus, human papilloma virus, and chlamydia, as well as pelvic inflammatory disease.
- Investigations should examine whether multiple sources of stress affect risk-taking behaviors and, in contrast, which factors render girls more resilient to stress.
- Investigations should analyze the impact of behavioral patterns on women's health and how individuals with these disturbances respond to disease.
- Research is needed on the relationships among exercise, body composition, nutrient intake, menstrual function, and osteoporosis in young women.

Mental Health

- Because rates of depression for girls rise after the onset of adolescence, an emphasis on the biological and psychosocial mechanisms that make women more vulnerable should be studied, and the importance of choosing appropriate treatment approaches should be emphasized.
- Subtypes of depressive illness that have higher rates in women, such as rapid cycling disorder, should be studied.
- Indicators of mental health risk in preadolescent and early-adolescent girls should be identified. Such indicators may include poor academic performance, a measure already linked to other adverse health outcomes.
- Research is needed to clarify the patterns and mechanisms of substance use by adolescent females, specifically, nonuse, experimentation, heavy use, and addiction. The influence of gender

roles and relationships with male partners should receive special attention in these studies.

- Studies should explore the link between high-risk behavior patterns — such as addictive behaviors and eating disorders — to neurobiologic abnormalities.
- Research is needed on the factors that either protect girls from, or increase their risk for, suicide gestures. These should include studies examining the nature of the linkages among suicide and drug use, depression, and eating disorders.

Injury

- Further study needs to be conducted on the risk-related behaviors that render young women more vulnerable to intentional and unintentional injuries. According to recent data, the impact of sexual abuse and molestation on subsequent psychosocial development (both sexual and nonsexual) has implications for significant numbers of young women.

Special Issues

- It is crucial that valid and reliable measures of behavior be developed for different ethnic and age groups. Such instruments can facilitate understanding of certain topics in behavioral research.
- Studies also should determine reliable and valid indicators, measures, and screening techniques for assessing the general health status of girls and young women at all stages of development.
- Longitudinal research is needed to follow the course of females through their entire life cycle. Studies of young girls should follow a cohort for several years or decades.
- Studies are needed that focus on within-gender differences, as well as male-female differences.
- Research should define normal health for girls from birth through young adulthood.

P R O G R E S S

These recommendations are ambitious and, although they have not been met completely as yet, successes have occurred during the 6 1/2 years since the Hunt Valley meeting in 1991.

- *Diagnosis of STDs.* Methods for diagnosing sexually transmitted diseases have improved. Embarrassing pelvic exams are no longer necessary to detect STDs like chlamydia.
- *CDC Survey of Health Behaviors.* The CDC Survey looks at adolescents cross-sectionally and across risks to document comorbidity and how concurrent illnesses manifest differently in boys and girls from 10 to 20 years of age. Agencies are beginning to study the patterns of behavior of both boys and girls. In the survey conducted by the CDC, it was revealed that boys are smoking and drinking less than in the past, but that more adolescent girls are beginning to smoke and drink.
- *Environmental impact on female health.* The impact of the environment on health has been well established; however, the particular impact of environmental pollutants on women's health, in the past, had not been the focus of research. Now, however, animal models are being used in studies to determine the effect of pesticides on girls. Scientists are beginning to look at the long-term impact of toxic chemicals on girls' health and reproduction.
- *Validation of diversity.* The tremendous diversity among adolescents is being increasingly recognized. Differences between sexes, race, and culture — and from one individual to another within sexes, races, and cultures — are beginning to be determined to bring greater understanding to health issues.
- *Improved access to health care.* Changes in school-based health programs have occurred, improving adolescents' access to health care.

- *Increased continuity of research.* A change in the focus in HIV has occurred. Women, who were previously viewed simply as vectors of the disease, are now being seen as having the disease with their own set of associated complications.
- *Reducing teen pregnancy.* According to the CDC, the overall rate of teen pregnancy in the United States is decreasing, with some State and locality rates increasing, some decreasing, and some remaining constant.

G A P S I N K N O W L E D G E

Adolescence is a time of life charged with upheaval. Although the outcomes of adolescent development are clearly visible, the mechanisms that bring about those outcomes remain obscure, primarily because adolescents have not been studied and have not been included in clinical trials. Although we know what happens during adolescence, we do not know why it happens. This working group believes that the following gaps in knowledge exist:

Biological Markers

Little specific research has been conducted to determine the biological markers across the adolescent age range. What are the differences among races? What are the differences between younger adolescents and older adolescents? What are the differences between boys and girls? Measurements are based on adult measures; adult norms are not tailored to the actual age, sex, race, and culture of the adolescent.

Mechanisms of Puberty and Development of Environmental Variables

Why does menarche begin earlier in African-American girls than in Caucasian girls? Does early start of menarche encourage African-American girls to associate with, and therefore imitate the behavior of, older girls?

No information exists on why two children in the same family turn out so differently. Why

can one cope with difficulties and one cannot? Are there genetic, but no biological, differences?

Adolescents do not feel safe because of widespread violence, including abductions. How do adolescents cope with loss of a loved one whether the loss is due to violence, accidents, or the normal changes of the life cycle?

Immunology of Women During the Life Cycle

Certain diseases are more common in adolescent teen girls. Is immunology distinctive for teen women? Do age differences in immunology exist?

Gender-specific Diseases of Adolescence

Do differences exist in how families respond to acute illness in boys versus girls during teen years? Why is asthma more common in young boys, but at puberty more girls have asthma? Is epilepsy more acute during teen years? Does chronic disease encourage adolescent girls to take greater risks? Does chronic illness encourage teens to develop coping skills faster than teens who are not chronically ill?

Normative Sexual Health

What are the normal sexual behaviors of adolescent girls? When do girls normally make their sexual debut? Research needs to be conducted to establish normal physiological development patterns, such as when does menarche start and when does breast development begin.

Health Outcomes of Risk Behavior

There is an accumulation of evidence that women are becoming more violent; girls are becoming violent as young as 14 years of age and the number of female gang members is increasing. Research needs to be conducted to find out why women are becoming more violent. Also, boys who are violent get caught earlier and, therefore, get treatment earlier. Girls are in far greater trouble than boys before they get caught or noticed. Why are violent girls not identified and treated earlier?

Diet and Nutrition

Adolescent eating behaviors are generally poor. How can strategies for healthy eating be translated to adolescents? This is particularly critical because many of the chronic diseases of adulthood begin with eating habits in childhood, e.g., osteoporosis and heart disease.

Body Image

Research needs to be conducted to describe the impact of body image choices adolescent girls make and how these choices affect them in adulthood. For example, what are the long-term effects of bulimia and anorexia on the body? How does striving to acquire a particular body type affect behavior?

Influences of Culture on Self Concept and Disease Outcomes

Many African-American girls straighten their hair. If they use too much chemical hair straightener, dermatological conditions of the scalp and face can result. Use of products to change skin or hair texture can cause bodily damage that, in turn, can affect behavior and health habits.

Adolescents develop their self concept during puberty. Some chronic conditions in African-American girls are the result of making poor decisions during puberty. Research needs to be conducted to identify cultural influences in self concept and disease outcomes.

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

During adolescence, every part of young women's lives are in flux. Cognitive, social, and mental health issues change in response to and in concert with the biological changes. Although great diversity in race/culture and age/gender exists among adolescent women, few norms have been established, little tracking of growth and development has been completed, and only a small amount of information has been collected. This working group makes the following research recommendations:

- Conduct a longitudinal study of a national cohort including common measures and youngsters from a wide variety of ethnic/racial, economic, specific-risk, and regional groups and subgroups. What are the common outcomes in this age group and how do they get there?
- No comprehensive guidelines exist for adolescent participation in clinical trials. The Society for Adolescent Medicine does have a statement of consent. The working group reaffirms support to adolescents as minors, but they must be allowed to participate in studies and to receive treatment.
- Because no guidelines exist for adolescent participation in clinical trials, NIH should be urged to convene a workshop to study the barriers and facilitators to adolescent research, including current guidelines, IRB approvals, and ethical and legal issues for gathering data from this age group.
- Alternatively, NIH might commission the Institute of Medicine to conduct an assessment of the legal, moral, and ethical issues involved in conducting clinical research in the adolescent population. The precedent for this assessment is in a previous Institute of Medicine report on the issues involved in including women in clinical studies (Women and Health Research. Washington, D.C.: Institute of Medicine, 1994).

O T H E R I S S U E S T O B E E X P L O R E D A N D E L U C I D A T E D

Development Issues Across the Adolescent Years

- Biological development. How does biology affect behavior? How does the immune system change body composition and affect behavior?
- Social development—how does body development affect social behavior?
- Psychosocial development.

- Environmental effects—how does the environment affect body composition and development?
- Cognitive development.
- Mental health.

Risk-taking Behaviors

- Sexual behavior. Primary and secondary prevention of pregnancy. What are the implications for STDs and pregnancy? (The best prevention for STDs may not be the best prevention for pregnancy.) Difficult questions, such as what are girls' masturbation habits, need to be addressed. What is the role of coercion in an adolescent girl's sexual debut? What is the age of the sex partner and how does that affect development? Male-female dynamics need to be examined.
- Substance use and abuse.
- Others: violence, injury, suicide, runaways, and homelessness among teens. Conduct a cross-sectional study of girls in gangs versus girls not in gangs.

Promoting Healthy Behaviors

- Nutrition. How can healthy eating habits be communicated to adolescents?
- Physical Activity. How can adolescent girls be encouraged to get regular exercise to prevent obesity? How do we promote healthy behaviors like delaying smoking, alcohol, and sex?
- Sexual health and hygiene.
- Oral health.
- Effective/accessible, user-friendly screening tools.

Adolescent Participation in Research

- Normed assessment tools must be developed.
- IRB issues around adolescent consent need to be explored.
- Diversity.
- Inclusion in clinical trials.
- Support of secondary analyses.
- Supplements for ongoing studies.

Coping Skills

- Chronic disease.
- Family issues. Teach parenting skills to teens.
- Life events.
- Violence.
- Resilience. What are the skills needed to deal with emotions like anger?

Communication

- Teach provider communication skills.
- Develop age/culturally appropriate sexual information.
- Examine and utilize channels and models of communication, i.e., providers, parents, teachers, media, and peers.

REPRODUCTIVE AND MIDDLE YEARS

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BACKGROUND

The past 6 years have brought tremendous advances in women's health research for women in the reproductive and middle years, especially with recognition that health needs of women in this age group go beyond reproductive issues. The 1991 Hunt Valley Report focused on issues of sexually transmitted diseases (STDs), reproductive morbidity, injuries, malignancies, and cardiovascular diseases, along with the major themes of racial and ethnic issues, biobehavioral issues, and social context.

SCIENTIFIC PROGRESS

According to a recent paper,¹ during the past 2 decades research in women's health has experienced unprecedented growth. Women's health is no longer limited to diseases of the reproductive organs, and research in women's health derives from social, economic, legal, political, and environmental factors. The group refers to the paper by LaRosa and Alexander for a more comprehensive discussion of the advances in women's health since 1991.

GAPS IN KNOWLEDGE

Sexual Reproductive Health

As recognized in the 1991 Hunt Valley report, because these years are the reproductive years, a woman's well being, productivity, and personal development depend largely on "her ability to live free of

morbidity in terms of sexual function, fertility, pregnancy, and delivery."² Therefore, issues in sexual reproductive health continue to warrant research. Two areas specifically require additional research: prevention of sexually transmitted diseases (including HIV) and use of effective contraceptives.

Prevention of Sexually Transmitted Diseases

Sexually transmitted diseases (STDs), and especially HIV, are still epidemic in this age group. The Centers for Disease Control and Prevention (CDC) reports that incidence of HIV in women is increasing at a rate four times that of men. It is a leading cause of morbidity and mortality in reproductive-aged women and especially of minority women.

Among the approximately 50 diseases that can be transmitted sexually, the most common are chlamydia, genital warts, genital herpes, gonorrhea, pelvic inflammatory disease, and syphilis. Because of the asymptomatic nature of many conditions in the female body, there is no effective screening mechanism and, often, symptoms either do not appear or appear only after the disease is quite progressed. Additionally, the social stigma of STDs prevent many women from seeking treatment. The untreated diseases advance, affecting surrounding and related systems. Consequently, the morbidity associated with STDs has a profound impact on women's fertility and gynecologic health, and also neonatal health. The long-term consequences of untreated STDs in women include increased risks for cervical and vulvular cancers, infertility, tubal

pregnancy, miscarriage, premature delivery, stillbirth, and pelvic inflammatory disease. In infants born to mothers who have or have had STDs in the past, complications include infant pneumonia, conjunctivitis, genital herpes, birth defects, blindness, and death.

Contraceptives

Contraceptive development in the United States has slowed appreciably during the past two decades, while researchers outside of the United States are continuing to work on improving existing methods and developing new methods of contraception. The AIDS epidemic has renewed interest in barrier methods to help prevent the spread of sexually transmitted diseases. Female-controlled barrier methods and agents with virucidal and microbicidal properties are needed.

Although there are presently various choices for contraception available to women and men, there still remains a high incidence of unwanted pregnancies and sexually transmitted diseases; clearly, men and women are still having unprotected sex. There are gaps in the scientific literature about the decisionmaking processes of women and men related to choosing and using contraceptives. Research about the psychosocial context in which women and men choose to use or not use contraceptives is needed to develop feasible contraceptive options for different populations and circumstances.

Access to Health Care

Managed care, the reduced physical and social resources of women, changing roles of women, changing demographics, and available communication technologies have changed the way health care and health information reach women, and how women access health care. Research is lacking to determine the most effective ways to reach the full spectrum of women, using the full potential of resources available.

Changing demographics in the United States indicate that, in the near future, the largest proportionate increases in the population across all age groups will be among Americans of African, Hispanic, Asian, and Native Indian descent. These groups differ greatly in social, political, and economic history; current

socioeconomic status; extent of acculturation; and cultural norms. The diversity in culture and socioeconomic status and the heterogeneity among and within racial and ethnic populations must be recognized and considered in the spectrum of women's health research.

Growing recognition of the importance of cultural and ethnic heterogeneity must be channeled into conceptual and theoretical models of care. Methodologies appropriate to the study of racial and ethnic group heterogeneity must be designed to be sensitive and effective in ethnic minority populations.

Research should explore how to educate providers, with an emphasis on population diversity, its capabilities and resources, and the need to tailor health care access and information accordingly. Currently, a struggle between the scientific community and the community it ideally can serve prevents beneficial collaboration to implement effective research initiatives. We must find ways to implore sensitivity within the scientific community to the need for community involvement in every phase of the research agenda.

Environmental Issues

Environmental exposures and the effects on women's health involve physical and chemical exposures (e.g., pollutants, chemicals, adverse weather conditions, structural and ergonomic designs) as well as exposures associated with the social environment (e.g., economic status, education, culture, residence, and view of self concept) that predispose women to stresses and other morbidity and mortality factors. These exposures affect every aspect of women's diverse roles — as homemakers, as spouses, as care givers, and as employees in the workforce.

We need to know more about hormonal disrupters in the home and the workplace. Injuries still account for a significant number of deaths and long-term morbidity of women in this age group. More effective gender-specific research regarding accident impact and prevention is needed; for example, car-crash tests simply use a smaller male model to determine the effects of impact on the female body.

Inclusion of Pregnant Women in Clinical Studies

Although more women have been involved in clinical trials, special populations of women, especially pregnant women, are not being studied. The inclusion of pregnant women in clinical trials presents a serious ethical dilemma. While knowledge about the effects of drugs and interventions in this population is clearly needed, there are unknown implications for the pregnancy, the health of the fetus, and the long-term health of the child. For example, children of mothers who used diethylstilbestrol (DES) to prevent miscarriage during their pregnancies have serious disorders of the reproductive, endocrine, immune, cardiovascular, and skeletal systems; these disorders are now, 25 years later, identified as transgenerational effects of the drug.

In 1993, the FDA revised its 16-year policy prohibiting the inclusion of women of childbearing age in Phase I and II clinical trials and stipulated gender-specific analysis of new drugs in development. However, pregnant women are still not allowed in studies other than those directly addressing pregnancy issues, and most internal review boards still request the exclusion of pregnant women and the use of adequate birth control during clinical trials. The FDA statement declares that pregnant women *can* be included in clinical trials, not necessarily that they *should* be.

We need to establish a clear definition of all issues surrounding pregnancy and clinical trials and to establish parameters for inclusion of pregnant women in clinical trials.

Alternative (Complementary) Medicine

Women in their reproductive and middle years are using “alternative therapies” in increasing numbers. According to a survey by researchers at the Harvard Medical School, about one-third of all U.S. adults rely to some extent on nontraditional methods of treating illness.³ These alternative therapies include the use of vitamins and herbs, acupuncture, massage therapy, hypnosis, chiropractic treatment, and pastoral and church-based mental health care. Patients are asking their physicians about the effectiveness and safety of

these therapies; however, little is known about the effects and interactions with medically supervised interventions that patients may be undergoing concurrently. Little is known about the population that seeks such alternative treatments.

The medical community must recognize alternative medicine and treat it as a valid form of therapy, if only because of its broad use. Like medical treatments, alternative therapies should undergo scientific review by using clinical studies that compile data regarding the population that uses them, overall effectiveness and failure patterns, long-term effects, and clinical caveats. Finally, the medical community must recognize the already-occurring shift from the concept of “alternative” medicine to that of “complementary” medicine.

C H A N G E I N Q U E S T I O N S S I N C E H U N T V A L L E Y

In the reproductive and middle years, there are recurring themes of existing voids, important issues, and recommendations for future initiatives for research in women’s health. Each research recommendation should be examined through a filter of the following four themes.

Treating Women Globally

We must treat the population globally, recognizing the effects of medicine and interventions over the life span of the woman and considering not only women and men as diverse, but women as part of a diverse and nonhomogeneous group. Research within various social, ethnic, racial, and cultural groups of women should be approached in the same manner as gender-specific research. The diversity among these groups necessitates that education, treatment, prevention, and access programs be tailored accordingly.

Recognizing the Holistic Nature of Disease States and Conditions

A holistic approach is necessary to the study of interventions and disease states. Diseases do not exist in a vacuum; the mind-body connection must be

recognized and explored. For example, women who were victims of sexual abuse or who suffered the threat of sexual abuse are more likely to have irritable bowel syndrome, which can cause gallbladder disease. Likewise, these women are vulnerable to substance abuse and risk-taking behavior, which increases their chances of contracting HIV or other STDs. These diseases, if left untreated, can cause subfertility, complicated pregnancies and birth, and cancer. Long-term, delayed, and transgenerational effects of drugs and other treatments must be considered as they relate to the incidence and risk of subsequent diseases.

Holistic research efforts should consider specific health endpoints that affect women in the middle years to the greatest degree. The following conditions or disease states should be given high priority: autoimmune diseases; cardiovascular diseases; DES exposure; endometriosis, infertility, and uterine fibrosis; female cancers; infertility; mental health diseases such as depression, panic disorder, and Posttraumatic stress disorder; STDs; stress-related gastrointestinal disorders; pregnancy; substance abuse; and urinary incontinence.

Empowerment of the Community

Research in women's health needs to re-establish the empowerment of the community, with an emphasis on information from the constituency. So that science can fit the needs of the community, research should be conceived, conducted, and followed through using partnerships among consumers and patients, scientists, clinicians, and federal agencies. Focus groups should involve participation of the consumer/patient, with special consideration to minority groups.

Enlightened Providers

Research efforts should encourage the development of enlightened providers who are sensitive to the social, psychological, and behavioral connections to physical ailments and who should be trained to disregard previous stigmas associated with the diagnoses. Providers need to understand the cultural, ethnic, and social communities in which women live, considering

the resources, education levels, perceived safety factors, and social mores that affect women's ability and inclination to access health care. For example, several studies of and programs to deal with violence against women have been initiated to improve outreach and assistance. The most successful efforts have partnered with community efforts to assist victims and have focused on training health care professionals to recognize signs of violence.¹

R E C O M M E N D A T I O N S A N D C O N C L U S I O N S

Sexual Reproductive Health

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

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

Access to Health Care

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

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

Environmental Exposures

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

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

Inclusion of Pregnant Women in Clinical Studies

Research involving pregnant women, and women of reproduction potential, in formal clinical trials requires careful thought and planning, with consideration to transgenerational effects and the effects of interventions on the existing pregnancy and fetus. Not all data needs to be collected on the gargantuan level, and opportunities for data collection are presently available. For example, women who use drugs and alternative therapies during pregnancy without the supervision of physicians or clinical investigators present an opportunity for passive data collection. Additionally, collection of followup data on subsequent pregnancies and children can be explored, using women who have participated in previous clinical trials.

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

- Recognize and use opportunities to collect passive data to study the effects of drug use on pregnancy.

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

Alternative (Complementary) Medicine

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

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

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

Autoimmune Disorders

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

Cardiovascular Diseases

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

Depressive and Mental Health Disorders

- Increase research on hormonal, behavioral, and genetic factors predisposing women to these disorders.
- Identify gender-specific pharmacokinetics.

DES Exposure

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

Endometriosis, Infertility, and Uterine Fibrosis

- Increase basic molecular/cellular regulation research with specific attention to defining the basic biology of these diseases and to identify components of their causes.
- Increase well-designed clinical research.

Female Cancers

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

Infertility and Fertility Control

- Develop more cost-effective treatments for ovulation induction.
- Increase understanding of fertilization and implantation, ovulatory disrupters, and male infertility.

Obesity

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

Polycystic Ovarian Syndrome

- Increase research on androgen impact on CVD and the insulin resistance mechanism.

Stress-related Gastrointestinal Disorders

- Educate and sensitize the medical community about early and/or preventive diagnosis of gastrointestinal disease in women, with special consideration of the brain-gut connection linking abuse, stress, anxiety, and panic disorder to gastrointestinal diseases.
- Implement existing technology and procedures to establish early diagnosis of symptomatic patients in order to define groups that will benefit most from early intervention and treatment modalities.
- Establish a safe therapeutic environment to deal directly with issues of safety in the clinical setting for women who perceive threats in the environment (e.g., use draping equipment and attune to background noise).

Substance Abuse

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

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PERIMENOPAUSAL AND POSTMENOPAUSAL YEARS

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BACKGROUND

In the 1991 report of the National Institutes of Health on opportunities for research on women's health, the Life Span Working Group on the perimenopausal to mature years delineated the major public health concerns facing women during this segment of their lives and issued a series of recommendations for research initiatives.

Since that time several important large-scale research programs have begun to examine issues important to the health of women in their peri- and postmenopausal years. The Women's Health Initiative (WHI) is a 15-year program begun in 1991 and scheduled for completion in 2007. It includes clinical trials, observational studies, and a community prevention program involving more than 164,000 women in all phases. The clinical trials are focused on studies of the effects of conjugated equine estrogen on coronary disease and breast cancer, diet modifications on breast and colon cancer, and calcium and vitamin D on osteoporosis and fractures. An ancillary study on Alzheimer's disease will evaluate 8,000 of the women participating in the hormone replacement therapy trials for changes in memory. The observational study is aimed at identifying biomarkers and risk factors in women who are participating in a variety of hormone replacement therapies. The community prevention program (with support by the Centers for Disease Control and Prevention) has components devoted to improving behaviors,

using lifestyle modifications in diet, exercise, and smoking cessation that have an impact on women's health, and to assessing attitudes of minority women toward surgical menopause (hysterectomy and oophorectomy).

NIH is also sponsoring the first large-scale national study to examine the health of women in their 40s and 50s. Based at seven research centers across the United States, the Study of Women's Health Across the Nation is designed to track the health of approximately 3,000 women during the transitional years of middle age, examining the physical, psychological, and social changes that take place at the midlife and as women approach and traverse the menopause. A special feature of this study is the inclusion of a large proportion of African Americans, Hispanics, and Asian Americans of Chinese and Japanese descent.

The 1991 Hunt Valley report identified a number of priorities for research in key areas affecting the health of women in their peri- and postmenopausal years. In the years since that report was prepared, a number of these issues have been addressed. However, four of the 1991 research priorities have yet to be fully explored and continue to be of utmost importance:

1. Studies should examine the transition from premenopausal to postmenopausal status, including the changes that occur in endogenous estrogen levels and in hormones other than estrogen.

2. Studies should elucidate the mechanisms by which estrogen, progesterin, growth factors, androgens, and neuropeptides may induce cell transformations and promote tumor growth.
3. Studies should assess the effects of early menopause (whether chemically, surgically, or disease induced) in breast cancer survivors, as well as the effects of hormone therapy in this group. Of particular importance is the effect of hormone therapy on recurrence of breast cancer, development of heart disease, and quality of life.
4. Studies should identify successful interventions for long-term weight management, including interventions to increase physical activity levels.

RESEARCH RECOMMENDATIONS

Since the Hunt Valley report of 1991, efforts have been made to include individuals from diverse ethnic and cultural backgrounds in clinical trials and observational studies. The basic premise of research on women's health is that it must be studied and understood in the context of culture, ethnicity, and socioeconomic status for research in all areas of peri- and postmenopause; all research hypotheses should start with ethnic-specific criteria. More specific research priorities in the area of peri- and postmenopause fall into three broad categories: the process of the menopausal transition, pharmacological aspects of peri- and postmenopause, and behavioral and psychosocial aspects of peri- and postmenopause.

The Menopausal Process

Since the natural history of menopause and the processes underlying the transition from pre- to postmenopause are not as yet well understood and since an understanding of these processes is critical to provide the foundation for further research into women's health in the postmenopausal years, studies should be undertaken to fully explore the process

of transition from premenopause to perimenopause to postmenopause.

- Work should be undertaken to clarify and define the various stages comprising the transition from premenopause to perimenopause to postmenopause.
- Studies should characterize the normal antecedents and sequelae of the menopause transition and, in so doing, distinguish this stage of the female life cycle from disease processes and the processes of aging. Specific areas of opportunity should also include bleeding abnormalities, the development of obesity in the menopausal years, and the role of the postmenopausal ovary on the manifestation of menopausal symptoms subsequent to morbidity.
- Research should be conducted to evaluate the effects of surgical versus spontaneous menopause on morbidity and mortality and on factors related to women's sexuality. Hysterectomy and the factors affecting it should be emphasized in the research agenda. Areas of investigation should include fibroids and their treatment, hormonal aberrations, physician and patient preferences, analysis of the outcomes of hysterectomy (with and without oophorectomy), and alternatives to hysterectomy (e.g., pharmacological and less-radical surgical approaches).
- Additional aspects to explore include environmental, cultural, and lifestyle influences on menopause. Questions to be addressed include: What constitutes optimal primary care for women in this stage of life? What are the effects of physician training on the health care of menopausal women? Would women be better served if gynecology were separated from obstetrics as a field of specialization? What are women's needs and what are appropriate strategies for contraception during the perimenopause? What is the influence of environmental agents on estrogen receptors?

Pharmacological Aspects of Peri- and Postmenopause

- The effects of endogenous and exogenous hormones on tissues and physiological processes of multiple target organs should be evaluated.
- Studies of hormone replacement therapy (HRT) should be continued and expanded. Specific areas to be explored include the effects of administering conjugated versus pure forms of estrogen, natural versus synthetic progestins (for women with a uterus), the route of administration (oral versus transdermal), the schedule in estrogen-progestin regimens (sequential versus combined-continuous), methods of reducing side effects and optimizing/individualizing regimens for patients, factors affecting pharmacokinetics (such as lifestyle, smoking, obesity, and diet and other ingested substances), and the effects of HRT on cardiovascular disease from the viewpoint of primary and secondary prevention (including CABG, angioplasty, and adjunctive devices).
- Research should be implemented on alternatives to HRT, including pharmacological agents such as Raloxifene and other selective estrogen receptor modulators (SERMS), diet and dietary supplements (for example, phytoestrogens), behavioral interventions, and the role of testosterone.

Behavioral and Psychosocial Aspects of Peri- and Postmenopause

- Studies should be developed to explore the psychological aspects of menopause and the transition to menopause, including women's attitudes toward bleeding and the symptoms of menopause.
- Research should be conducted on the effects of caregiving in the menopausal years. Because the burden of caregiving on menopausal women has increased due to recent social trends, such women often find themselves taking care of family members of two or three generations. How does the

stress of this increased burden affect the menopausal process? How do caregiving responsibilities affect women's participation in preventive health practices and clinical trials and other studies?

- Studies should be designed to determine the attitudes, knowledge, and perceptions of women, health care providers, and society in general toward menopause and toward the aging processes. What are the barriers to health care in this period of life and how can they be overcome?
- The psychosocial (as well as the biomedical) aspects of genetic susceptibility testing should be explored. These include such issues as appropriate interpretation of data, confidentiality, psychological impact of knowledge of the potential for genetic defects, implications for health care, and insurability.
- Research should be undertaken on the health effects on menopausal women of such stressors as bereavement, abandonment, the "empty-nest" syndrome, and other forms of loss.
- Strategies and channels for disseminating new medical and health promotion information to a variety of audiences (including women, health care providers, and society at large) should be devised and implemented.

In addition to the new initiatives outlined above, meta-analyses on data from prior studies on weight management and hysterectomy should be undertaken to maximize the value of the extensive research that has already been conducted in this area of women's health.

ELDERLY AND FRAIL ELDERLY YEARS

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BACKGROUND

The social context of health — including religion, ethnicity, and culture — has an important effect on health behavior, and research must understand this context. Socioeconomic status (SES) plays a major determining role in health status. The United States has the highest poverty rate for older women among industrialized nations — one out of four are poor or near poor. Many women slip into poverty upon the death of their spouses, losing both income and companionship, and low income is a major barrier to health care access for older women. Although Medicare covers almost 98 percent of the population (according to an estimate of the U.S. Health Department), it may cover only one-half of services to beneficiaries. Co-payments, deductibles, and out-of-pocket expenses present major problems to the elderly poor, particularly those with chronic conditions.

The health of elderly women is increasingly important because of the rapidly growing numbers of women in this age category. Progress has been made; for example, the prevalence of disabling conditions has declined from 24.9 percent to 21.3 percent in the 12-year interval between 1982 and 1994. Nevertheless, women are at higher risk than men for chronic conditions like arthritis, osteoporosis, and depression. Arthritis affects more than half of all women 65 and over. Rates of activity limitation and disability among women aged 65 to 74 are 1.5 times those for men. Osteoporosis

increases dramatically with age, affecting more than 50 percent of women 80 years and older.

RESEARCH RECOMMENDATIONS

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

Social and Behavioral Issues

- Focus on changes in family and social structures. What implications do the changing social and family structures have on women's health issues — for example, smaller families, increased numbers of women in the workplace, and reduced availability of support systems? What are the economic effects when women drop out of the workforce to become care givers when family members, parents, or spouses become ill? With more women in the workforce, more services such as advice on health insurance and retirement and financial planning should be available to them.
- Focus on the feasibility and intergenerational impact of formal and informal caregiving: stress, coping, training lay providers, and respite care. Caregiving almost always is provided by women and carries hazards for women's health. What stresses are involved and how can these stresses

be ameliorated? What configuration of formal, informal, and respite care can support a family's ability to provide long-term care, thereby delaying both morbidity and placement in a skilled nursing facility? What are the best methods to educate lay providers to care for elderly women? How can families be helped to adapt to the structural and lifestyle changes required for providing elder care at home?

- Promote personal choice and autonomy in living situations. Low socioeconomic status almost always shapes the quality of life and the health of elderly women. How can women be assisted to retain a sense of autonomy and personhood even when choices are limited?
- Identify the antecedents and consequences of mandatory elder-abuse reporting. How can physicians and nurses be educated to increase their awareness and identification of elder abuse? What questions should they ask? From experience with reporting child abuse, what might be the effects of legislation requiring reporting elder abuse? What strategies and policies protect against elder abuse?
- Develop ways to empower older women in their use of health care. How can elderly women be assisted in their interactions with the health care system? For example, how can older women be encouraged to ask for second opinions? Despite the increased recognition of the importance of mammograms and clinical breast examinations, too few elderly women are asking for and receiving these services; how can women be educated to insist on them? How can ethnic and cultural prohibitions against some of these services be overcome? How can physician performance be monitored?
- Increase efforts in health promotion and disease prevention. Educate women about risk factors, causes of increasing disability, and the availability and importance of immunizations for preventable illnesses. How can older women be encouraged to

participate in clinical studies, particularly women in disadvantaged and underserved populations? How can research results be shared with these groups of women?

- Encourage research on the impact of managed care on the health and well being of older women. How does managed care impact elderly women, particularly those with chronic conditions and with comorbidities? For example, managed care companies often require shorter hospital stays than have been customary. What impact does this have on elderly women who live alone and on those who provide home-based caregiving? How can policy makers in managed care companies be educated about research results? How can managed care companies be encouraged to respond appropriately to the health needs of elderly women?
- Continue research on mobility and safety issues. Continue researching older women drivers and pedestrians and how to prevent accidents and promote safety.
- Develop research on the use of assistive technologies. The use of assistive devices for augmenting hearing, vision, and speech loss should be studied in home-based, community-based, and institutional settings.

Mental Health Issues

Depression affects many more women than men. Why does this occur, and why does that gap narrow among the elderly? Why is the suicide rate among older men higher than among older women? Why is there an increase in alcoholism among older women?

- Study gender differences in depression.
- Continue studies of alcoholism and other drug abuse and dependence, including dependence on prescription drugs.

The issues in these two categories relate to some of the questions asked in the section on social and

behavioral issues. For example, is the increase in alcoholism among older women affected by living conditions? By loneliness? By changing family and support systems or lack of those supports?

- *Study effective coping strategies.* What are the stresses both for the elderly and frail elderly and for their care givers? What mechanisms could help both parties cope better? Can more respite care be provided?
- *Investigate dementias.* Dementias influence women directly and as care givers. Why are women at greater risk than men for dementias? What can be done to reduce the toll of dementia? To reduce the stress for the families? To enhance cognitive function in the elderly? To educate care givers on appropriate modes of care?
- *Study the impact of living arrangements on mental health.* What are the effects of facilities that allow aging-in-place (the movement from independent to assisted living and then to nursing care)? What stresses are caused by the necessity of relocation? By loss of independence?
- *Study the impact of chronic pain on mental and physical health.* As women age they often face comorbidities that can result in chronic pain. How can this pain and the fear of suffering be relieved?
- *Study the impact of fears of death and dying and/or terminal pain.* How do the spiritual beliefs of older women affect their attitudes toward health and toward illness and death? Are there special ways that women prepare for death and dying? What legal, social, and health care supports should be provided?

Physiological Issues

Cardiovascular Illness

Recent understanding of the effect of cardiovascular illness on women has included greater awareness that

women are treated less aggressively than men. Research should continue to examine treatments and outcomes for men and women.

Osteoporosis and Osteoarthritis

These conditions cause significant pain and suffering for older women as well as serious functional impairment, impacting the quality of women's daily lives and producing financial burdens.

- Continue research on the long-term effects of HRT.
- Research interventions to help women 65+ who have not taken HRT.
- Study alternatives for women 65+ who have taken HRT.
- Research methods for delaying frailty.
- Study the impact of musculoskeletal fitness on comorbid disease progression.
- Research musculoskeletal and cardiovascular response to exercise.
- Investigate why disability rates are decreasing among the elderly, and the impact of this decrease.

Urinary Incontinence

Urinary incontinence is a major clinical problem and a significant cause of disability and dependence in older women. In 1995, a U.S. Public Health Service Task Force on Aging Research stated that urinary incontinence affects more than 10 million Americans, approximately 85 percent of whom were women.

- Study normal and abnormal bladder physiology in order to suggest treatment for incontinence.
- Research adjunctive treatments, such as pharmacologic therapy.
- Investigate behavioral interventions for persons at risk.

- Conduct clinical trials to examine effective therapies for specific types of urinary incontinence.
- Increase educational efforts for health providers and patients regarding the effectiveness of bladder training.
- Review staff management techniques to ensure compliance with treatment protocols.

Pain and Its Impact on the Elderly

The recommendation to study the impact of chronic pain on physical health is repeated here because of its connection with physiological issues. More research is needed to find ways to relieve that chronic pain of comorbid conditions in older women.

Surgery

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

Delaying and Correcting Sensory Impairments

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

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

Is there a genetic basis for chronic diseases? Is there a genetic basis for retention or loss of physical functioning in old age?

H E A L T H P R O M O T I O N A C T I V I T I E S

Health promotion activities should be targeted to increasing appropriate exercise, boosting nutrition awareness and habits, and decreasing disability.

Impact of Improved Health in the Elderly

There has been a decrease in the numbers of older women suffering from disabling conditions and an increase in life expectancy, perhaps reflecting changes in nutrition and lifestyle as well as medical advances such as the use of HRT. Studies should be undertaken to investigate the social and physiological impacts of women living longer—implications in the job market, for example, as well as in the development of chronic conditions and comorbidities.

Issues of Pharmacology and Aging

The Women's Health Initiative is currently studying nearly 165,000 women nationwide, with a major focus on Hormone Replacement Therapy. This important research study should be supported with additional clinical studies on pharmacology.

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

Research Design and Methods

Before 1994, much of the data on drug use came from studies that excluded women and elderly people. As a result, physicians are currently prescribing drugs on the basis of data that may or may not be relevant.

Since that time, inclusion of women has been mandated and studies have begun to collect data on women. However, because of insufficient numbers of participants, the studies lack the statistical power to identify gender differences. Changes in research design and methods would address this situation.

- Develop data-mining techniques to extract from existing databases critical health information pertinent to the health of elderly women; for example, risk factors associated with certain conditions and the use of concomitant medications.
- Identify the toxic drug interactions associated with the use of concomitant medications, including the concomitant use of HRT.
- Intensify federal guidelines regarding the inclusion of women and minorities in research to ensure that sufficient numbers are included to have statistical power and to ensure that diversity can be addressed; for example, subpopulations within ethnic groups and institutionalized versus community-based populations.
- Develop better guidelines that focus on the regulatory and financial issues of conducting research on diseases, disorders, and conditions especially prevalent in elderly women.
- Improve techniques to access existing databases needed by investigators for exploring critical health issues in elderly women, including the use of appropriate key words for searching databases like those of the National Library of Medicine.
- Conduct more research on the process and outcomes of obtaining more appropriate informed consent from older women for research and medical procedures.
- Identify the barriers encountered by older women that prevent them from joining research studies.
- Encourage the development, use, and evaluation of more creative and innovative research methods and designs to study the health of older women.

- Foster multidisciplinary international collaborations and partnerships to conduct research on the health of older women, including international comparisons.

Education and Translation Issues

Key issues in education are the absence of teaching in medical schools about women's health (except for reproductive issues) and about aging. Efforts have been made to rectify these omissions, but more commitment is needed. Curricula have been developed but not yet fully implemented to study geriatric medicine.

Low socioeconomic status has been identified as a risk factor for poor disease outcome in the elderly. However, research has identified critical areas that can be affected by education. Self-efficacy — a person's knowledge and belief that she or he can accomplish certain things — is one area in which education can affect behavior change. Chronic health problems can be significantly ameliorated with appropriate intervention and education; therefore, additional research is needed to appropriately train lay leaders to teach self-efficacy and other skills for managing health problems.

- Promote the use of lay leaders or others skilled in translating health information into language for consumers.
- Educate older adults about consumer rights and health care-related assertiveness.
- Develop education programs that emphasize lifelong learning and its importance in continuing a high quality of life.
- Educate managed care company personnel by translating research findings and encouraging them to incorporate the results of such research into their practice.
- Develop procedures that require outcome information from managed care organizations and translate that information for appropriate groups for policy decisions.



PLENARY PRESENTATIONS

This article examines common suppositions about the reasons for female predominance in the autoimmune rheumatic diseases. It suggests that estrogenic hormones are insufficient an explanation, and that further work in the fields on environmental, genetic, chromosomal, and in utero sex differentiation is indicated.

The Hormone Hypothesis

Three concepts are now regnant: (1) autoimmune illnesses mostly afflict women; (2) autoimmunity, in rheumatic diseases, is defined by autoantibodies; and (3) gonadal hormones drive autoantibodies and, therefore, rheumatic disease. Gonadal hormones are thought to be the reason for the gender skew.¹⁻⁴ This syllogism is the hormone hypothesis.

This paper argues against the hormone hypothesis for the reasons that autoimmune illness is not a single entity, rheumatic illness consists of more than autoantibodies, and the effects of hormones are too complex to yield so simple an explanation. Furthermore, gonadal hormones modulate autoimmune illness, but causation, and therefore gender ratio, is a different issue.

Table 1 lists five hypotheses about disease incidence and disease severity. Hypothesis 1 (gonadal hormones drive disease), absent a second (threshold) hypothesis, predicts more severe rather than more frequent disease in women. Hypotheses 2 through 4 predict equal severity and gender discrepancy, consonant with clinical data. Few data bear directly on disease incidence. Much of what follows is speculation.

TABLE 1. Five Hypotheses and Predictions About Incidence and Severity of Disease

Hypothesis*	Effect on Susceptibility	Ratio	Effect on Severity
#1 Gonadal hormone increases autoantibodies	Equal susceptibility	m=f	Women worse
#2 Gonadal hormone lowers threshold	Women more susceptible	f>m	Equal severity (once threshold is passed)
#3 Gonadal hormone increases autoantibodies and lowers threshold	Women more susceptible	f>m	Women worse
#4 Nonhormone factors lower threshold	Women more susceptible	f>m	Equal severity
#5 Women exposed more	Equal susceptibility	f>m	Equal severity

* For clarity, the hypothesis, "Gonadal hormone increases," is shorthand for stating both alternatives, i.e., "estrogenic hormone increase or androgenic hormone lowers" for female predominant diseases. The inverse formulation would be valid for male predominant diseases.

Why the Hormone Hypothesis May Be Wrong

Inflammatory diseases with skewed gender ratios usually have genetic or environmental causes.

Skewed gender ratios are common in human illness (Table 2), but in most illnesses genes, behavior, and infections — not hormones — are either known or strongly suspected reasons for gender skew. There are other illnesses in which severity differs in men and women. In these as well, the reasons for the different phenotype are genetic, not hormonal.

Some inflammatory rheumatic diseases with gender skew are not demonstrably autoimmune. Many rheumatic diseases clinically and pathologically resemble the autoantibody (rheumatic) diseases, but intensive search has to date documented the presence of only a few autoantibodies (anti-Scl-70 and p- and c-ANCA) or immunogenetic traits (HLA DR3 or B27) and has failed to suggest a mechanism by which these autoantibodies

TABLE 2. Some Illnesses with Unequal Gender Ratios and the Putative Reasons

Illness	Gender	Cause
Known Cause		
Lung cancer	male	smoking
Alcoholic cirrhosis	male	alcohol
Myocardial infarction	male	smoking, cholesterol, heredity, etc.
HIV	male	infection (sex practice, IV drug use)
Kuru	female	infection (cannibalism)
Leprosy	male	infection
Tabes dorsalis	male	infection
X-linked diseases	male	genetic
Putative Cause		
Autism	male	specific (genetic?) brain injury
Spondyloarthropathies	male	genetic, infection?
Post-streptococcal nephropathy	male	infection
IgA neptiropathy	male	altered immunity
Unknown Cause		
Autoimmune diseases: SLE, ITP, Takayasu, MS, primary biliary cirrhosis, thyroiditis, Graves' disease	female	unknown
Scoliosis	female	unknown
Depression	female	unknown
Buerger's	male	unknown
Goodpasture's nephropathy	male	unknown
Fibrosing alveolitis	male	unknown
Lesser Disease in One Gender		
Sickle cell anemia	female	genetic control Hgb F
RA, cardiopulmonary	female	unknown
Spondyloarthropathy	female	genetic, infection

might be pathogenic. The absence of defined autoantibodies in these illnesses needs explanation. It may be that the right antigens have not been sought, or it may be that autoantibodies are not necessary for the clinical phenotype defined by sterile arthritis, fever, rash, vasculitis, and possibly even glomerulonephritis.

Some chronic inflammatory diseases that clinically resemble autoimmune diseases have no gender skew. Several chronic inflammatory diseases have no gender ratio skew (Table 3). Crohn's disease, ulcerative colitis, and sarcoidosis have chronic inflammation, relapsing courses, and other features suggesting that they should be subject to the same hormone modulation as the autoimmune diseases. In this case, however, there is no gender skew and no autoantibodies. If gonadal hormones induce or modulate autoimmunity, these illnesses ought to be explained.

TABLE 3. Diseases Inconsistent with the Hormone Hypothesis of Autoimmune Disease

1. Chronic inflammatory diseases that clinically resemble autoimmune diseases but do not have skewed gender ratios
 - Ulcerative colitis
 - Crohn's disease
 - Sarcoidosis
2. Chronic inflammatory diseases that have skewed gender ratios, but the skew is attributable to exposure
 - Reiter's disease (male)
 - Tuberculosis (male)
 - Leprosy (male)
 - Tabes dorsalis (male)
 - HIV (male)
 - Kuru (female)
4. Inflammatory rheumatic diseases that have skewed gender ratios but are not demonstrably autoimmune
 - Ankylosing spondylitis (male)
 - Polyarteritis nodosa (male)
 - Wegener's granulomatosis (male)
 - Scleroderma (female)
 - Takayasu's arteritis (female)
5. Hormonal diseases that do not alter frequency or severity of diagnosable autoimmune disease
 - Thyroid disease (Graves', thyroiditis)
 - X-Y chromosomal abnormalities (including Klinefelter's syndrome and testicular feminization)
6. Hormonal interventions that do not demonstrably alter frequency or severity of autoimmune disease
 - Postmenopausal estrogen replacement
 - Leuprolide treatment
 - Estrogen treatment (male)

Abnormal Gonadal Hormones Do Not Predispose to Autoimmune Disease

Patients with endocrinopathies do not have unusual susceptibility to autoimmune disease. Case series and a few controlled surveys from rheumatic disease clinics state that SLE patients are prone to develop thyroiditis and Graves' disease,⁵⁻⁷ but the converse does not seem to be true. Patients with Turner's syndrome (XO female) develop thyroiditis but, estrogen-treated or untreated, not other autoimmune disease. Contemporary endocrinology texts mention a high frequency of schizophrenia in XXX females and of neoplasms in androgen-insensitivity syndrome, but do not comment on occurrence of autoimmune disease in any gonadal hormone-abnormal patients. Although rheumatology texts quote a high frequency of systemic lupus erythematosus among patients with Klinefelter's syndrome (XXY male), endocrinology texts ignore this association note and instead report an excess of chronic pulmonary disease, varicose veins, breast and lung cancers, and acute lymphocytic leukemia.^{8,9*}

* Absence of information is not proof. Nonetheless, an association between endocrinopathy and rheumatic illness is likely to be weak if it exists at all.

Hormonal interventions do not demonstrably alter frequency or severity of autoimmune disease.

Large-scale epidemiologic studies have failed to demonstrate a marked increase in rheumatic disease among women treated with either oral contraceptives or postmenopausal estrogen.^{10–12} Rheumatic arthritis is common after menopause more than before.¹³ Case reports and animal studies about castration and replacement lend credence to the idea that hormones modulate severity of extant autoimmune disease.^{14–16} They are less compelling regarding incidence or causation.

Little comment has been heard about whether women with lupus who suffer ovarian failure after cyclophosphamide treatment are more likely to remit than similarly treated women who do not suffer ovarian failure. There are no data on occurrence of autoimmune disease in castrated, estrogen-treated men, although many men are thus treated for prostate cancer. There are no reports of ameliorated rheumatic disease in patients treated with leuprodile for endometriosis and other disorders.

Pregnancy. Rheumatic arthritis (RA) patients regularly enjoy remission during pregnancy. The concept that remission is due to hormone, as opposed to other pregnancy changes, is under challenge.¹⁷ Many papers (not all¹⁸) argue that pregnancy causes SLE to flare.¹⁹ The reason why pregnancy should cause opposite responses in SLE and RA, if gonadal hormones are responsible for female predominance of both diseases, has not been addressed or answered. Pregnancy induces many non-hormonal physiological changes, for instance in the endothelium, vascular bed, and kidneys, which may be relevant to rheumatic disease.²⁰ Although some of these changes may be under hormonal control,²¹ it is not necessary to invoke hormones to explain changing disease activity during pregnancy.

Nonhormone Explanations of Gender Skew

Gender Biology

X and Y Chromosomes

X and Y chromosome genes. The X chromosome contains genes that code for components of immune capability: those genes responsible for chronic granulomatous disease, Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID), and agammaglobulinemia. Because a large number of X chromosome genes are still unknown, it is no leap of logic to imagine that a to-be-discovered X-linked gene influences the gender ratio of autoimmune disease. Because it is small and contains mostly sex-determining genes, a Y chromosome gene less likely down-regulates disease phenotype in men, but, in the BXS^B lupus mouse, a Y-linked factor appears to be the cause of male predominant disease.²²

Imprinted genes. An imprinted gene is one in which identical alleles code different phenotypes, depending whether the gene's origin is the father or the mother. A variant of imprinting is the inheritance of part or all of an entire chromosome from one parent (uniparental disomy). Imprinting controls disease phenotype in Beckwith-Wiedemann syndrome (congenital overgrowth abnormalities and Wilm's tumor), Huntington's disease, insulin-dependent diabetes mellitus, and psoriasis. (For recent reviews, see Gregersen²³ and Sapeinza and Hall.²⁴) Chorionic villus sampling suggests that 1 percent of all pregnancies carry uniparental disomy for particular chromosomes. An hypothesis that predicts that gender skew will result from imprinted genes, or from mutations in imprinting genes, will be complex. Such an hypothesis is not a *priori* rejectable.

X-inactivation. In order not to have a double dose of X chromosome genes, women inactivate (Lyonize) one X-chromosome. Which X — the paternal or the maternal — is selected for inactivation in a given cell line may be non-random. Women heterozygous for X-linked traits are normally mosaic (different cell types express either the paternal or the maternal X). Five to 10 percent of normal women show skewing of X-inactivation toward one parent's X, probably on a random statistical basis. Some X-chromosome genes do not participate in X-inactivation (review by Willard²⁵). X-inactivation is controlled by the XIST (X-inactive specific transcript) gene. In some families XIST function is abnormal, causing X-inactivation to be always non-random. Trisomy results from failed X-inactivation. In embryonic life, trisomy is not rare, but blastocystic cells can and do heal trisomy. By preferentially deleting an abnormal chromosome, this process may result in skewed X-inactivation.

Skewed X-inactivation is responsible for the variable clinical phenotypes of X-linked diseases, such as Lesch-Nyhan syndrome, Wiskott-Aldrich syndrome, SCID, and agammaglobulinemia. X-inactivation is a sufficiently powerful and variable process that identical twins can be discordant for heritable disease, such as Duchenne muscular dystrophy, on the basis of selective X-inactivation alone. Scenarios can be constructed in which an autoimmunity gene resides on the X-chromosome and is subject to non-random inactivation or is not activated and causes a high female:male ratio of illness.

X and Y chromosomes determine gender-specific anatomy and physiology, including hormones. Genes on the X or Y chromosomes constitute the major alternative hypothesis for gender-discrepant illness.

Non-gonadal hormones. The influences of prolactin,^{26,27} corticotrophin-releasing hormone, and thyroid hormones²⁸ in autoimmunity have been reviewed elsewhere. These hormones are closely linked to the action of gonadal hormones but are separate entities whose role is now being explored.

Gender-specific exposures. Sexually active women have gender-specific exposure to sperm, pregnancy hormones and products, and circulating fetal cells. Because autoimmune diseases occur in girls and women with no prior sexual or pregnancy exposure, such exposure cannot be obligate causes of illness.

Beeson used epidemiologic evidence to argue that the hormone hypothesis is insufficient to explain gender skew, but offered no alternative hypothesis.²⁹ Nelson suggested that maternal immune response to fetal HLA induces the remission characteristic of RA pregnancy.^{17,30} Mullinax and others suggest that circulating fetal cells induce scleroderma, postulated to be a form of graft-versus-host disease.^{31,32} However, pregnancy-based hypothesis such as these fail to account for illness in non-transfused children, nulligravidas, and men.

Gender-specific (nonhormone) physiology. By virtue of menstrual loss, mature, pre-menopausal women may be chronically less iron-replete than men. Pregnancy changes, whether or not linked to pregnancy hormones, may trigger other physiologic adaptations that alter expression of disease. Ligamentous loosening in late pregnancy, for example, may stress inflamed joints and cause the inflammation to increase.

In many small ways, female and male physiology differ. Preterm and term newborn boys have demonstrably less developed hearing mechanism than do girls.³³ Neuroimaging demonstrates anatomic and physiologic differences between male and female brains.^{34–36} These differences are not directly relevant to autoimmune disease, but they do demonstrate that the genders differ in surprising ways. More obviously relevant, immune competence itself may be driven by neuroendocrine mechanisms that differ between men and women.^{37,38}

Cultural differences between women and men, such as aggressiveness or direction-finding by landmark or vector clues, may be biological rather than learned.³⁹ Recent studies suggest that pentazocine and related kappa-opiates produce better analgesia in women than in men.⁴⁰ These pharmacological differences are of sufficient magnitude that they could, speculatively, influence disease frequency or phenotype by altering processing of an as yet unknown toxin chemical. Admittedly, these types of gender differences may result from gonadal hormones, but they may also be independent phenomena.

Intrauterine events may influence a fetus' post-natal gender biology. Monozygotic twins differ importantly, for instance in gene imprinting, more if they share one placenta, demonstrating that acquired characteristics, including gender characteristics, can be modified very early in early embryonic life.⁴¹ In the bicornuate uteri of rats, male fetuses located caudally or between female fetuses later display more ambiguous sexual behavior than do male fetuses located between male fetuses or cephalad. In gerbils, females located *in utero* between male siblings have masculinized anatomy and behavior, and subsequently produce more male pups than do females who are located *in utero* between females.^{43,44} In humans, dizygotic twin women whose twin is male may be more masculine than are women whose dizygotic twin is female.⁴⁵ These influences on gender might also influence disease susceptibility.

Gender-specific anatomy. Claims of anatomic differences between men's and women's brains and between brains of heterosexual and homosexual men have received wide press.⁴⁶ The differences (if they exist) may be gene-, development-, or hormone-driven. Anatomic patterns of lymphatic drainage from the genitourinary organs (in closer proximity to the vertebral column in males) remains an open hypothesis concerning different outcomes with ankylosing spondylitis in HLA B27 positive men and women. More subtle anatomic differences between men and women, for instance, relative quantities of fat, muscle, or bone, whether or not caused by hormones, may in as yet not understood ways influence disease susceptibility or expression. The relationship among estrogens, body fat, and osteoporosis in women athletes is a case in point.

Biological clocks. The effects of biological clocks on health and illness is a new field of inquiry. The menstrual cycle is obvious evidence that women's and men's clocks differ. Non-gonadal hormones participate in short and long-term cycling, for instance melatonin in circadian rhythms and leptin in triggering puberty.⁴⁷ It is not known whether the fact of cycling itself, rather than the specific levels of hormones undergoing cyclic variation, is important. Many immune and endocrine functions vary diurnally.⁴⁸ Diurnal and seasonal rhythms influence onset and prognosis of many diseases.⁴⁹ Lupus activity possibly varies with the menstrual cycle.⁵⁰ To distinguish the effect of long-term cyclicity independent of the hormones undergoing cycling would be a very difficult experiment to perform. Nonetheless, the effects of disrupting diurnal cycles on health are broad. That women and men have different health experiences attributable to their different biological clocks is a reasonable, testable hypothesis.

Medical experience of homosexuals. There is increasing consensus that homosexuality has biological rather than psychological origins. Assuming this consensus is correct, and ignoring for the moment the seminal fluid and infectious agent exposure differences that distinguish homosexual men from heterosexual men, a different biology of homosexuals from heterosexuals might result in different disease experiences. Some papers have commented on *worse*, and possibly more frequent, Reiter's disease in male HIV-infected homosexuals,⁵¹ attributing disease expression to HIV rather than to some other aspect of sexual practice. No literature exists on conventional autoimmune disease (as opposed to autoantibodies) in male homosexuals.

Male and Female Illness Phenotypes May Differ

Defined by advanced spinal ankylosis, ankylosing spondylitis is an uncommon disease, of which the victims are 90 percent men. Defined by modest low back pain and radiographic sacroiliitis, the disease occurs equally in genetically susceptible men and women.⁵² Either of two interpretations is possible: men have more severe disease (more often pass the clinical threshold, spinal ankylosis, that leads to diagnosis), or women with the illness are misclassified. The former interpretation is likely, making ankylosing spondylitis one of the few rheumatic (but not autoimmune) illnesses consistent with hypothesis 1 of Table 1.

X- or Y-linked (non-hormone) genes may explain gender-related differences in severity of disease. In sickle cell anemia, the F-cell production locus, an X-linked gene, regulates the production of hemoglobin F,⁵³ high levels of which protect against erythrocyte sickling. As a result, girls have less severe sickle cell disease, and survive longer, than do boys.⁵⁴

Gender Skew May Have a Cultural Cause

The influence of culture on gender ratios can be dramatic. In depression, female predominance is the rule, but in different cultures gender ratios range for depression from 1.5:1 to about 4:1.⁵⁵ Schizophrenia occurs world-wide, but different phenotypes (hebephrenia, catatonia) vary strikingly in incidence and gender distribution, suggesting that onset of schizophrenia is dictated by biology but its phenotype is dictated by culture.⁵⁶ Kuru had a 3:1 female predominance because Fore women, but not men, ate the brains of recently deceased tribe members.⁵⁷ Women with or around small children have different infectious disease exposures than do men. Hypotheses that hair dye or lipstick cause lupus, frivolous as they seem, have been seriously tested but found wanting.^{58,59} Women culturally differ from men in many ways, including diet, social contacts, contraceptives, and use of sanitary products, to name a few. Hormones are subject to cultural control: the amenorrhea of women athletes is an example. If dominant and subordinate hamsters are caged together, subordinate dams have far smaller litters and far fewer male pups than do dominant dams, probably because the stress of being dominated reduces prolactin secretion.⁶⁰ Women's stress hormone thermostat is set differently from that of men, leaving open the suggestion that the different setting can be invoked to explain gender discrepancy of disease.^{2,37,61}

Much of the preceding information is based on non-definitive studies. Nonetheless, this information argues that non-hormone aspects of gender may be powerful determinants of biological health, and, by extension, of illness of phenotypes.

Where Next?

Deconstruct the Autoimmune Disease Are Women's Diseases Argument

The question of why autoimmune (rheumatic) illness preferentially select women remains important. The terms of the question, however, may not be valid. Autoimmune diseases are not monolithic. The pathogenesis of a disease like SLE may be very different from that of rheumatoid arthritis, and both may be very different from scleroderma, yet they are all called autoimmune. Other than autoantibodies, there is no intuitive reason to link organ-specific autoimmune diseases like thyroiditis with systemic illnesses. Diseases that attack young women (SLE) may have a completely different relationship to gonadal hormones than do diseases that attack older

women (RA). Even were one to attribute female predominance of autoimmune disease to a single cause, for instance gonadal hormones, the up-regulation and down-regulation of different components of the immune system is exceedingly complex and delicately balanced. A single, unifying hypothesis may not be possible.

The basic facts — the gender ratios themselves — need better quantitation. Additional data on the influence of castration or hormone manipulation in human disease will be helpful.

Consider Nonhormone Aspects of Gender

Alternatives to the hormone hypothesis, and explanations that acknowledge the differences between incidence and severity of illness, are needed. Might autoimmunity be only a female-specific phenotype of a more general illness? Might spondyloarthritis and autoimmune disease be essentially the same illness presented in male and female contexts? What are the roles of imprinted genes or X-inactivation? Have environmental causes for the skewed gender ratios been fully excluded?

Understand the Difference Between Disease Initiation and Disease Modulation, or the Difference Between Incidence and Severity. Is a Threshold Operative?

To raise alternative suggestions is not to ignore a plethora of published evidence that gonadal hormones influence autoimmunity.¹³ Animal models of autoimmunity constitute one of the strengths of this literature.²² Another strength is that experimental animal autoimmunity can be modulated by castration and by administration of gonadal hormones. Studies of the effects of pregnancy on immune function add further support, as do reports that exogenous hormones alter disease activity in humans. However, the available evidence speaks far more strongly to *modulation* of disease by hormones than it does to the role of hormones in *causation* of disease. It speaks to disease properties that can be manipulated for patients' good, but it does not answer the gender ratio question, why is autoimmunity a woman's disease?

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My task is twofold. First, I will present an overview of the gender differences in mental disorders. The second, which I consider the most critical, is a discussion of how the psychosocial context contributes to differences in women's health status and how their health behaviors and the implications of these differences impacts the development of a research agenda with the goal of providing gender-specific treatment for women. I have been asked to use and given permission to employ as the foundation for my remarks two American Psychological Association (APA) publications. The first is entitled *Research Agenda for Psychosocial and Behavioral Factors in Women's Health* (APA, 1996). The second is entitled *Health Care for Women: Psychological, Social and Behavioral Influences* (Gallant, Keita, and Royak-Schaler, 1997).

Psychosocial and Behavioral Factors that Contribute to Gender Differences in the Physical Health Status of Women

Despite an increased focus on the medical, biological, and epidemiological aspects of women's health, research has not adequately highlighted the central role that psychosocial and behavioral factors play in contributing to these differences in women's health status (APA, 1996) or the role they could play in the management of these chronic diseases. If we are to conduct research that is meaningful to women, we must not be fooled into thinking we have solutions when we merely successfully document differences in the rates and risks of diseases in women. Rather, it is important that we ask why these differences exist and search for the factors that brought about these differences. It is important that each of us remembers that a woman's health is a function of complex interactions between her personal behaviors and the economic, social, and physical environment in which she lives and works (Brown et al., 1996). While a woman's knowledge and attitudes are important components that influence her health-related behaviors, her behaviors are also strongly influenced by supports and barriers that she encounters in her personal intimate relationships, her friendship networks, her community, and her interactions within society (Brown et al., 1996). As an example, a 17-year-old woman struggling with an eating disorder is struggling against the societal message that thin is pretty, a social group norm among her friends that thin is popular, and, at times, the social reality that thin gets Mr. Right.

The focus of our research on women's health should also be on understanding how the experiences of different groups of women affect health-related issues, rather than on simply documenting differences between women and men as distinct groups. Health needs, barriers to obtaining services, styles of coping, or the basis for well being may vary among diverse cultural and socioeconomic groups (APA, 1996). It is important to remember that women are a heterogeneous group whose experiences may vary with ethnicity, race, marital or relationship status, parental status, education, income, occupation, sexual orientation, the type of job we hold, and where we live (APA, 1996). Where women live should no longer be reduced to urban versus rural but rather should include a focus on the quality of their neighborhoods. Do they live in neighborhoods with a high rate of violence, little public transportation, and few grocery stores with fresh produce? Sometimes not getting a prescription filled after leaving the doctor's office at 5 p.m. has more to do with the fear of getting home in the dark in a neighborhood where robbery and drive-by shootings are more commonplace than non-compliance or cultural conflicts with a health directive.

Physical Health and Psychological Experiences

It is important in our research on women’s health that gender-related psychological, behavioral, and social factors be examined within their interrelationships with biomedical factors (APA, 1996). Like ethnic status, social class, and age, gender is also associated with social realities that are different for women and men.

One area that illustrates the relationship between a physical and psychological experience is in the victimization of women. Table 1 offers insight into the link between violence and physical and/or psychiatric disorders (Mellman and Bell, 1996). Victimization, particularly in its physical forms, appears to have long-term mental health consequences (Glied and Kofman, 1995). Glied and Kofman found that major depression is two to three times as common among women who report that they have experienced a sexual assault (including child sexual abuse) in contrast to those who have not been victimized. Mellman and Bell (1996), in examining the consequences of violence, cite several studies that document higher rate of visits to physicians by victims of violence. In one study of rape victims, it is reported that the victims of violence had an 18 percent increase in physician visits in the year of the assault, 56 percent in the next year, and 31 percent in the following year compared with the women’s pre-assault level. There are a host of psychiatric disorders (e.g., alcohol and drug abuse or dependence,

TABLE 1. Summary of Psychiatric, Behavioral, and Physical Effects of Violence Against Women

Short Term	
Psychiatric and Behavioral	Physical
Acute stress disorder	Broken bones, bruises, cuts
Short or Long Term	
Psychiatric and Behavioral	Physical
Depression, low self esteem	Miscarriage
Suicide attempts	Preterm labor
Substance abuse	Fetal injury
Self-mutilation	Rupture of uterus, spleen, or liver
Running away	Sexually transmitted diseases
Anxiety	Hearing or vision loss
	Pain
	Physical complaints
Long Term	
Psychiatric and Behavioral	Physical
Posttraumatic stress disorder	Chronic headaches
Dissociative disorder	Low-birthweight babies
Multiple personality disorder	Functional bowel disorder
Stormy interpersonal relationships	Death by homicide
Revictimization	

panic disorder, obsessive-compulsive disorder, and posttraumatic stress disorder) that are found more frequently in persons with a history of sexual assault. In thinking about the differences in the health and mental health of women and men, studies like the above highlight the contributions that the social context of women's lives play in their physical or mental health status.

For the most part, the leading causes of death for women and men, if they live long enough, are heart diseases and cancers (see Table 2; Leiman, et al., 1997). However, there are gender differences in the pattern of mortality. A number of explanations have been offered to account for these gender differences. Some of these include the role of biology, technological advances in health care, stress exposures, stress responses, and differences in lifestyle (Woods, 1995). Yet, lost in this comparison is that life expectancies are not the same for all women. Currently, there is an almost 6-year difference in the life expectancy between white and African-American women (Woods, 1995; NCHS, 1993). Across the board, with the exception of Asian women, heart disease is the number one cause of death for women, followed by cancer, with diabetes, pneumonia and influenza, and cerebrovascular and chronic lung diseases bringing up the rear (Table 2; Leiman, et al., 1997). Despite a steady decline in the rate of cardiovascular disease mortality in the United States since the 1980s, heart disease is still the number one cause of death in American women (Leiman, et al., 1997). Women also have a worse prognosis for survival after myocardial infarction (MI) than men, and African-American women have the worst prognosis of all (APA, 1996). The research agenda for women's health must accommodate studies drawn from a variety of methodological approaches to explicate the causal mechanisms linking psychological, behavioral, and physiological processes in disease. For example, APA (1996), in its behavioral research agenda on women's health, suggests several areas of research that focus on the psychological mechanisms in cardiovascular disease in women. It would be well to broaden the research agenda to include these psychosocial studies in cardiovascular disease.

TABLE 2. Leading Causes of Death for Women and Men, 1993

Women	Rank	Men
Heart diseases	1	Heart diseases
Cancer	2	Cancer
Cerebrovascular diseases	3	Accidents and unintentional injuries
Chronic obstructive lung diseases	4	Cerebrovascular diseases
Pneumonia and influenza	5	Chronic obstructive lung diseases
Accidents and unintentional injuries	6	Pneumonia and influenza
Diabetes	7	HIV infection
Nephritis	8	Suicide
Septicemia	9	Diabetes
Atherosclerosis	10	Homicide

Source: P. Gardner and B.L. Hudson. "Advance Report of Final Mortality Statistics, 1993." Monthly Vital Statistics Report. Hyattsville, MD: Centers for Disease Control and Prevention, National Center for Health Statistics, 44 (7s), 1996.

TABLE 3. Health Problems More Common In Women Than Men

Health Problems	Number of Women (Percent)
Musculoskeletal-connective tissue	37 million
Osteoporosis	20 million (80)
Juvenile rheumatoid arthritis	61,000 (86)
Osteoarthritis	11.7 million (74)
Rheumatoid arthritis	1.5 million (71)
Systemic lupus erythematosus	450,000 (90)
Cardiovascular	(82 percent of women aged 45 to 74 years vs. 71 percent of men)
Hyperlipidemia	
Hypertension	16 million (58)
Kidney/urologic	
Incontinence	9.6 million (80)
Neurologic	
Migraine	12 million (70)
Glaucoma	1.5 million (67)
Psychiatric	
Depression	(9.7 percent of women vs. 4.7 percent of men)
Bulimia	7 million (87)
Respiratory	
Acute bronchitis	5.3 million (60.5)
Asthma	6.02 million (53)
Influenza	66 million (54)

Source: Pharmaceutical Manufacturers Association, *New Medicine in Development for Women* (Washington, D.C.: Pharmaceutical Manufacturers Association, 1991).

Litt (1993) presents health problems that are more common in women than men (Table 3). Beside the psychiatric categories, several of the health problems, rheumatoid arthritis, asthma, lupus, and even cardiovascular disease, are influenced by a variety of behavioral and psychological factors. Woods (1995) gave us a good context to think about differences in patterns of morbidity between women and men. Women and men are exposed to different risks of disease as a function of differences in the jobs they occupy in society, which not only provide differences in exposures but also access to health care through private insurance. There are also gender differences in lifestyle, socialization of response to illness, use of health services, and the stress exposures of women, especially for ethnic women as their ethnicity acts as a marker for social experiences like racism (Woods, 1995). So clearly a woman's health status is not just a matter of genetics.

Psychological and Behavioral Factors and Physical Health Status

Psychological and behavioral factors are important predictors of well being, vulnerability to disease, and disease outcomes (APA, 1996). For example, studies have begun to document that the negative emotions of psychological distress, anxiety, anger held in, and depression are psychological variables that can influence the course of postmyocardial infarction (see Knox and Czajkowski, 1997 for a fuller discussion). Recent research has suggested that each of these negative emotions may influence behavior, thrombogenesis, and arrhythmogenesis

in a variety of ways. Frasure-Smith and her colleagues (1996) suggest examining whether anxiety may be more important than depression or held-in anger in accounting for thrombogenesis, while depression and anger may be crucial psychological factors in arrhythmic events. As presented later, both anxiety and affective disorders, which include depression, are more prevalent in women than men.

Quality of Life

Quality of life is an important outcome measure and includes a sense of well being, functional health, and engagement in the psychological and social world (APA, 1996). One area that illustrates the gender differences in the quality of life for women is rheumatoid arthritis. Arthritis is among the most common self-reported chronic condition affecting women (see APA, 1996, for fuller discussion). Many of the more common and also debilitating forms of arthritis and rheumatic disease (e.g., osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia) affect two to five times more women than men (APA, 1996). DeVellis and her colleagues report that people with rheumatoid arthritis experience difficulty in leisure and religious activities, visiting family and friends, and using different forms of transportation (DeVellis, Revenson, and Blalock, 1997). DeVellis, et al. cite a study by Reisine and Fifield (1992) that illustrates differences in the impact of these difficulties on the quality of life of men and women. More men reported difficulties in their abilities to do yard work and care for the car. For women however, their arthritis had an impact on nurturant activities such as making arrangements for others, taking them places, maintaining social ties by writing or calling, listening, and taking care of sick people. Women who experienced these type of limitations were less satisfied with their ability to be a nurturant support provider.

In two previous reviews by DeVellis (1993, 1995), she finds that depression and/or depressive symptomatology have a high co-occurrence in persons diagnosed with rheumatoid arthritis. Research suggests that people with serious chronic diseases are at greater risk for developing depressive disorders and symptoms (Wells, Golding, and Bumam, 1988, in APA, 1996). When depressive symptoms occur in combination with other chronic diseases, levels of functioning decrease (Wells et al., 1989). As the APA agenda so aptly points out, as women are at greater risk for depression and for some of the more debilitating forms of arthritis and rheumatic disease, they bear a double burden of potential disability (DeVellis, 1993). A better understanding of the scope and impact of depression in arthritic and rheumatic diseases as well as research on how to prevent and treat depression in this population is needed (APA, 1996). Of course, it is not surprising that when depression occurs with a health condition like rheumatoid arthritis, the decline in functioning is worst (DeVellis, et al., 1997). We already know that the rate of depression in women is about twice that of men. For women with rheumatoid arthritis, if depression is mistakenly overlooked, declines in functioning may be attributed to the rheumatoid arthritis and not treated, while the rheumatoid arthritis is overtreated. In addition to gender differences in response to this disease, two studies seem to indicate cultural differences as well (Abraido-Lanza, in press; Abraido-Lanza, Guier, and Revenson, 1996). Abraido-Lanza in her study of Latina women suffering from rheumatoid arthritis found not only were these women likely to exhibit depressive symptomatology but also their coping responses reflected a culture-based notion of coping and culturally valued norms that they turned to for help. As epidemiological studies have consistently demonstrated worse health outcomes among women with arthritis and rheumatic diseases, especially for ethnic minority and lower socioeconomic groups, it is important to determine what mechanisms are at work. As illustrated in Abraido-Lanza's studies, cultural differences may play a defining role in how women manage their health care. Other potential constructs that could explain these relationships include stress, social support and coping mechanisms, and access to health care, as well as differential treatment patterns.

Contextual Contributions to Gender Differences in Women's Health Status

There are a series of contextual factors that should be considered in designing, implementing, and interpreting research if the goal is discovery of gender-specific conditions of women's health. This approach will help to enhance traditional biomedical research and offer new insights (APA, 1996). There are contexts that behavioral research findings imply may be critical to consider in the development of a gender-specific research agenda for women.

Relationships

How do women's relationships affect health status, health behaviors, and health attitudes? How do health behaviors, attitudes, and health status affect women's relationships (APA, 1996)? We know that being married is more advantageous to men's health than women's health. Marriage appears to confer a protective advantage against depression for men, which is less true for women (McGrath, et al., 1990). In unhappy marriages, women are three times more likely as men to become depressed (Weissman, 1987; McGrath, et al., 1990). Marital disruptions are not good for either sex, but women seem to suffer the most (see Glied and Kofman, 1995, for a fuller discussion). Glied and Kofman cite research that indicates that those who are separated or divorced are 2.5 times more likely than married people to suffer a depressive disorder (Regier, et al., 1988). Those women who experience marital disruption were found to have rates of depression 3.1 times higher than happily married women, 2.1 times higher than unhappily married women, and 1.7 times higher than women who were already divorced or separated (Bruce and Kim, 1992, in Glied and Kofman, 1995). For men, the protective effect of a continuing happy marriage is even stronger (Glied and Kofman, 1995).

There are other studies on relationships that raise questions on the extent to which women's caretaking and provider roles in the family have resulted in their own health care needs being delayed or ignored. In their role as caretakers of children and parents, we find that vulnerability to demoralization and depressive symptoms to be higher in mothers of young children; women who have responsibilities to care for aging parents are also at higher risk (McGrath, et al., 1990). Similar stresses also affect those caring for medically or mentally ill family members (Thurer, 1983). Knox and her colleagues note that fewer women, for example, attend and adhere to cardiac rehabilitation programs (Knox and Czajkowski, 1997). They suggest that this may be a function, to a greater extent for older women, of lifestyle constraints, as the women are more likely than men to have caregiving burdens. Social support and social isolation are important in coronary artery disease and postmyocardial infarction. Social isolation, which is defined as lacking an intimate confidant, having few friends or social activities, or not having access to practical assistance when needed in everyday situations, has been associated with cardiovascular mortality (Knox and Czajkowski, 1997). It is important to remember that women live longer than men, and, therefore, when they suffer from the problems associated with heart disease, they may be living without a spouse.

As a psychologist, it is also important that I discuss the concept of negative social support. Not all social support has a positive effect, so assuming that a person has a network of people does not always imply that the network is furnishing positive helpful support. What can be found is that even when women are sick and or disabled, they still are in the caretaking and head of household role in which their nurturance, guidance, and support are relied upon and needed to maintain their family system. This may result in their own health care needs receiving lower priority.

Ethnicity

How do women's ethnic backgrounds shape their health, health behaviors, and attitudes (APA, 1996)? Abraido-Lanza's studies of Hispanic women's coping with rheumatoid arthritis is an example of how culturally valued norms and culturally based notions influence the coping process.

Resources and Status and Power

There are the two additional elements, namely resources and status and power. How do financial and structural resources enhance or limit women's health options? (APA, 1996). How do women's social status, work status, and power within relationships limit health options or affect health status? Epidemiological studies have repeatedly shown a relationship between socioeconomic status (SES) and coronary heart disease (CHD) with poorer populations suffering from higher rates of CHD. It is thought that lifestyle behaviors are associated with lower SES populations such as unhealthy diets, higher rates of smoking, and health behaviors, i.e., higher rates of obesity. More recent research shows a larger proportion of chronic physical and psychosocial stressors, such as jobs with high demand and low decision latitude, low social support, high job dissatisfaction, unemployment, residential areas with high crime rates, and poor access to medical treatment among people with low socioeconomic status. Many of these psychosocial factors are related to cardiovascular risk.

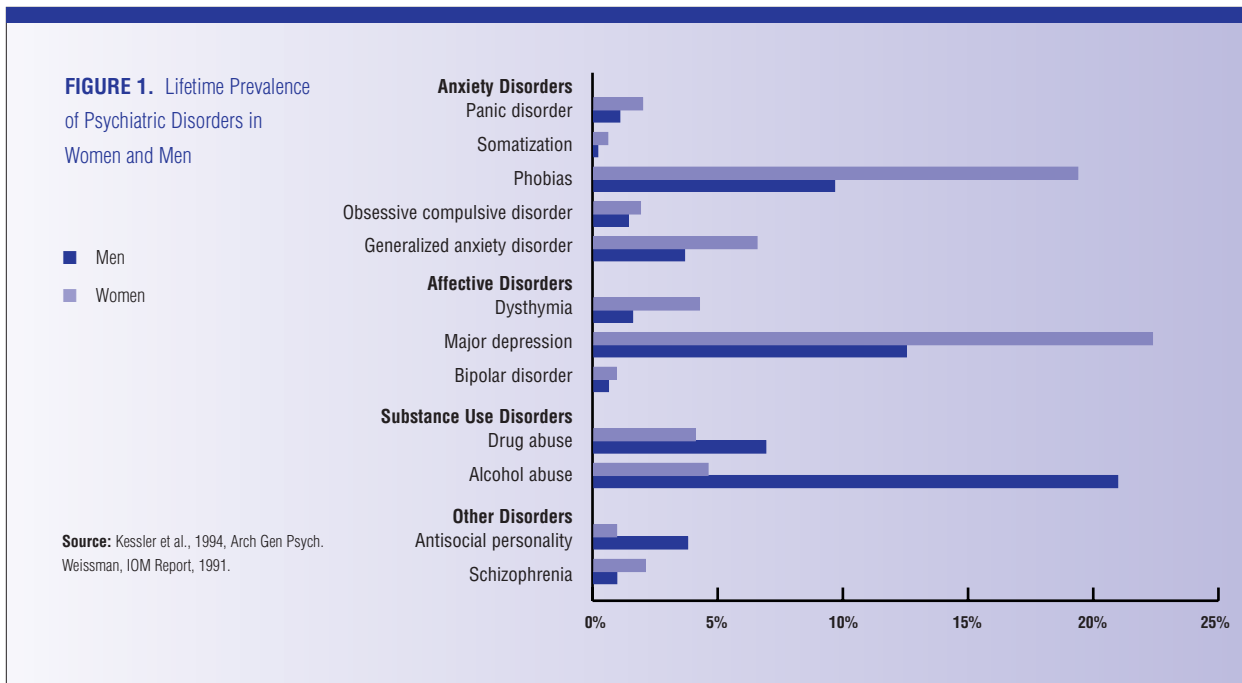
Gender Expectations

The final contextual issue presented by APA is gender expectations: how is health status affected by gender expectations, such as expectations for mothering/primary parenting and caregiving for others who are sick or in need, expectations to serve as an emotional support system for others, and expectations for housework and other household tasks. Women are usually supportive in helping implement lifestyle changes for their husbands and other family members (e.g., dietary changes, exercise, and stress reduction) that are necessary for increasing the probability of survival. However, the lifestyle changes that are important for women's own rehabilitation of CHD may engender negative responses from immediate family members because these changes may conflict with gender role expectations of women (e.g., traditional caretaker and nurturer). Research is needed that examines the effect of these gender role expectations on the ability of women to affect and maintain health-related lifestyle changes and the subsequent effect on quality of life, depression, and disease course.

Gender Differences in Mental Health Occurrences

Turning now to the first charge, I will say a few words about gender differences in mental health status. First, an important and surprising finding that emerged from the data collected by the Epidemiology Catchment Area study was that men and women are equally likely to suffer from mental disorders. This finding has been underscored in the more recent National Comorbidity Survey (Kessler, et al., 1994). Prior to the 1980s, small-scale studies were likely to indicate that women had a higher prevalence of mental illness than men, accounting for the perspective that we still encounter that mental illness is a woman's issue. However, while men and women may in equal numbers suffer mental illness, the patterns and types of illnesses as well as responses to treatment differ profoundly and have significantly different implications in terms of their impact on the lives of women and men.

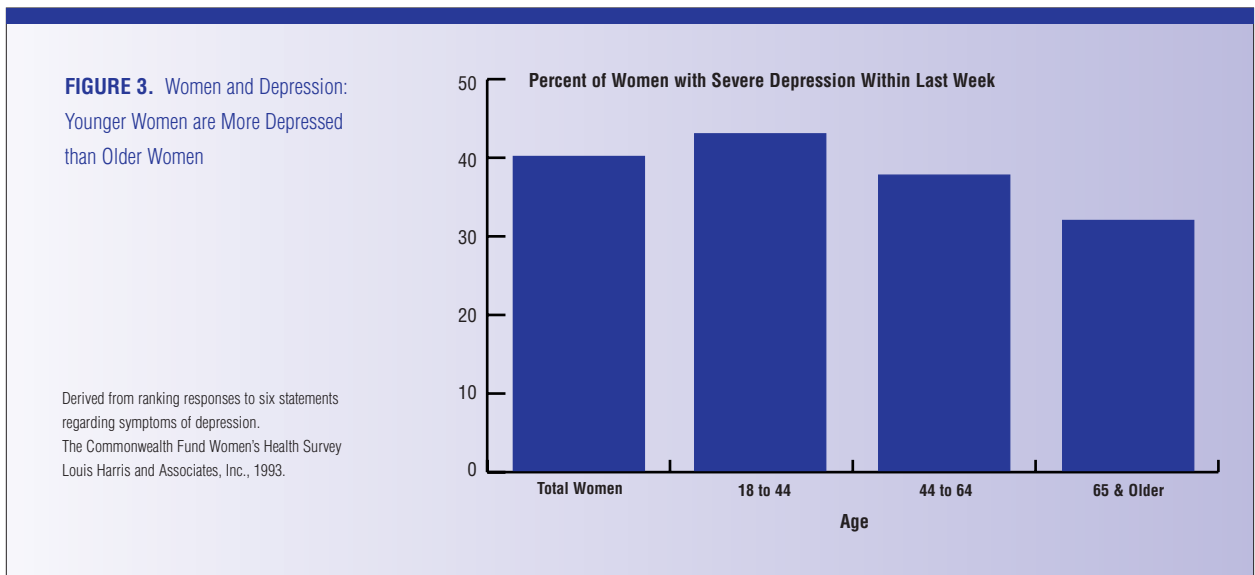
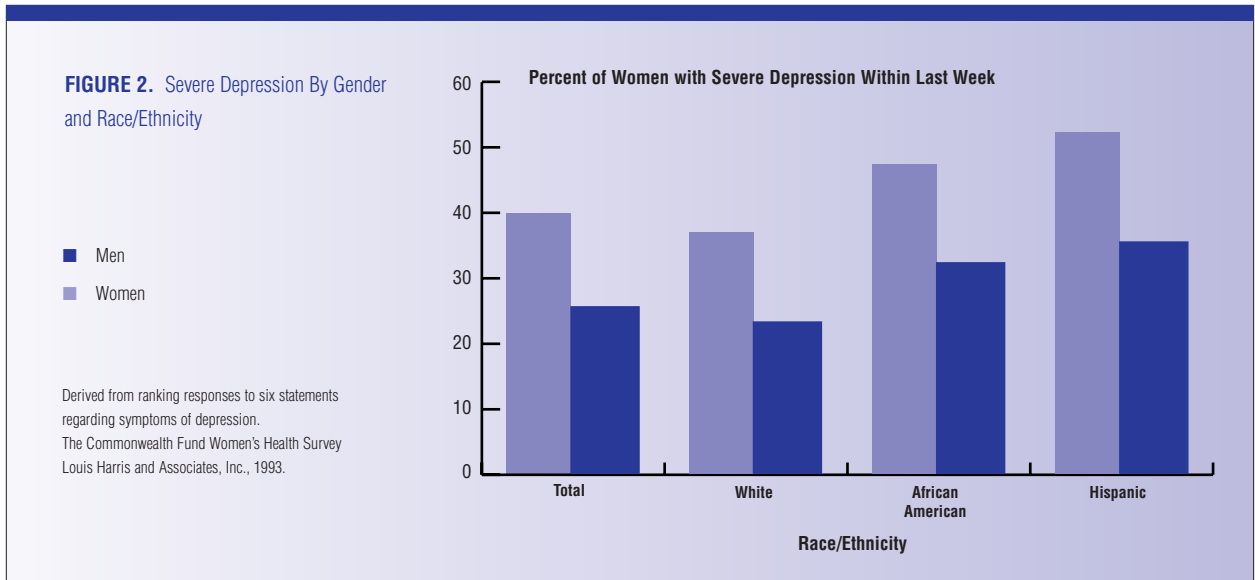
To look at these differences, I have combined data from National Comorbidity Study and the Institute of Medicine's 1991 report. Figure 1 shows that women are more likely to have anxiety and affective disorders (with the exception of mania), while men are found in greater numbers to be diagnosed with antisocial personality and



substance use disorders (Kessler, et al., 1994). In the area of anxiety disorders, the lifetime prevalence of phobias for men is about 10 percent, while women is 18 percent (Glied and Kofman, 1995). The same approximately 2 to 1 women to men pattern is found for generalized anxiety disorders (Glied and Kofman, 1995). One area not on the chart is eating disorders. Approximately 90 percent of those diagnosed with eating disorders are women.

Looking at the affective disorders, women are significantly more likely than men to suffer from this debilitating health problem. Depression is one of the nation's most serious mental health problems. People suffering from depression experience reductions in functioning as severe (and sometimes more severe) as those associated with a variety of serious medical conditions including hypertension, diabetes, and arthritis (Wells, et al., 1989). Depression that is untreated can linger for 6 months or longer, and is likely to recur (APA, 1990). APA's Task Force on Women and Depression estimated in 1990 that more than 7 million women in the United States were suffering from a diagnosable depression (McGrath, et al. 1990). Lifetime rates of depression in women as compared to men in both the ECA and NCS are two to three times greater. Consequently, research on depression should be a major focus of a women's health research agenda.

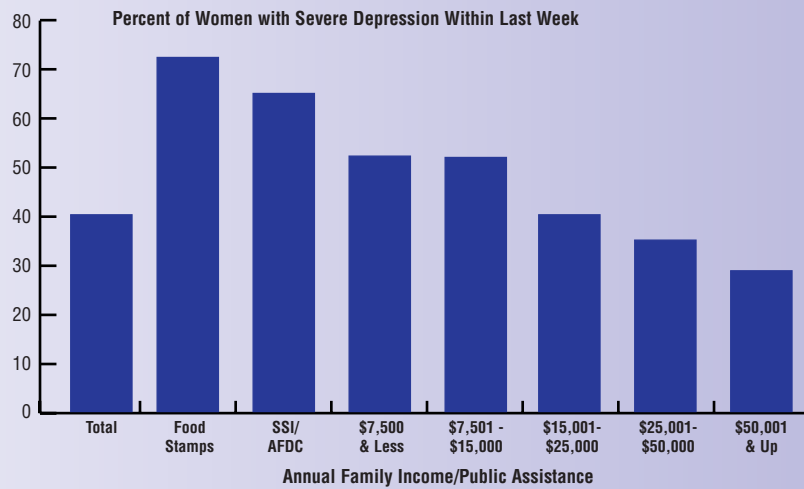
Differences in the rates of depression between women and men are found in every age group among blacks, whites, and Hispanics after controlling for income, education, and occupation (Glied and Kofman, 1995; McGrath et al., 1990). The Commonwealth Fund Women's Health Survey found that not only is depression more severe in women than men, but that the percentage of women reporting severe depression was highest in Hispanic followed by African-American women (see Figure 2). Younger women were more likely to report severe depression (see Figure 3), and poor women were the most likely to report severe depression (see Figure 4). Several studies show an increasing prevalence of major depression in younger age groups, with the onset of depression now occurring in the teenage and early adult years (Regier, et al., 1988). Increasing experience of life events and loss of attachments, shifts in family structure, women's changing position in society, and increasing social anomie have been put forward as possible explanations for this trend (Weissman and Klerman, 1977, 1992). Biological



susceptibility, sociocultural and psychosocial explanations, and reproductive and endocrine-related factors have been advanced as explanations for the preponderance of depression in women, but, according to the APA Depression Task Force, these theories cannot fully account for the observed gender differences (Weissman and Klerman, 1977; McGrath, et al., 1990).

Recently studies have identified gender differences in how men and women synthesize serotonin (Nishizawa, et al., 1997). The rate of serotonin synthesis was found to be 52 percent greater in men than women, which may have implications for the higher incidence of major unipolar depression found in women (Nishizawa, et al., 1997). Equally a problem is the fact that little research has focused on differential treatment response patterns to pharmacological treatments for major depression in women and men (APA, 1996; Glied and Kofman, 1995). Response to psychopharmacological treatments can be considerably affected by psychosocial experience and hence has an implication for differences in response between men and women.

FIGURE 4. Depression and Income
Levels: Poor Women on Public
Assistance Most Vulnerable



Derived from ranking responses to six statements regarding symptoms of depression.
The Commonwealth Fund Women's Health Survey
Louis Harris and Associates, Inc., 1993.

These gender differences in psychological disease as well as gender differences in psychosocial aspects of the disease process are critical variables for study in a new research agenda focused on women's health.

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THE PHARMACOLOGIC DIFFERENCES BETWEEN WOMEN AND MEN

For the most part, the only practical opportunity to critically evaluate potential differences between the actions of drugs in subsets of the population (in this case women and men) is during a drug's clinical development. Once a drug is in general clinical use, only the most dramatic differences in response are likely to be detected. Until recently, women have been underrepresented in clinical trials during drug development, and differences in response were not detectable or even anticipated during data analysis. Therefore, few of the drugs in clinical use today have been carefully examined for differences in response between women and men. Yet, as increased awareness of these potential differences has grown, it has become clear that there are major unforeseen differences in how some drugs are handled (pharmacokinetic differences) and how the body responds to drugs (pharmacodynamic differences).

Pharmacokinetic and Pharmacodynamic Differences

Because of advances in analytical chemistry, it has become possible to examine the pharmacokinetics of most drugs and compare their fate in women and men. These studies can often be performed in normal volunteers and are far easier to conduct than a clinical trial seeking to measure a surrogate for the drug's actions or, more difficult yet, clinical benefit. Therefore, far more pharmacokinetic studies have been performed comparing plasma drug concentrations in women and men. Relatively few pharmacodynamic comparisons are available. This has become an important point because one cannot assume that higher or lower plasma concentrations in one sex will always yield the expected difference in response. The best example is propranolol. Several studies have demonstrated the higher clearance of propranolol in women and the resulting lower concentrations in plasma. However, our recent study, funded by the Office of Women's Health of the FDA, demonstrated that, at the same plasma concentration, women were more sensitive to propranolol than men, resulting in the same clinical response to a given dose. In this case, increasing the dosage for women to account for their lower plasma concentration would have been unnecessary and potentially dangerous.

I will not attempt to summarize the numerous examples of gender differences in pharmacokinetics and drug response that have been documented in the medical literature. These have been reviewed by Harris, et al. (*Drugs*, 50(2):222, 1995) and by Dr. Mary Berg (*Proceeding: Gender-related Health Issues, 55th World Congress of Pharmacy and Pharmaceutical Sciences, Aug. 29-30, 1995, Stockholm, Sweden, ISBN 0-917-330-80-3*). These reviews cite ample evidence that one of the more relevant pharmacokinetic parameters (absorption, distribution, clearance, half-life, metabolic or renal clearance, protein binding) may be different for a specific drug when women and men are compared. What is often missing are data to show that these differences are clinically relevant. It is unlikely that small, even statistically significant, differences in pharmacokinetics will be clinically relevant. A possible exception would be for a drug with a narrow therapeutic index, i.e., the range of dosages required for efficacy are very near those that cause side effects. There are numerous reasons why such differences in response, even if present, might not be detected. Many drugs (especially those with a narrow therapeutic index) are titrated to a clinical endpoint, and the differences would only appear as a slightly higher or lower final dosage for women compared

to men. However, when there is no readily available endpoint for titration (e.g., cancer prevention), a pharmacokinetic difference could mean that women would be less likely to receive an effective dosage. More rapid clearance and lack of titration were considered as the reason why women with subarachnoid hemorrhage failed to respond to the investigational drug trilizad.

Drug Metabolism

Recent advances in our knowledge of drug metabolism have identified fruitful areas of research that have not as yet addressed the potential importance of gender. The ability to determine the specific isozyme responsible for oxidative metabolism of drugs by cytochrome P450 (CYP) enzymes has made it possible to predict how drugs are likely to be metabolized in humans and to predict which drugs are likely to interact. Only a few of the CYP family of enzymes have been carefully studied for gender differences, but the CYP3A family, which is responsible for metabolism of most drugs, has shown consistently higher activity in females resulting in lower plasma concentrations for many drugs. Important enzymes, such as CYP2D6 and CYP2C19, which have polymorphically distributed activity, have not been adequately studied for differences in men and women. Important detoxification enzymes, such as conjugation, have been found in some studies to have lower activity in women. Fluorouracil dehydrogenation, responsible for clearance of the anticancer drug 5-fluorouracil, was found to have lower activity in women, raising concern that they should be given a lower dosage than men. However, a clinical study comparing efficacy at equivalent exposures would be required to be sure that the differences in metabolism justify a change in dosage for this potential life-saving and, at the same time, potentially toxic drug.

Gender-specific Factors

Numerous studies have demonstrated that sex-specific factors, i.e., menstrual cycle, menopause, pregnancy, oral contraceptives, and hormone replacement therapy, can be responsible for pharmacokinetic differences between women and men and within an individual studied at different times. Importantly, there are many studies in the literature that have conflicting results, often because they have small sample size or design errors. In many cases, the mechanism responsible for the influence of menopause lies in the effects of hormones to competitively inhibit drug metabolism or in some cases to induce the metabolism of drugs.

Gender and Adverse Drug Reactions

Case report: A 29-year-old female was taken to the emergency department because of an episode of syncope. She had been taking terfenadine (Seldane) for seasonal allergies and her podiatrist had prescribed ketoconazole (Nizoral) for a fungal infection. Four days later, she was working in the garden and suddenly lost consciousness, fell to the ground, and then regained consciousness in a few seconds. In the emergency department, the physicians recorded a negative physical and laboratory evaluation. However, her ECG was later noted to have a QT interval of 520 msec (normal <440).

She was discharged and sent home with instructions to return if she had recurrence of her symptoms. The next day, she was found dead on the floor of her living room holding her 3-month-old infant.

This tragic case is one of several dozen similar reports with terfenadine, a normally very safe antihistamine. It is now known that the cause of death in cases such as this and others with astemizole (Hismanal) is most likely a form of ventricular tachycardia, torsades de pointes (TdP). TdP is a syndrome in which the arrhythmia has a

characteristic appearance on the ECG, “twisting of the points,” and is preceded by prolongation of the QT interval. This arrhythmia has been observed with a broad range of drugs that have as a common feature the ability to block potassium channels in the heart. These are the channels responsible for repolarization of the action potential and, when blocked, result in QT interval prolongation on the surface ECG. Although originally described with antiarrhythmic drugs (quinidine, procainamide, disopyramide, sotalol), TdP has also been reported with antihistamines (terfenadine and astemizole), antibiotics (IV erythromycin, pentamidine, trimethoprim/sulfa, halofantrine), and pimozide, haloperidol (Haldol), thioridazine (Mellaril), cisapride (Propulsid), bepridil (Vascor), and several other drugs.

It has become apparent that the risk of developing TdP with many of these drugs is greater in women than in men. For the antiarrhythmic drugs, terfenadine, prenylamine, halofantrine and pimozide, there is a clear preponderance of women in the reports in the literature or in the FDA’s Medwatch database. The mechanism of the increased risk is not known. It is not explained by higher plasma concentrations in women or other obvious clinical factors. One possible contributing factor is that women normally have a longer QT interval at baseline than men. Animal research has shown that the longer QT interval can possibly be explained by effects of sex hormones on the expression of potassium channels in the heart. These studies also found that sex hormones can modify the sensitivity of the heart to potassium channel blocking drugs, in this case quinidine. Estrogen-treated hearts, when studied in vitro, were more sensitive to quinidine than hearts previously treated with androgens. The results of another recently completed clinical study, funded by the Office of Women’s Health at the FDA, has confirmed these findings in normal men and women. When given intravenous doses of quinidine, the women had ~50 percent greater prolongation of their QT interval than the men at any given concentration.

These studies have not yet identified the mechanism for the greater sensitivity of females to potassium channel blockers. Additional factors are clearly necessary to explain why some women are especially sensitive and develop the clinical arrhythmia. However, understanding the mechanism would have the potential to indicate ways to predict and then prevent the occurrence of this rare, but potentially lethal arrhythmia.

In summary, there are documented differences in the pharmacokinetics and pharmacodynamics for drugs in women and men. While many of these are not clinically relevant, some have been found to result in increased risk of adverse effects, even life-threatening arrhythmias. Research into the mechanism of this and other gender-specific adverse drug reactions is necessary to reduce the unwanted consequences of drug therapy for women and may additionally lead to improved therapy for men, children, and the elderly.



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

New Orleans, Louisiana
June 11, 1997

Welcome to the second of three regional public hearings that the Office of Research on Women's Health (ORWH) of the National Institutes of Health (NIH) is pleased to sponsor, to receive public testimony on the women's health research agenda for the 21st century.

We are grateful to our regional hosts, Tulane University Medical Center, Xavier University of Louisiana, and Meharry Medical College. They have worked so diligently with us to assist in bringing this facet of NIH's fact-finding process on public views of important issues for research on women's health to New Orleans.

In reviewing and renewing our priorities for women's health research at NIH, we look to the broader community of scientists, health care providers, and women's health advocates to ensure that we have the most up-to-date information about continuing and emerging concerns that confront women in preserving their health and well being and in overcoming adverse health consequences from conditions or diseases that affect them.

Because NIH is the primary agency within the Department of Health and Human Services that performs, promotes, and supports biomedical and behavioral research, our focus is on research which should be initiated, expanded, or enhanced through NIH programs on women's health, as well as to promote career opportunities for research on women's health, especially that of women in biomedical careers. Therefore, we are delighted that so many of you are here to support our efforts and provide your wisdom and insights into our consideration of issues of importance for the NIH research agenda

on women's health for the 21st century. Your participation provides us continuing support and inspiration for the future improvement of women's health through biomedical and behavioral research, and we are very appreciative of being a part of this process.

ORWH was established within the Office of the Director of NIH in September 1990, and was charged with the critical objective to give a central NIH focus to women's health issues and to establish a science base that will permit reliable diagnoses and effective treatment and prevention strategies for women through NIH-supported biomedical and behavioral research.

The major objectives of our office are:

- 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;
- To ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially clinical trials, that are supported by NIH; and
- Direct initiatives to increase the numbers of women who are participants in biomedical research careers.

In determining directions for these objectives, we look for guidance and input from the scientific and advocacy communities. One of the most effective ways for us to accomplish this is through public hearings, such as this at which you are gathered today.

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, *National Institutes of Health: Opportunities for Research on Women's Health*, is based upon public testimony and a scientific meeting held in Hunt Valley, Maryland in 1991, and is available from the offices of ORWH.

In September 1996, at our first regional meeting in Philadelphia, we began our process of re-examining our research agenda to ensure that it is relevant as we move towards the next century, thus, the name of this series of meetings is, "Beyond Hunt Valley: Research on Women's Health for the 21st Century."

During this scientific workshop in New Orleans, we shall examine aspects of the research agenda based upon sex and gender differences, i.e., physiological, psychosocial, and pharmacologic differences between women and men. At our third and last regional meeting in Santa Fe, New Mexico on July 21-23, hosted by the University of New Mexico Medical Center and the University of Iowa School of Pharmacy, we shall focus on factors that contribute to differences in health status and health outcome among different populations of women.

Finally, on November 17-19, we shall bring together the results of all three regional meetings in a workshop which will be held in Bethesda, Maryland, to provide an opportunity for our participants to guide our Task Force in developing recommendations for the NIH research agenda for the beginning of the 21st century. I invite all of you to join us in these further steps.

During today's Public Hearing, we have specifically requested perspectives about:

- The state of knowledge and continuing or emerging gaps in knowledge about women's health across the life span;
- Sex and gender differences and their impact on women's health;
- New priorities for research on women's health;
- Environmental, genetic, hormonal, non-hormonal, and other factors that impact on women's health; and
- Career issues for women scientists and how to overcome barriers.

Your testimony will be received and reviewed by our Task Force on the NIH Women's Health Research Agenda for 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 who are serving as members of this important Task Force.

We are grateful for the dedicated leadership of this Task Force by the cochairs: Dr. Marianne Legato, a distinguished cardiologist and women's health researcher and advocate of Columbia University, who is a member of our Federal Advisory Committee, and Dr. Donna Dean, Chief, Biological and Physiological Sciences, Division of Research Grants at NIH, who serves as a member of our NIH Coordinating Committee and Chair of our NIH Research Subcommittee which provides advice to ORWH about priorities and funding programs.

We look forward to your contributions to this process and thank you for your role in reassessing women's health research as we enter the next century.

PUBLIC TESTIMONIES
NEW ORLEANS, LOUISIANA
JUNE 11, 1997

Gerald S. Berenson, M.D.

Tulane Center for Cardiovascular Health

James E. Dill, M.D.

Behavioral Medicine Solutions of Virginia

Carolyn Evans, M.S.W.

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Gerald S. Berenson, M.D.

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 young adults 19 to 32 years of age shows that some 10 percent of white females and 22 percent of black females have a BMI greater than 32.3kg/m², representing morbid obesity. Fifteen percent of black females 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 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. 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.

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James E. Dill, M.D., F.A.C.P.

The Gallbladder, the Gut, and the Brain: Connections and Implications for Women's Health

My name is Dr. James Dill. I represent Endoscopic Ultrasound of Virginia and Behavioral Medicine Solutions of Virginia, both of which are Divisions of Roanoke Gastroenterology, P.C., headquartered in Roanoke, Virginia. I am a gastroenterologist in private practice with graduate training in rehabilitation counseling. My interest areas are research involving the diagnosis of gallbladder disease with endoscopic ultrasound and the biopsychosocial aspects of irritable bowel syndrome (IBS). Both of these conditions predominantly affect women.

My goals in testifying are to stimulate interest in new diagnostic and treatment modalities, respectively, concerning the above disorders. It is hoped that these diagnostic and treatment methods will be utilized to benefit women — relieving suffering through quality, cost-effective health care.

Today, I have the privilege of speaking to you about two medical conditions that are not usually discussed together, both of which are important to women's health. The first condition is gallbladder disease of the type that is often difficult to diagnose. Our most recent article on this research, "Symptom Resolution or Relief Post Cholecystectomy Highly Correlated with Combined Endoscopic Ultrasound and Stimulated Biliary Drainage (EUS/SBD),"¹ which has been accepted by the journal *Endoscopy*, deals with this issue.

Gallbladder disease is common in the general population with the incidence of gallstone disease reported to be as high as 10 to 40 percent in women, depending on the age range.² In the United States, it has been estimated that approximately 20 million individuals have gallstones.³

Treatment decisions are straightforward for symptomatic patients having gallstones on transabdominal ultrasound (TUS). These decisions are much more difficult in patients with classical biliary pain symptoms and negative TUS. Many of these patients, the majority of whom are women, continue with severe bouts of abdominal pain and undergo multiple, costly, and at times uncomfortable tests. Worse yet, many are labeled as having functional disease and are told that their problems are "all in their head." Evidence is accumulating that significant numbers of patients with biliary symptoms and negative TUS have clinically significant gallbladder disease manifested by gallstones or gallbladder inflammation and possibly cholesterosis.⁴⁻⁸

Recently, evidence has been accumulating that a new technique, combined endoscopic ultrasound and stimulated biliary drainage (EUS/SBD), has the ability to select out symptomatic patients with histologic gallbladder disease not evident on other tests, but more importantly who will benefit from cholecystectomy.^{7,8} EUS/SBD is performed under sedation by placing an endoscope with an attached ultrasound probe into the patient's stomach — this allows a superior view of the gallbladder and its contents, including tiny stones and sludge when present. The gallbladder can then be stimulated with an intravenous substance named sincalide and bile collected for microscopic examination looking for the presence of crystals. These crystals represent the building blocks of gallstones.

Eighty patients were selected for a study from a group of 81 with biliary pain, negative TUS (except for gallbladder sludge on three) and positive EUS/SBD.¹ All 81 patients underwent cholecystectomy consecutively. One patient was eliminated from the study because multiple attempts to contact her were unsuccessful. Seventy-one of the patients were female (89 percent) ages 14 to 82 (average 45); and nine were male (11 percent) ages 23 to 61 (average 44).

The 80 patients were surveyed an average of 15.4 months post-cholecystectomy with a range of 7 to 27 months. Seventy of the patients were 1 year or more post surgery. Contacts were made by telephone and the patients were questioned as to the presence or absence of their original biliary pain and the presence or absence of improvement in that pain pattern if not resolved.

Cholecystectomy 76 of the 81 original patients had abnormal histopathology of either cholecystitis, cholesterolosis, or both. This gave a sensitivity of 93.8 percent and a positive predictive value of 100 percent for EUS/SBD. In the outcome study, 70 of the 80 patients (with positive EUS/SBD) for whom data was available (87.5 percent), remain free of biliary pain an average of 15.4 months post-cholecystectomy. The range of followup was 7 to 27 months. Seven patients (8.8 percent) remained with biliary pain but were improved. These figures gave an overall total of 77 (96.3 percent) patients who were either free of biliary pain or improved. Only three (3.7 percent) of the patients were unimproved.

These outcome results are important in that they represent the only lengthy outcome study in a patient population this large who were post-cholecystectomy for biliary pain and negative (or nearly negative) TUS, but positive EUS/SBD.

In summary, EUS/SBD shows great promise in the detection of subtle gallbladder disease, not evident on TUS or other diagnostic tests. Even more importantly, positive EUS/SBD predicts pain relief post-cholecystectomy in a high percentage of these patients; the overwhelming majority of whom are women.

I have undertaken a preliminary study of the relationship between gallbladder disease and IBS.⁹ The charts of 20 patients who had been diagnosed by EUS/SBD and who had been proven to have gallbladder disease at surgery were reviewed. Ten of the patients had a diagnosis of IBS and 19 had gastroesophageal reflux disease (which is considered part of the spectrum of IBS). This is consistent with the finding that many of our gallbladder patients had poor motility of the gallbladder suggesting a global motor disorder.

Next, I would like to discuss IBS further, specifically our paper "Abuse, Threat and Irritable Bowel Syndrome: What is the Connection?" which has been accepted for publication in *Gastroenterology Nursing*.¹⁰

IBS continues to claim the attention of clinicians and researchers alike as the mysteries of the "brain-gut connection" are unveiled. Drossman and others have led us to fully understand that chronic functional abdominal pain, including IBS, is best viewed from a biopsychosocial framework.¹¹ Nurses who have had daily experience working with patients with IBS know firsthand the degree of suffering, shame, and disability that can accompany a diagnosis of severe IBS.

Several years ago we, as a physician and a nurse in a solo gastroenterology practice, targeted the patient with IBS for extra attention and support and developed an integrated treatment model which proved to be helpful to patients.¹² This collaborative practice approach involving physician, nurse, and counselor enabled us to focus on the psychosocial aspects of care instead of symptoms alone. That same year researchers labeled IBS as a multi-billion dollar problem and proved what we had long suspected; the enormity of the cost to society.¹³

There is increasing awareness in the medical community of the association of interpersonal abuse and functional bowel disorders including IBS. Our research study was designed to determine the percentage of patients with both IBS and histories of sexual abuse in a solo gastroenterology practice, as well as the effects of that abuse and threat on symptom severity.

The sample consisted of 77 consecutive patients attending routine outpatient appointments in a solo gastroenterology practice. Each patient had been previously diagnosed with IBS using Manning criteria¹⁴ after a gastroenterological workup to rule out organic disease.¹³ Patients ranged from 24 to 84 years with a mean of 53.7 (SD = 14.1). Seventy-nine percent were female; 94 percent of the subjects were white, 1.4 percent were African-American; 2.9 percent were Hispanic; and 1.4 percent were American Indian.

After signing voluntary consent forms, the patients were administered a questionnaire packet, in a private setting, consisting of various measures. The instruments included a demographics questionnaire, a modified IBS symptom checklist,¹⁵ and a modified version of the Sexual Abuse History Inventory.¹⁶

Thirty-eight percent of the patients reported histories of childhood or adult sexual abuse. Patients with histories of abuse alone had a mean symptom score similar to those without such histories (32.5 vs. 30.5). Patients reporting abuse plus threat of abuse had a significantly higher mean symptom score (44.1) than patients reporting no abuse (30.5).

The study results confirm the idea that threat combined with abuse is a more significant predictor of IBS symptomology than abuse alone (when both are compared with no abuse) even after accounting for socioeconomic status and other variables. The results of this study raise some important considerations. The first point is that of demographics: namely that 38.5 percent of the study population had a history of childhood or adult sexual abuse which is greater than the 30 percent figure reported by Talley¹⁹ for a general population with IBS who were surveyed by mailed questionnaire. However, the percentage in our study is less than the 44 percent reported by Drossman¹⁸ in a tertiary care academic setting.

Another point of interest in this study was the finding that 68 percent of the patients with histories of childhood or adult sexual abuse reported that they were also exposed to the threat of abuse. Patients exposed to both threat and actual abuse had much higher symptom scores (mean 44.1) than those not exposed to abuse (mean 30.5). This raises the possibility that abuse is more likely to affect symptom severity when combined with the threat of abuse.

This important connection between threat, stress, and gut response is underlined by the recent study of Silverman, et al., that demonstrated a brain activation pattern, involving the central vigilance network, that was abnormal by positron emission tomography in subjects with IBS.²⁰

Individuals who develop posttraumatic stress disorder (PTSD) are hypervigilant and quite sensitive to perceived threats in their environment.²⁰ This factor, combined with the tendency to activate the cerebral vigilance network in patients with IBS as mentioned above, has particular clinical relevance in dealing with patients with IBS who have been abused. The establishment of a “safe” therapeutic environment, involving primarily the relationships between key office personnel and patients, is paramount. We have developed an integrated treatment model²¹ which deals directly with the issue of safety in the clinical setting. In this model the RN functions as a “bridge” between the physician and counselor, facilitating mental health referral through reimbursable nurse visits. This is possible when the RN genuinely demonstrates such characteristics as empathy and kindness toward these patients with special needs in an environment created to be as nonthreatening as possible (i.e., draping equipment, attuning to background noise).²¹

An additional unifying factor between IBS, abuse, and gallbladder disease is suggested by the research of Stuppy who found deposits of met-enkephalin in the cholesterosis of gallbladders of certain patients with panic disorder.²² These patients had been exposed to chronic, inescapable stress and had developed not only panic disorder, but gallbladder disease as well. This connection is worthy of further study.

In conclusion, I would like to challenge the medical profession to heed the needs of patients with the conditions I have discussed. Physicians in particular must become more sensitive to the issues these predominantly female patients represent. Now is the time to respond!

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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 — addressing 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.

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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 my 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.

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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 than five times as likely to begin ERT than those seen by male physicians according to Seto, et al. (*J Gen Intern Med* 11 (1996): 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.

About the Organization

Within the mission of Xavier University of Louisiana, the College of Pharmacy is dedicated to develop pharmacists who are competent to deliver pharmaceutical care as required in a dynamic health care environment; to serve the profession and community by providing contemporary, innovative, and quality patient-centered health care; and to acquire and disseminate new knowledge through collaborative research.

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Barriers for Women in Alcohol and Drug Abuse Treatment

Women have made great strides in gaining equality in the workplace and power in the political arena. Society's view of women and alcoholism and drug addiction has not made similar strides. One assumption is that the alcoholic or drug-addicted woman is promiscuous. Another assumption is that she has failed as a wife and mother.

Disapproval of female intoxication has been prevalent in Western societies throughout history. This can be attributed to two major concerns according to Gomberg: Western man's concern for female sexual virtue and for spouse/mother roles. Alcohol is believed to cause women to lose sexual control and engage in immoral behavior. Any level of intoxication could result in loss of sexual inhibitions or result in an inability to fend off sexual advances. Women's roles throughout history have demanded more consistent attention than male roles. Child, Barry, and Bacon (1965) reason that the temporary incapacity of a woman is more threatening than the temporary incapacity of a man because the care of a field can be abandoned for a day, but the care of a child cannot.

With society's harsh view of women's drinking and drug use, women have hidden their problems more successfully than men. This has resulted in far fewer women receiving treatment and when they do receive treatment the disease has often progressed much further and is more difficult to treat. Many men enter treatment as a result of contact with the legal system or as a requirement of his employer. Women have far fewer contacts with the legal system and are not as represented in business and industry as men. Women are often employed in lower-paying positions and do not have access to employee assistance programs which are instrumental in providing referral services to treatment.

Female alcoholics now account for approximately one-third of the total number of alcoholics. In the United States there are about 5 million alcoholic women. Women who are separated, divorced, or single are more likely to drink more heavily than married or widowed women, although wives of alcoholics have a high rate of drinking problems.

Alcohol has a more severe physical impact on women. Both sexes experience severe physical problems associated with alcohol abuse but the effects are more profound on women after a shorter period of abusive drinking and with less alcohol intake. Female alcoholics have a 50 to 100 percent higher death rate than those of the male alcoholic. Alcoholic women lose an average of 15 years in life expectancy as a result of cirrhosis, circulatory disorders, suicide, homicide, and accidents. Women tend to develop alcoholic hepatitis and cirrhosis after much shorter periods of heavy drinking and at lower levels of daily consumption.

Women are generally smaller than men, therefore, if a physically smaller woman drinks the same amount of alcohol as a larger man, the woman will have a higher blood alcohol content. In addition, women have less body water which would make the blood alcohol content even higher.

A report in the *New England Journal of Medicine* in 1990 of a study by Frezza found that after consuming comparable amounts of alcohol, women have higher blood alcohol concentrations than men, even when allowances for difference in size are calculated. Women are also more susceptible to alcoholic liver disease. The results indicated that the bioavailability of alcoholic is much greater in women than in men because women have less gastric first-pass metabolism of alcohol.

Alcohol and drugs consumed during pregnancy can have devastating effects on the fetus. Women who consume alcohol while pregnant put their babies at risk for fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). FAS is one of the major contributors of mental retardation today and elimination of alcohol consumption

is the leading preventable cause of mental retardation. The fetus is not capable of efficiently processing alcohol which it receives from the mother through the placenta. Symptoms of FAS include mental retardation, physical deformities especially in the facial area, retarded growth, organ malformation, central nervous system dysfunction, and emotional and behavioral problems. There has been no determination of what a safe amount of alcohol consumption would be for a pregnant woman.

Barriers to effective treatment of women include lack of child care for dependent children, unwillingness of family members to acknowledge a problem exists, treatment programs designed by men for men, and the added burden of sexual and physical abuse endured by a high percentage of women clients. Additional barriers include the need for detox beds for women with their children, lack of medical coverage, dual diagnosis beds for women with children, and medical conditions needing attention prior to treatment.

Women who need alcohol/drug abuse treatment and have dependent children have far fewer treatment options available to them. These women need services to help them to arrange appropriate child care or should have treatment centers available that allow the client to bring her children with her to the treatment center.

Family members are often reluctant to confront the female alcoholic especially if she does not match the stereotype such as being promiscuous, unkempt, and detached. Some of the alcoholic women in a study by Smith (1986) described resistance by their husbands, and even their primary care physicians, to engage in enabling the woman alcoholic to obtain treatment. These women relied on their own self diagnosis of alcoholism in order to obtain treatment. Greater public education of signs and symptoms of alcohol abuse by women, especially those that counter current stereotypes, may decrease the extent of denial by family members.

Traditional alcohol and drug abuse treatment was designed to treat the male alcoholic and addict. Women respond well to treatment, especially when their special needs receive attention from the treatment staff. Treatment facilities should provide services, such as child care, and all female groups should be led by female counselors. Groups containing only women provide the members a safe environment to discuss issues that they would be hesitant to discuss in the presence of men. It is becoming more apparent that a large percentage of addicted women have been sexually and/or physically abused. Female groups provide a safe environment for the newly sober woman to discuss feelings and issues that they could not discuss with men in the group.

Doshan and Bursch recommended several treatment components that should be included in an effective treatment program for women. Group therapy should be the primary mode of treatment; the group should be made up of women only, including the therapist. The treatment program should contain an assertiveness training component as many alcoholics lack effective interpersonal skills. This training should enable the patient to increase her ability to express personal rights and feelings and to improve effective communication and interpersonal problem solving.

Social skills training and socialization activities are an important component to include in treatment due to the tendency for alcoholic and/or addicted women to isolate themselves. In order to stay sober, addicts must often abandon old user friends and develop new friends.

Child care issues must be addressed. Some treatment facilities allow the patient to bring dependent children to treatment with them. Treatment includes parent training and counseling directed at helping the client deal with guilt about not fulfilling the mother role as they and society expect. In many instances, the children of addicted women in treatment are also in need of services due to physical and emotional neglect and/or abuse by the mother. A resource for treatment of the children must be considered if the cycle of addiction is to be broken.

The following recognizable health-related issues were reported among our state-operated facilities for women:

- Gastrointestinal problems
- Respiratory problems
- Dermatological problems
- Eye Infections
- Dental problems
- Urinary tract infections
- Insomnia
- Sexually transmitted diseases
- High blood pressure
- Seizure disorders
- 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 benzodiazepines, 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:

- 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.
- 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.
- Research projects with a focus on the needs of women need to be expanded.

Council Woman, 29th District
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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 and 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 understands 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 of the base of research areas to find answers on the impact that socioeconomics 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.

Chemically Associated Neurological Disorders (CANDO)
Houston, Texas

Marlene Keeling, B.S.B.A.

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. Women have been experimented on for the last 30 years. FDA has never approved a single breast implant. 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 implants, 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 D-4 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, 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 United States 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; 12 percent, scleroderma; 55 percent, esophageal reflux; 63 percent, gastrointestinal dysmotility; 95 percent, chronic fatigue; and 47 percent, Sjögren's syndrome. While I have not had any training in epidemiology and there may be some bias in that women attending support group meetings may be having more problems with their health, I have trained myself to be a better consumer by reading peer-reviewed research articles and believe these numbers reflect a growing health crisis in this country. The average age of these women was 51 years.

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 and loss of cognitive function (it appears to be an adult form of attention deficit disorder). Many former hard working, productive women with implants are now disabled, without insurance, and unable to take care of themselves or their families. This health care crisis grows daily, while the manufacturers would try to blame it on anything but the implants.

Is it possible that silicone or silica is a lipid-soluble neurotoxin? Over 1,300 peer-reviewed research articles indicate the harmful effects of silicone/silica in the body. The NIH-sponsored panel concluded on April 17, 1997, that there does appear to be a connection between silicone breast implants and atypical rheumatic disease. Clinical studies are now needed to verify what implanted women have known for some time — something has gone disastrously wrong.

According to the Robert Wood Johnson Foundation, 99 million Americans suffer from chronic ailments which cost \$470 billion a year in direct health costs. And, indirectly, they cost \$234 billion in lost productivity from those who are disabled or die prematurely. Only 26 percent of people with chronic conditions are 65 or older. It is time to spend our research dollars on preventative investigations into possible causes of disease and remove harmful non-life-saving devices from the market.

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Judith H. LaRosa, Ph.D., R.N.

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:

- 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.
- Allot sufficient funds to support behavioral research and make it a priority across the myriad of diseases, disorders, and conditions which affect women — and men. Without such research we cannot successfully apply and have individuals adopt the health preserving findings.
- 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 effectively use the continually emerging research knowledge as individuals and as a nation.

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Marva L. Lewis, Ph.D.

Little research 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 that 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 has defined urban settings in the 90s. What will our psychological legacy be for 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 for 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 the 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 a sense of self and may 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, aged 20 and older with daughters aged 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 the hair-combing task as a valid method of research.

In conclusion, I recommend the following actions:

- 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.
- Researchers, clinicians, 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, there must first be a clear understanding of the construct.
- 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.
- 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.

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Jennifer C. Lovejoy, Ph.D.

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.

The Pennington Center was created by a gift of over \$125 million by Baton Rouge oilman and philanthropist C.B. "Doc" Pennington. Its mission is to improve the health of humankind through research in

nutrition and preventive medicine. With an operating budget of \$17 million for 1996-97, the PBRC conducts basic, clinical, and applied research in the following major program areas: obesity, diabetes and metabolism, nutritional neuroscience, diet and heart disease, and nutrition and health promotion.

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 Life Cycle" as the theme for PBRC's statement because nutritional issues, such as obesity and eating disorders, have major implications for the nation's health; there are important gender differences in the prevalence of these health problems. Furthermore, as in many other areas of clinical research, women have been understudied 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.

Nutritional Factors and Women's Life Cycle

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. In the United States and a number of other developed and developing countries, the prevalence of obesity is higher among women than among men. The prevalence of obesity in the United States is highest among African-American women (48.6 percent), and is also increased in women from other ethnic minority groups. Furthermore, body composition differs markedly between the sexes. The typical percentage of body fat for 20-year-olds is 10 percent for men and 20 percent for women. By age 40, it is 20 percent for men and 30 percent for women. Thus, obesity should be considered a preeminent women's health issue.

One aspect in which women differ from men is in the experience of fluctuating hormone levels across a monthly cycle. These changing levels of hormones throughout the menstrual cycle in reproductive-aged 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 are briefly discussed below.

Childhood and adolescence. Both undernutrition and overnutrition are potential problems for young girls. Undernutrition can occur as a result of poverty, lack of health education, actual child neglect, or other factors. Overnutrition, manifesting as obesity, is a major problem for U.S. children with the prevalence of childhood obesity nearly doubling over the last few decades. This increase in obesity in children has been related to the availability of "junk" foods, reduced physical activity, and television watching. Nutritional risk in children may also be related to socioeconomic status, ethnic background, geographical location, or other factors. Finally, teen pregnancy is a major public health problem that puts adolescent girls and their offspring at considerable risk for nutritional deficiencies.

Pregnancy and lactation. Pregnancy and lactation impose a significant physiological and nutritional stress on women. Undernutrition during pregnancy is associated with adverse maternal and fetal outcomes, while overnutrition and excess weight gain during pregnancy can lead to permanent obesity. Several studies have suggested that excess weight gain in pregnancy may be a contributing factor for life-long obesity in women. Excess weight gain during pregnancy has recently been identified as a greater problem for African-American women than for Caucasian women, a fact which may be linked to the high prevalence of obesity in middle-aged African-American women.

Mid-life and menopause. With increasing age, all individuals tend to gain fat mass and lose lean body mass. This unfavorable shift in body composition is related to a number of age-related chronic health problems in this country. Research has suggested that menopause may be associated with an increase in body fat and a shift in location of body fat from the periphery to the abdomen. This hormone-associated change in body composition has been suggested to explain, in part, the increase risk for heart disease that women experience after menopause.

Aging. Elderly women are at risk for a number of nutrient deficiencies which may impact their health status. Nutritional issues in the older population range from inadequate intakes of antioxidants, which can alter immune function, to low calcium intakes, which can exacerbate osteoporosis. Furthermore, nutrition-related chronic diseases, such as diabetes and heart disease, exact a greater toll in the older population.

Current Research

We describe several of the ongoing research projects at the Pennington Center exemplary of nutritional issues in women's health research which cross the spectrum from the laboratory to the clinic to the field. The Pennington Center's director's, George Bray, M.D., own research career has spanned this spectrum. Our team of researchers in basic, clinical, and field research have all explored aspects of issues related to women's health that shed greater light on this area.

Basic research. Gender differences in the severity of obesity in humans are mirrored in animal models of obesity. David York, Ph.D. leads the basic obesity research program and has conducted experiments exploring gender differences in obesity. Dietary obesity in female rodents is more profound than in male rodents when both genders are fed a high-fat diet. Similarly, ovariectomy reduces body fat accumulation in the rat, which signals the important role of estrogen in body fat accumulation.

Gary Truett, Ph.D. studies the genetics of obesity in the Zucker rat. He recently observed that heterozygosity for the *fa* gene may confer a survival advantage in female, but not male Zucker rats. Early in life, heterozygous female rats are plumper than those not carrying the gene, while later in life there is no difference. This observation may help explain the persistence of obesity genes in populations.

Clinical research. It is vitally important to identify behavioral and physiologic factors that uniquely predispose women to overeating and thus to weight gain. In the psychosocial area, much of our clinical

research has focused on the following groups of women: (1) women with a history of dieting; (2) women with a history of binge eating; (3) women with a history of both dieting and binge eating; and (4) women who have not had a history of either dieting or binge eating.

Results of studies performed by Paula Geiselman, Ph.D. show that a high-fat, high-sugar, chocolate food provokes overeating in all four groups of women. Furthermore, in a study of women across their menstrual cycle, Dr. Geiselman has shown that a high-fat, high-sugar chocolate food provokes overeating in women during both the follicular phase, when estrogen is elevated, and the luteal phase, when estrogen levels are lower and progesterone peaks. Preferences for other types of foods, however, show differences between the follicular and luteal phases.

In the area of eating disorders, an on-going study by Monique Smeets, Ph.D. will investigate how the visual system constructs visual images; particularly, why females who have anorexia nervosa construct visual images of their own body as being fatter than they actually are. This study will focus on whether the visual body image is constructed in the same manner by young women with body dysphoria and women with anorexia nervosa.

Jennifer Lovejoy, Ph.D. has conducted research on the relationship of pregnancy to later development of obesity. She found that women who retained 25 pounds or more of excess weight following delivery of their first infant differed significantly in their eating behavior, with higher scores on disinhibition (overeating) and perceived hunger. There were no differences between lean and postpartum obese women in their dietary intake, exercise, breast-feeding habits, depression scores, or other psychological factors.

Dr. Lovejoy has also evaluated the effects of an androgen or anti-androgen on abdominal fat and health risk in obese, older women. Postmenopausal women were treated for 9 months with one of the drugs or a placebo, and they were also instructed in weight loss by dietary means. Androgen treatment increased lean body mass (presumably muscle) and caused a greater loss of body fat, especially in the abdominal subcutaneous fat compartment. Visceral fat was not lost to as great an extent, resulting in a worsening of the visceral/subcutaneous fat ratio. The researchers concluded that increased levels of male hormones in women, which occur naturally at menopause, may be associated with worsening of the abdominal fat distribution; and that androgens appear to independently regulate visceral and subcutaneous abdominal fat.

Finally, Dr. Lovejoy has recently received a grant from the National Institutes of Health to perform a longitudinal study of the perimenopausal period. This study will focus particularly on changes in body composition, energy balance (intake and expenditure), and insulin action in African-American and Caucasian women before and after the menopausal transition.

In a series of studies funded by NASA, PBRC has examined the effect of simulated weightlessness using 28 days of complete bedrest. The purpose of these studies was (1) to improve upon the ground-based model of space flight by adding low doses of thyroid hormone to the bedrest protocol, and (2) to develop countermeasures that will help prevent muscle and bone loss in astronauts on extended space flights. We studied five women and nine men in the first round of these studies to determine whether there are differences in the response to bedrest by gender. Initial results suggest that there may be ways in which female astronauts are at greater risk for problems and, in some areas, at lesser risk for problems than their male counterparts.

James DeLany, Ph.D. is performing studies in Baton Rouge school children to determine predictors of obesity, and to assess whether there are gender or race differences in risk factors for overweight in young children.

Field research. As part of the three-state, Lower Mississippi River Delta Human Nutrition Research Initiative, PBRC, along with five other institutions and the USDA-ARS, are planning a longitudinal survey of a cohort of area residents that will combine state-of-the-art dietary and lifestyle surveys; food supply assessment; and human biochemical, anthropometric, and physiologic measurement. The survey will provide genetic samples for the Pennington Center database and tissue and blood archives. This resource will be a treasure for use in expanding our knowledge of nutrition, obesity, and other health risks, particularly in low-income, rural African Americans.

A project directly related to primary care treatment of obesity is currently planned by Drs. Phil Brantley and Pam Martin. The PCOMO (Primary Care Office Management of Obesity) project will enroll 640 low-income women across the state of Louisiana to study the efficacy of primary care obesity treatment. Pharmacological and behavioral treatments will be studied alone and in combination for 24 months; comorbid conditions, such as diabetes and high blood pressure, will also be assessed.

Dr. James DeLany has a grant from the U.S. Army to study energy expenditure in female soldiers. This study will determine the energy requirements of service women in a variety of military settings in order to provide critically important data for the determination of appropriate nutritional guidelines, including nutrient densities of rations and appropriate energy intakes to satisfy body composition standards. The principle assessment of energy expenditure will be made using a state-of-the-art, doubly labeled water technique. Assessments will be made in five key studies of women (with smaller groups of men for comparison) over a 3-year period in different military settings. These data will provide a foundation for the adequate and appropriate nutritional guidelines of service women and improve readiness of the services.

Why is research on nutrition and preventive medicine important with regard to women's health?

It is now widely recognized that diet is an important factor in a number of chronic diseases that affect both men and women. Recognition of obesity as a condition for which women may have a stronger predisposition, and identification of the importance of hormonal changes in the onset or worsening of obesity, can have significant public health impact. The ability to target particular times in women's lives, such as pregnancy and menopause, where increases in body weight may be more likely to occur, allows for the design of intervention programs that may reduce the health burden of obesity for U.S. women. Similarly, research on the disorders of anorexia and bulimia may help to decrease the incidence of these serious conditions in young women. Finally, understanding of the role of nutrition in chronic disease development in women, which may differ from its role in men, will help us tailor treatments and reduce morbidity and mortality from conditions such as heart disease and diabetes. Through a combination of basic, clinical, and field research, PBRC hopes to be at the forefront of these types of investigations in women's health.

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Frances J. Mather, Ph.D.

The Importance of Research in Identifying Factors Associated with Reduction of Preterm Births

This testimony addresses the need for further research into identification of the factors associated with the reduction of preterm births.

The Problem

Preterm birth. A preterm birth is a birth that occurs when the fetus is less than 37 weeks gestational age. Preterm birth 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.¹ Nearly 60 percent of early infant deaths are found in the 1 to 2 percent of infants born at less than 30 weeks gestational age or weighing less than 1000 grams at birth.² It is the major contributor to low birthweight. Although rigorous estimates of costs of low-birthweight infants are not precise,^{16,17} annual direct costs attributed to preterm births in the United States have been estimated to be at least \$4 billion.^{15,3}

Who Is Affected?

Demographics. Preterm birth among black women occurs in about 12 percent of live births, approximately twice that of white, Hispanic, and Asian women.

Sequelae of preterm/low birthweight. Low birthweight is associated with an increased risk of subsequent hypertension and death due to cardiovascular disease.⁴ Weight at birth and social conditions of childhood are found to affect reproductive capacity.^{5,6} Neurological conditions found in children with very-low-birthweight (< 1500 grams) include cerebral palsy, and attention deficit disorders. Other conditions include retinopathy of prematurity, SIDS, bronchopulmonary dysplasia, and other chronic pulmonary conditions.^{7,8} Since 1989-91, declines in infant mortality, largely attributed to the use of surfactant and other neonatal interventions, have resulted in increasing survival of these extremely preterm deliveries at risk to sequelae.

Work to Date in the Reduction of Preterm and Low Birthweight

Determinants of preterm and low-birthweight births. Much work is available in the determinants of gestational age and low birthweight, in the case of gestational duration pre-pregnant weight, prior history of prematurity or spontaneous abortion, in utero exposure to diethylstilbestrol and cigarette smoking; and in the case of low birthweight/IUGR [IUGR - IntraUterine Growth Retardation], infant sex, racial/ethnic origin (IUGR associated with black/Indian births), maternal height (IUGR associated with short stature), pre-pregnancy weight (IUGR associated with low pre-pregnancy weight), paternal weight and height, maternal birthweight, parity, history of prior low-birthweight infant, gestational weight gain and caloric intake (IUGR associated with poor weight gain), general morbidity and episodic illness, malaria, cigarette smoking, alcohol consumption, and tobacco chewing.⁹

Intervention/programs. Standards of prenatal care incorporating nutritional counseling, fetal monitoring, testing for sexually transmitted disease, identification of genetic and other diseases, monitoring weight gain and blood pressure, and patient education on preterm delivery have been established through the American College of Obstetrics and Gynecology. Social and professional support programs including nurse home visits, case management and media campaigns to encourage early prenatal care, prenatal classes, parenting classes, and male involvement have been instituted through the National Healthy Start program and other maternal and child health programs.

Failure of preterm prevention programs. A recent analysis of trends in adverse outcomes of pregnancy in Orleans Parish, Louisiana, over the period 1989-1995, shows increases in the proportion of women who initiate prenatal care in the first trimester, increases in the adequacy of prenatal care as measured by the indexes of Kessner and Kotelchuck, and declines in the infant death rates. These trends in improved prenatal care are, however, *not* accompanied by increased gestational duration and birthweight. In fact, there is a slight increase in the proportion of births with low (<2500 grams) birthweight and preterm (<37 weeks) birth. The twofold increase in low birthweight and preterm births among black women compared to white women remains in spite of this increased prenatal care. Findings comparable to this are to be found in most large cities in the United States.

In summary, little or no evidence is available that preterm prevention programs,¹⁰ 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 contractions¹¹ have been successful.

Potential Factors Explaining Preterm Birth and Low Birthweight

Determinants of gestational duration currently under investigation include genital tract infections; antenatal care; maternal employment; physical activity; stress and anxiety; low-birthweight caloric expenditure; antenatal care; and vitamins and trace elements.⁹

Role of infections in preterm births. Promising new developments include the assessment of the role of infections in preterm births.¹² There is some evidence that differences in colonization with bacteria associated with spontaneous delivery — *Ureaplasma Urealyticum*, *Mycoplasma hominis*, *Bacteroides*, and *Gardnerella vaginalis* — may explain the excess prevalence of potentially pathogenic organisms among black women when compared to white, Hispanic, or Asian women.¹³ Bacterial vaginosis is associated with the preterm delivery of low-birthweight infants, independently of other recognized risk factors. Treatment with metronidazole and erythromycin has reduced rates of premature delivery in women with bacterial vaginosis and at increased risk for preterm delivery.¹⁴

The Need

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 longlasting and, certainly among the very low birthweight, severe and irreversible. Recent innovations in neonatal intensive care makes it possible for greater proportions of the tiny infants to

survive, but not without the sequelae associated with this condition. There are about 40,000 to 50,000 of these very-low-birthweight infants per year in the United States who 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.

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African-American Women and Terminal Illnesses: Cancer, HIV/AIDS/STD, and Community Violence

It does not matter what any census will say. It does not matter how many teenage pregnancies we have. It does not matter about welfare reform (and we know how true those numbers are). We die more often than any other race!

Cancer

Lung cancer. Between 1973 and 1992, the rate of lung cancer among African-American women increased more than 100 percent, and so did the death rate. For African-American women, lung cancer is now the leading cause of cancer deaths.

Breast cancer. Breast cancer was the second leading cause of cancer deaths among African-American women between 1973 and 1992, with breast cancer among those between the ages of 50 and older increasing more than 38 percent. The death rate among this group has increased by 25 percent.

Cervical cancer. Between 1973 and 1992, overall cervical cancer diagnoses and deaths among American women decreased; however, African-American women over the age of 50 remain more than twice as likely to develop cervical cancer and die of it than their Caucasian counterparts. For African-American women under age 50, the incidence of cervical cancer was higher than Caucasian women in the same age group.

We die more often than any other race!

HIV/AIDS

The Louisiana Department of Public Health and Hospitals' Office of Public Health produced a summary of epidemiological data in the statewide HIV/STD Prevention Plan for 1997 recognizing the important trends toward increased risk for African-American women. Louisiana's rate of HIV infection in childbearing women is 50 percent higher than the national average and rising. New Orleans is the third poorest city in America, with a disproportionate percentage being African-American women.

Nationally, females represent 14 percent of the cumulative adult and adolescent AIDS cases. Of all the incident cases of HIV infection reported for the 20 to 24 year-old age group in 1995, 36 percent were female. The national trend toward a sharply increasing proportion of females in new AIDS and HIV cases is reflected in the epidemic in Louisiana. In Region I, females represent 105 of the cumulative adult and adolescent AIDS cases. National-level data on new AIDS cases reported during 1995 indicated that heterosexual contact was the mode of exposure in 38 percent of female cases, proportionately equal to IDU exposure.

In Louisiana, the trend toward greater female risk through heterosexual transmission is ever more marked. Forty-four percent of new female AIDS cases reported in 1995 indicated heterosexual contact as the mode of exposure, compared with 25 percent attributed to injection drug use (27 percent unspecified). The rate of HIV infection in childbearing women in Louisiana is 50 percent higher than the national average, and still increasing. Proxy measures for HIV-risk behavior, such as case rates of syphilis and gonorrhea, indicate the potential for increases in rates of HIV infection. Among women in Louisiana, *HIV is following in their footsteps!*

We die more often than any other race!

Community Violence

I have lived in the community of my fellow African Americans for a long time. They have taught me some excellent survival skills. I have learned to be grateful for what I have, and that there is always more than one way to get what you need from those who have it. I have also seen a change in my community. A change where violence has become normal and community rape occurs every time a house is not maintained. Hopelessness is evident in the eyes of the women I see in my communities. These women place no faith in a “system” that they have seen take the lives of their children and their own, and they have no trust in a system that characterizes them as worthless.

A myth exists that suggests that we, African-American women, want to be the head of the household. I suggest that it is instead an issue of survival. We have families to care for and histories of doing for ourselves last. Everyone else comes first. We practice emergency room medicine and have little time for reading or watching the news. We feel all right, so everything is fine.

Prevention messages are never a part of our everyday existence. They are in the clinics where we go, but not in the neighborhood laundromats, corner stores, or beauty shops where we live. We have to go somewhere “special” to see these messages. Why leave the community for help when the service providers we go to see do not care? When they say, as if we were not there, “why did she wait so long?” Why leave your community, when none of the messages look like you? Why leave, when you have to survive? Why leave, when you have low self esteem, and feel you are all alone?

Gaps

Hopefully, the existing gaps should be evident. Here are the top five reasons as I see them.

1. The continuing separation of women from their families. *Answer:* One-stop treatment. Current medical treatment occurs between the hours of 9:00 a.m. to 5:00 p.m. Children do not get sick at prescribed hours.
2. Why separate women’s health care by illness? One illness will have an effect on many levels of an individual’s well being. The effects of sexually transmitted diseases, HIV, abnormal Pap smears, or cancer are not isolated to purely physical manifestations.

3. Why isolate research to people who are in treatment? Individuals who are not receiving treatment should be questioned as to why they wait until a medical incident occurs to receive treatment. If researchers are afraid of the communities they serve, then they should take a look at the street outreach model, or leave the community alone!
4. Researchers need to be more community minded. Scouring communities only for the information that they seek, and then disappearing, only leaves a sour taste in the mouths of the community members.
5. After these women die from such illnesses as cancer, AIDS, and violence, what happens to their children?! Do they go to bigger and better jails, overpopulated graveyards, or seldom-used colleges?
We die more often than any other race!

Organizational Description: Women With A Vision (WWAV), Incorporated

Women With A Vision (WWAV), Inc., is a minority, nonprofit community-based organization with a mission espousing women and their families entitlement to health services that are appropriate and responsive to their needs. WWAV is committed to promoting wellness and disease prevention through health education, early intervention strategies, and referrals among women and their families living at or below the poverty level. We have a history of providing HIV/AIDS/TB/STD and substance abuse resources to minority communities comprising individuals practicing high-risk behaviors. It is our intent to empower a neglected minority community with the tools necessary to make informed choices concerning their health. We continue to inform such communities of available resources before they reach critical stages of illness or before a medical crisis. WWAV provides a vital link between the community and service providers through one-on-one street outreach and community outreach.

Since the inception of our organization in 1991, we have focused our attention on a geographic area called Central City. Central City is a crime-ridden, impoverished, and drug-inundated community. Seventy-three percent of the families living in this area have incomes 200 percent below the poverty level. The Center City area, with a population of approximately 65,000, is 93 percent African American. Three housing developments, the C.J. Peete, the B.W. Cooper, and the Guste high-low rise, are also located within its boundaries. WWAV brings information directly to the community by recognizing and empathizing with the barriers that face many of its citizens (i.e., poverty, high crime, inadequate child care and transportation to traditional agencies providing services, the unpreparedness of traditional agencies to handle diverse clients, and a general unawareness of available resources or prevention approaches).

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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 fiscal year 1995-96, approximately 200,000 women (72,841 – family planning; 53,541 – maternity; 30,000 – STD/HIV; and 50,000 – WIC) and 148,117 children utilized our medical and nursing services. Similar to other public health programs, 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, as are interventions that are successful. Yet, without them, funding to address these issues is not forthcoming.

The other side to this testimony must emphasize how, 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.

Why? 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 will involve women who are from multiculturally and socioeconomically diverse backgrounds, we suggest research in the following areas.

- How the perception of being a public health recipient (particularly from a young age onward), where choice of provider and 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.
- How gender identity and responsibility are affected and contributed to by reproductive health clinics that primarily focus on females.

- How well informed are women regarding informed consent as it pertains to research involving reproductive health, contraception, and STD/HIV. How comfortable are women 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.
- Infant mortality and low birthweight disparities between blacks and whites.
- Effects of the media on healthy gender identification and sound health practices on female adolescents and adult women.
- Continued multicultural, sound contraceptive research and development since 60 percent of all pregnancies continue to be unintended.

These issues focus mainly 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.

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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 experience 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 of 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 of women's sexual functioning and the potential for new research programs to revolutionize current knowledge in 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 the understanding of 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.

*Chair
Committee on Women's Affairs
New Orleans, Louisiana*

Jayashree Rao, M.D.

Career Issues for Women Scientists and How to Overcome Them

Barriers

- Women are biologically different and that has an impact on how they view science and their contribution to the advancement of science.
- 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.
- 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.
- The traditional type of mentoring process does not address the gender differences in fostering the careers of women scientists.
- 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.

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Colonel Irene M. Rich

A REPORT ON CONGRESSIONALLY DIRECTED WOMEN'S HEALTH RESEARCH BY THE DEPARTMENT OF DEFENSE

Introduction

The United States Army Medical Research and Materiel Command (USAMRMC) is pleased to participate in the Office of Women's Health Research "Beyond Hunt Valley: Research on Women's Health for the 21st Century." In the last few years, targeted Congressional biomedical research funding to the Department of Defense (DoD) has resulted in significant advances in the spectrum of women's health research. The DoD Breast Cancer Research Program (BCRP) is the largest DoD women's health research effort. A background of this program will be provided with further discussion on program stewardship, program execution, targeted populations, partnerships, scientific management innovation, research dissemination, research achievements, and emerging issues. This paper will conclude with brief overviews of other DoD women's health research programs.

DOD BREAST CANCER RESEARCH PROGRAM

Background

Responding to diverse groups seeking to increase breast cancer research funding, Congress has appropriated a total of \$490 million for the DoD BCRP from fiscal year 1992 to 1996. An additional \$112.5 million in FY 97 funds have been received and the Broad Agency Announcement (BAA) for these funds has been released. The USAMRMC was tasked to manage the BCRP. Due to the importance and visibility of the program and the fact that breast cancer research was outside its historic scientific experience, the U.S. Army commissioned the National Academy of Sciences' Institute of Medicine (IOM) to provide an assessment of

breast cancer research and to advise the USAMRMC on scientific management strategies. The IOM recommendations were published in a 1993 report entitled *Strategies for Managing the Breast Cancer Research Program: A Report to the U.S. Army Medical Research and Development Command*. Based on this document, the USAMRMC has created a research funding program and management infrastructure that is innovative, scientifically sound, and responsive to the needs of both scientific and advocacy communities.

From an administrative perspective, it is important to note an aspect of the DoD BCRP that distinguishes it from other federal research efforts: DoD Congressional Special-Interest Research Program budgets are neither requested in the President's Budget Request nor programmed in either the Program Objectives Memorandum (POM) or the Future Years Defense Program (FYDP). Each annual appropriation made to the DoD can only be considered a single budget-year appropriation with no out-year funding stream. Therefore, awards for the research proposals funded, as well as the funding required for the scientific oversight or management throughout the period of grant performance, are provided from the single-year appropriation to fully fund both the research proposal and the support contract to facilitate the review of annual and final progress reports and other grant/contract requirements, such as patent compliance.

The DoD Congressional Special-Interest Research Programs are managed by a small staff of Army and other DoD personnel. The program is administered with the assistance of contractors and under the recommendations of expert panels consisting of scientists, clinicians, and consumer advocates spanning the entire spectrum of interests related to breast cancer. To optimize its limited research resources, the DoD BCRP has been challenged to devise a funding strategy with high impact that is not duplicative of other research 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.

Program timeline. Most federally funded programs receive funding from one year to the next to accommodate a regular cycle of proposal submission and review over the course of many years. In contrast, the DoD Congressionally directed research programs have no lifetime beyond that allotted by a single budgetary cycle and have tight restrictions on how and when funds may be spent. Therefore, management of the program requires a thorough understanding of Congressional intent and strict adherence to the timeline for obligation of funds. The timeline begins with the Congressional appropriation. Once funds have been officially appropriated to the DoD, there is a 2-year period for program execution. However, the timing of the release of funds of each appropriation has varied.

During the first program year, Congressional language is analyzed, a blue ribbon advisory panel is formed, an investment strategy is developed, and a solicitation for research proposals is crafted and released. During Year 2 of the program, proposals are received and reviewed, awards are negotiated, and funds are obligated. Years 3 to 6 provide for the management of funded research projects. Projects are monitored for technical

progress and compliance, and site visits are made to institutions based on regulatory requirements. Multidisciplinary conferences are held for scientific exchange, transfer of ideas, and dissemination of research findings.

Program execution of congressional directives for the BCRP. From FY 92 to 96, Congress appropriated \$490 million for the DoD BCRP. The program has funded research at 828 different institutions in the United States and abroad with a variety of funding categories to support basic and clinical research projects, training grants, and infrastructure enhancement awards. Efficiency of operation and cost containment are hallmarks of the DoD effort. Administrative costs incurred in managing this nearly half-billion dollar research program have averaged 7.6 percent.

Targeted populations. Despite improvements in diagnostics and treatment, access to health care resources and care-seeking behaviors among underserved populations remain critical concerns and objectives for the BCRP. Consistent with the IOM recommendations, each BAA has encouraged participation by women and minorities and has been widely distributed to maximize exposure to scientific and medical communities. This outreach has been successful. For example, in FY 93/94, 70 percent (67/96) of the research proposals submitted by female investigators were funded, 48 percent (17/38) of the research proposals submitted by minority investigators were funded, and 89 percent (16/18) of the research proposals submitted by female minority investigators were funded. Further, programmatic goals include addressing the needs of minority, elderly, low-income, rural, and other underserved populations.

Partnerships. Since breast cancer is a complex, multifaceted disease, the fulfillment of the BCRP goals requires an atmosphere of cooperation and communication across many scientific and clinical disciplines. The DoD BCRP supports collaboration among disciplines that traditionally may not interact with hopes of facilitating communication, generating innovative approaches to tackle molecular causes of breast cancer, and translating the knowledge gained into increased/improved detection, treatment, prevention, survival, and quality of life for those living with the disease. The DoD BCRP is administered as a partnership of the military, the scientific community, and the public. This unique partnership is one of the most important program elements. Through this distinctive interaction, the BCRP has developed a new and unique vision for breast cancer research and biomedical research in general. The BCRP is committed to developing continuing public/private partnerships between scientists and consumers that will have a lasting impact on the breast cancer research field.

The DoD BCRP fosters partnerships, collaborations, and interdisciplinary studies at several levels: (1) Universities, hospitals, laboratories, and government agencies are encouraged to work together on multi- and interdisciplinary efforts. (2) Military/civilian collaborations are encouraged. (3) Diverse teams of basic and clinical researchers, breast cancer survivors and advocates, and cancer center administrators participate together in the scientific and programmatic evaluation of proposals. (4) The DoD has worked with other federal funding agencies including the National Institutes of Health (NIH), the National Cancer Institute (NCI), the Department of Health and Human Services (HHS), Office of Women's Health (OWH), and the Agency for

Health Care Policy and Research (AHCPR) to co-fund research projects. For example, NCI and USAMRMC have jointly funded 12 BCRP awards in support of the National Action Plan on Breast Cancer (NAPBC).

Scientific management innovations. Among the most notable accomplishments of the DoD programs are the scientific management process innovations that have been developed and implemented by the USAMRMC and support contractors in program development, scientific and programmatic evaluation of proposals, and management of funded projects. Process innovations will be detailed further in the discussions of research stakeholders, the process of two-tiered review, consumer participation, the Idea award philosophy, criterion-based scoring in scientific review, internet access to program information, Arden logic modules, and the BCRP “Era of Hope” meeting.

Stakeholders. The USAMRMC is committed to providing the soundest investment of public funds for Congressional Special-Interest Research Programs. To accomplish this goal, the BCRP seeks to address gaps and urgent areas of unmet need. A standard USAMRMC strategy is to bring together key stakeholders at the outset of a program to harvest the collective wisdom of experts currently engaged in the battle against a particular disease. The BCRP stakeholders include key scientists, national leaders, and consumers from government, academic, and consumer advocacy organizations. Each representative presents perspectives on the most critical gaps in current research funding. Input from the stakeholders represents the foundation for an investment strategy that most effectively targets the current and critical gaps in research.

Other benefits are derived from this approach. Communication among diverse disciplines and between scientists and consumer advocates provides a forum from which fresh perspectives emerge transcending traditional parochial interests. This networking also catalyzes the team building needed for a shared program vision. In addition, the stakeholder meeting provides an opportunity for the USAMRMC to solicit nominations from recognized leaders for the scientific and programmatic review panels.

Two-tiered review process. Applications to the DoD BCRP are rigorously reviewed for scientific merit and recommended for funding based on how well the proposals fulfill defined programmatic goals. This approach is in keeping with the IOM recommendations for a two-tiered review process: a first tier for evaluation of scientific excellence and technical merit; a second tier to assess relevance to programmatic goals. For peer review, the USAMRMC established a system to accommodate novel program goals while maintaining the traditional rigor of federal peer-review systems. Emphasis is placed on utilization of technological resources to expedite administrative processes and ensure prompt referral, review, and summary statement production for each application. Ad hoc peer-review panels are convened to address the precise expertise of submissions. Panels are oriented to programmatic goals and rigorous efforts are employed to ensure standardized review across the many scientific panels. Diverse representation of scientific disciplines with multiple perspectives, expertise, and career levels is emphasized. Concerted efforts are also employed to ensure a balance of gender and racial/ethnic participation in scientific peer review. Consumer representatives also participate in peer review and are full voting members for each application.

The second tier, known as programmatic review, is conducted by an expert advisory panel, known as the Integration Panel (IP). The IP is comprised of civilian scientists and clinicians from multiple disciplines and research settings including clinical, basic, and applied health sciences, representing gender, racial/ethnic, and geographic diversity. The IP also includes representatives of consumer or public interests. The primary responsibility of the IP is to programmatically review proposals deemed scientifically meritorious by the peer-review panels and to make recommendations for award to the Commander, USAMRMC.

In order for a proposal to be funded, it must be recommended by both levels of the system. While scientific merit is an important criterion for award, proposals that receive high scientific merit scores in peer review, but are judged to have low programmatic relevance, are likely to be rejected for funding. Scientifically excellent studies that directly address the unique focus and goals of the program are most likely to receive funding support.

The two tiers of review are fundamentally different. Unlike programmatic review, scientific peer review evaluates proposals as distinct submissions: they are not collectively compared. Peer review is a *criterion-based* process whereby proposals are evaluated on their individual scientific and technical merit. The evaluation focuses on issues such as the scientific innovation, rationale, feasibility, originality, and qualifications of the investigator. In peer review, proposals are considered in panels from a single discipline. The goal of peer review is to establish the scientific merit of each proposal through the assignment of a scientific merit score.

In contrast, programmatic review is a *comparison-based* process in which proposals from multiple disciplines compete within a common pool. At this level, proposals are compared on the basis of their scientific merit (as judged in peer review), programmatic relevance, and other factors such as gender, minority, and geographic distribution. The goal of the combined review processes is to develop funding recommendations that balance the most meritorious science across many disciplines and offer the highest promise for fulfilling programmatic goals.

Consumer participation. Consumer participation in decisionmaking was a key recommendation of the IOM. The value of consumer involvement is derived from their unique professional and personal histories. Their first-hand experiences with the disease add a sense of passion and urgency, ensuring that the human dimensions of breast cancer are incorporated into program policy, investment strategy, and research focus. The model of consumer participation developed in the BCRP has been applied to all subsequent DoD Congressional Special-Interest Research Programs. The inclusion strategy for consumer participation in scientific peer review is the assignment of two consumers to each panel. Consumers are intentionally included as lay participants to ensure that consumer perspectives are not lost in the scientific deliberations of peer review. They are asked to review applications according to the relevance of the research to breast cancer patients and their families. Participation of consumers in peer review was implemented within the framework of a qualitative and quantitative evaluation effort. This evaluation consisted of a pre/post-meeting questionnaire distributed to all participants. Preliminary findings demonstrate an increase in positive views and appreciation of consumers among scientists and an increased appreciation among consumers of the difficulties in breast cancer research.

Idea award philosophy. The IOM recommended the creation of a science management environment in which innovative and creative scientific ideas would be supported. In response, the DoD implemented the Idea award category. In its original configuration, the goal of the Idea category was to stimulate and reward speculative but especially promising and creative ideas. Ideas were specified as 2-year grants for \$150 K that were intended to give investigators the opportunity to explore research topics that might lack sufficient pilot data needed to apply for a traditional award. Since FY 93, the BCRP has allocated approximately 60 percent of the research funds for Idea grants. The primary intent of the DoD BCRP is to promote this novel Idea generation, which will impact the harvest of research outcomes in the future. The vision is that the work funded now will invigorate mid-level research development by the year 2000.

Criterion-based scoring. Though peer review has been the standard approach for evaluating the scientific merit of research proposals, optimizing the peer-review process to ensure fairness and consistency has been a primary DoD concern. Unique USAMRMC award categories, such as the Idea award which does not require preliminary data, break from existing scientific paradigms and compound peer-review challenges. The USAMRMC has expended great effort in confronting the multiple challenges of peer review. A key result was the introduction of a new scoring system in the FY 96 BCRP peer review. It was hypothesized that focusing the reviewer's attention on specific, published evaluation criteria would result in a more consistent, uniform, and equitable review process for all proposals.

This hypothesis was tested in the FY 96 peer review, where panel members rated each proposal based on the specific evaluation criteria articulated in the BCRP BAA. Two types of ratings were used: Each of the evaluation criteria was rated on a scale of 1 (low merit) to 10 (high merit). The overall proposal was also given a global score using the standard NIH scoring system — scale of 1 (high merit) to 5 (low merit). Using this scoring methodology, criteria scores were not averaged or manipulated to determine the global score. Instead, reviewers were asked to use the criteria scores as a guide in determining a global score. The new scoring system is currently under evaluation by USAMRMC. Further, there are reports that other federal funding agencies are now moving toward a criterion-based scoring system.

Research dissemination. A primary goal of the DoD BCRP has been to provide timely dissemination of program information and research findings. Internet web sites, the Arden Knowledge Management System (AKMS), and an upcoming multidisciplinary meeting are the primary DoD research dissemination modalities.

The Congressional Special-Interest Research Programs web site (<http://mrmc-rad6.army.mil>) was created to disseminate information about the DoD research programs. A searchable database of funded research information is provided along with abstracts of funded proposals. Links are also provided to related sites, and a calendar of events of interest to the research community is maintained. In addition, the web site contains biographical information on the USAMRMC Program Management Team (PMT) along with an e-mail directory to allow researchers to communicate directly with members of the PMT.

The AKMS is another database resource currently under development by the USAMRMC. This database is a multicomponent software tool designed to aid in the acquisition, transformation, and delivery of biomedical knowledge. The core technology of this knowledge management system is a modular knowledge system developed by an international consortium of medical schools and health care facilities for the purpose of creating a powerful method of sharing decisionmaking knowledge. A major advantage of the AKMS is that it permits users to encapsulate their research findings into modular units of a medical knowledge base. An important feature of these knowledge modules is that they contain language text for reading and easy comprehension, and computer code for decision support and computer interaction. Authoring tools under development will facilitate module creation. Additionally, a database structure to permit assembly and storage of multiple knowledge modules for use by various reasoning and decision-support applications is being developed.

The BCRP firmly embraces the concept of cooperation and communication across the many scientific and clinical disciplines funded by the BCRP. The intent of the "Era of Hope" meeting, scheduled for 31 October through 3 November 1997, is to provide the opportunity for interplay of ideas and to present the work being accomplished in the DoD BCRP. The meeting will have three unifying themes: (1) prevention and detection, (2) genetics and biology, and (3) treatment and quality of life. Funded investigators from the FY 93/94 BCRP will report advancements made since the initiation of the program and will share the progress with fellow scientists. Accordingly, FY 92-95 award recipients have also been invited to attend and present their findings, although it is recognized that the most recent awardees will have had less than a year to conduct their research and findings may not be yet available.

FY 93/94 BCRP research achievements. The accomplishments data provided in this document reflect progress made during the first 2 funding years of the FY 93/94 BCRP only. Data are not yet available from subsequent funding years. Although the FY 93/94 program is still in its infancy, many of these grants have yielded research products and publications. To date, these projects have resulted in the publication of 380 manuscripts. Seventy-nine additional manuscripts have been submitted to journals and are currently in press. BCRP-funded research from this period has also been presented at over 300 national and international meetings, and investigators currently hold nine patents or licensures for advances made as a result of funding from this program.

Research accomplishments resulting from BCRP-funded projects are also numerous. (Accomplishments from other DoD programs are not yet available.) These BCRP accomplishments are reported within the general areas of prevention, detection, treatment, quality of life, general biology, genetics, epidemiology, infrastructure, and training/recruitment. Many research products are multi- or interdisciplinary and, consequently, can be classified in more than one discipline or research focus area. The following discussion represents only a highlighting of innumerable breast cancer research achievements from this early year of DoD funding.

Prevention. 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. For example, BCRP investigators found that the ratio of omega-3 to omega-6 polyunsaturated fatty acid showed a protective effect against breast

cancer, especially in Mediterranean populations. Estrogen analogs such as soybean estrogens were identified as compounds that can inhibit the proliferation-inducing effects of estrogens when given in combination with them. Other investigators have shown that immunization with neu-DNA is effective in reducing tumors in mice. Also, in another study, polymeric DNA showed potential to be used as an immunizing agent against tumors.

Detection. With the funding of the BCRP, several single- and multi-center clinical trials have been initiated to aid in the diagnosis/detection of breast cancer. In FY 95, a special initiative was launched to promote research in observational and interpretational errors in breast diagnostic imaging. A major goal for this program was to foster the transfer of optical correlator technology to diagnostic imaging. Representative achievements include the following examples. A reconstruction algorithm has been developed to improve the image quality of whole body studies. The optimization of intensity and texture features has increased the sensitivity of detection algorithms and decreased the incidence of false positive images. Mammographic work stations have been installed, and it has been demonstrated that mammograms can be compressed and digitized simultaneously. Online data compression was found to be potentially useful for telemammography and other digital applications, improving overall digitization and compression performance. BCRP investigators have demonstrated that capillary x-ray optics are suitable for enhancing contrast and performing beam shaping to match with digital detectors. Capillary optical devices can also significantly improve contrast and resolution of digitized phosphor plate imaging systems. Using ultrasonic tomography, investigators have shown that tissue type can be reliably differentiated by this technique.

Advances have also been made in the detection of cellular abnormalities in breast cancer. Investigators have identified deletions and rearrangements in specific chromosome regions in breast cancer. An assay has been developed to detect BRCA1 germ line mutations. Investigators also discovered that loss of imprinting (LOI) in tumor stromal cells may lead to novel clinical strategies for better management and treatment of breast cancer.

Treatment. Funded BCRP investigators have made progress in several different areas of breast cancer treatment. Nearly 400 patients have been entered into the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial for therapy, treatment, and aftercare. Investigators demonstrated that deferoxamine appears to interact successfully with doxorubicin to inhibit the growth of some breast cancer cell lines. The efficacy of doxorubicin was improved by delivery of the drug in anti-Her2 immunoliposomes, which also reduced systemic toxicity. Several drugs that affect micronucleation and could be useful for the treatment of breast neoplasms have also been identified. Investigators have demonstrated the potential of polynucleotide immunization for tumors. In addition, CEA- and HER-2/neu-expressing polio virus-based vaccines have been developed. Proliferative effects of estrogen have been successfully blocked with ICI164384 and antibody. Antigen mimicry to HER-2/neu has been determined, and the anti-idiotypic monoclonal antibodies (Ab2) generated have been evaluated. An adenovirus vector that is selectively lethal to breast cancer cells has been generated, and strategies for tumor-specific gene delivery are being developed. Researchers performed a study that showed that psychotherapy conducted via the telephone is an effective approach for reaching patients who have difficulty accessing care, but is not an effective approach for influencing disease outcome.

Quality of Life. The BCRP has maintained the goal of improving the quality of life of breast cancer patients. Some examples of BCRP-funded projects include pain management, benefits of counseling, access to care, and care following treatment. In one study, investigators completed survey data collection on a needs assessment from health professionals providing pain management for minority women with metastatic breast cancer. Another study showed that most respondents preferred using an automated message system to accessing a live counselor. In addition, claims data reflected a low use of radiographic surveillance testing but high use of physician office visits in the 36 months after initial treatment for early-stage breast cancer in the population studied.

Results also indicate the need to further address specific concerns/issues of ethnic groups. For example, culturally sensitive trends have been identified among elderly Puerto Rican women regarding the belief that it is inappropriate to examine one's own breasts or to have clinical breast examinations. Researchers have also shown that increasingly larger numbers of women with breast cancer resort to one or more unconventional therapies and that there are ethnicity/race-dependent differences in the unconventional therapies chosen.

General Biology. Investigators funded by the BCRP have developed model systems that can be used to characterize mechanisms involved in the pathology of breast cancer, tumor progression, and metastasis. New cell lines expressing molecules relevant to breast cancer (e.g., MHCII, B7, etc.) have been generated, and model systems for studying apoptosis in MCF-7 breast carcinoma cells have been developed. Additionally, animal models have been developed and used to study parathyroid-related protein and androgen biosynthesis. Investigators have also developed a variety of biological assays for the measurement of essential molecules or their complexes. BCRP investigators have elucidated cell cycle kinases, such as cyclin D1 and cyclin E1, and have demonstrated that cyclin D1 is overexpressed specifically in breast cancer cells. In addition, novel substrates for protein kinase C (PKC) and epidermal growth factor receptor (EGFR) have been identified.

In the area of tumor progression, funded investigators have identified an angiogenesis factor that increases with tumor growth; found that epithelial vascularity increases with tumor progression; shown a positive correlation between tumor microvessel density and tumor size; identified five peptide inhibitors of the estrogen receptor; demonstrated that factors like Matrilysin (MAT) and transforming growth factor (TGF)-alpha accelerate mammary tumor formation, whereas factors such as corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG) Type II are negative regulators of breast cancer cell growth; identified several variants of the estrogen receptor in both normal and breast cancer cells; shown a correlation between the overexpression of certain variants of estrogen receptor and poor prognosis; and identified a tyrosine protein kinase in the focal adhesion complex that is essential for tumor growth and invasion.

Additionally, BCRP-funded projects have advanced biomedical knowledge of metastatic processes. Investigators have identified novel monoclonal antibodies that act against degradative enzymes (e.g., EMMPRIN, Sepsin, and DPPIV) involved in metastasis and invasion. Biological factors have been produced and are being tested as inhibitors of proteases involved in metastasis. Researchers identified new markers (e.g., Trf, Cytostatin I,

and lysyl oxidase levels) that are present in breast cancer and may show a correlation with metastasis. Laminin-5 and alpha-6 integrin were characterized as potential indicators of invasive potential and were shown to be essential in sustaining the growth and survival of highly metastatic breast cancer.

Genetics. The BCRP investment in genetics research has yielded a significant gain that will benefit both the research community and the general public. Funded investigators have identified and/or characterized novel oncogenes and proto-oncogenes (e.g., alternative *Her-2/neu* proto-oncogene, *int-3* oncogene, and *Notch-4 proto-oncogene*); tumor suppressor genes (e.g., a new breast cancer tumor suppressor gene on chromosome 17, which is not p53); promoters, regulatory elements, and DNA-binding proteins (e.g., FAP-1, crf, and Brn-2); and genes involved in cell cycle regulation and tumor development (e.g., Nova-1, CD44, Muc-1, and DCC). In addition, the roles of different oncogenes (e.g., H-ras and K-ras) in chemical carcinogenesis are being elucidated. Investigators have made great strides in the characterization of the tumor suppressor gene p53 and its mutants, demonstrating that it is the transcription transactivation function of p53 that is essential for tumor suppressor activity.

Epidemiology. Funded BCRP investigators have added significantly to the epidemiological understanding of breast cancer risk factors. 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. One study provided a comprehensive and descriptive statistical analysis of risk factors and genetics of breast cancer in a large sample of African-American women. Data collected in another study indicate that racial/ethnic and socioeconomic disparities in breast cancer survival are unlikely to be explained by differential distributions of prognostic biomarkers. In the area of breast cancer prevention, investigators demonstrated that monounsaturates have a very strong protective effect against breast cancer in Mediterranean populations.

Infrastructure Enhancement. BCRP accomplishments in the area of infrastructure enhancement have had far-reaching effects. Eleven new mutant strains have been developed, as have new, cost-effective techniques for mouse embryo cryopreservation. Ten new breast-related cell lines have been developed. New repositories have been established — over 8,000 samples have been collected and over 5,000 tissue products have been provided to investigators. Twelve investigators have used the University of California, Los Angeles/University of Southern California (UCLA/USC) Tissue Bank to perform 12 studies, and more than 50 investigators have utilized the Breast Cancer Cell Line Resource Core Facility resulting in at least 48 publications.

Training Programs. An important goal and success of the DoD BCRP has been the infusion of new investigators into breast cancer research. Predoctoral training programs have been established at 17 institutions — 30 trainees have been recruited into these programs, and three have graduated with doctoral degrees. Individual fellowships were awarded to 72 predoctoral trainees and 83 postdoctoral trainees. In addition, 41 career development awards were made, and five established investigators have taken sabbaticals in breast cancer research that were funded by the BCRP.

EMERGING BREAST CANCER RESEARCH ISSUES

While the DoD BCRP has made tremendous strides in addressing the complexity of breast cancer research requirements and developing contemporary and responsive science management strategies, there is an acute realization that tremendous gaps remain and many questions are yet to be answered. The following is but a very brief highlight of the myriad emerging requirements, but these patient and system issues must be addressed if the current momentum in breast cancer research is to be maintained and optimized.

Patient Issues

Heightened concern remains for the patient afflicted with breast cancer. Increased sensitivity to the spectrum of issues surrounding patient care including psychosocial-sexual, quality of life, and cultural dimensions is needed on all fronts. 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. Finally, prevention of breast cancer is perhaps the most important and complex arena yet to be addressed. Preventing breast cancer includes addressing the multiplicity of amorphous factors including genetics, environment, and lifestyle.

System Issues

System issues with breast cancer research are formidable. Initial gene research and vaccine development efforts are offering immense promise but still remain in their early infancy. New detection and treatment modalities addressing the total human system, not only regional dimensions, are required. An urgently needed requirement is an intense focus on translational research affording an opportunity to merge interdisciplinary expertise and insights for all model systems including invertebrate, non-mammalian, and human systems in addressing the myriad breast cancer questions. These requirements are complex and enormous. Perhaps most important are (1) the recognized requirement for enhanced coordination among all agencies and researchers, and (2) the creation of additional national infrastructures supporting technologies and rare specimens.

OTHER DOD WOMEN'S HEALTH RESEARCH PROGRAMS

While the DoD BCRP is certainly the largest and most recognized Congressionally mandated research program, other targeted efforts are also making significant contributions in the women's health research arena.

Defense Women's Health Research Program

With a combined total strength of 340,000, women represent nearly 14 percent of the total active duty force of the U.S. military and 16 percent of reservists. Despite the increasing role of women in the military,

there is a dearth of research into the demands and specific health risks facing military women. Congress responded to these issues by appropriating \$40 million in FY 94 for the DoD Defense Women's Health Research Program (DWHRP). This program was continued in FY 95 with an additional \$40 million. The goal of the DWHRP was to combat health problems that are unique to military women, are especially prevalent among military women, or have a large impact on mission performance. The DWHRP emphasized four broad research areas: operational effectiveness, health promotion and disease prevention, psychological health issues related to female integration into a hierarchical male environment, and access to and delivery of gender-specific health care.

Collectively, the DWHRP has awarded 142 grants for intramural and extramural research projects across a spectrum of basic, clinical, and applied research areas. Many unique dimensions of military health issues were addressed with funding in occupational and material hazards, performance issues, protective clothing and equipment, and psychosocial aspects of military life. In addition to the research projects, the DWHRP made a substantial investment in infrastructure enhancement. In FY 95, Congress directed the DoD to develop a database to facilitate long-term research issues related to the health of military women and to develop an information clearinghouse to serve as a resource for clinical, research, and policy issues affecting military women. In response, the DWHRP allocated \$2.6 million and \$1.2 million for the Defense Medical Epidemiologic Database (DMED) and the Defense Women's Health Information Clearinghouse (DWHIC), respectively.

The DMED was developed to facilitate long-term research on issues related to the health of military women. As a comprehensive Triservice effort, the DMED provides access to longitudinal personnel and hospitalization data, enabling cohort or case-control studies and analysis. Epidemiologic studies can be completed on the DMED in less time than was previously required. The DMED structure accommodates a public access web site and both remote and direct access user capabilities. This database was designed to incorporate additional data (death, disabilities, deployments, etc.) as they become available in a semantically equivalent format across the three services. The system is currently in the final phases of development and is expected to be available for use in September 1997.

The DWHIC was directed by Congress to ensure that military women, those who provide their health care, and those charged with ensuring their safety and effectiveness all have the required medical knowledge. The DWHIC is available on the internet at <http://www.4woman.org>. Key resources in the DWHIC include health information beneficial to all women, special features addressing the needs of military women, listings of past and present research studies on Defense women's health, forums to ask questions or provide input, special reports on selected military topics, listings of military health care facilities around the world, an up-to-date directory of researchers active in military women's health, and links to the National Women's Health Information Center. As part of the DWHIC, a toll-free referral phone line (1-800-994-9662) is available to provide access to skilled health information specialists who can provide tailored referrals to valuable sources of women's health information.

Osteoporosis Research Program

Congress appropriated \$5 million in FY 95 for a DoD Osteoporosis Research Program. Following the model used to implement the BCRP, an IP was constituted to provide input for the program focus. A BAA was released, and 108 proposals were received in response. Ultimately, five grants were awarded that addressed genetic analyses of peak bone density; optimization of fibroblast growth factor (FGF)-1 as an anabolic agent for osteoporosis; assessments of bone turnover, menopause, aging, and ethnicity as risk factors; mechanisms of thyroid hormone-induced osteoporosis; and oral bone loss as a risk factor for osteoporosis.

Ovarian Cancer Research Program

For FY 97, Congress appropriated \$7.5 million for a DoD Ovarian Cancer Research Program (OCRP). The Congressional language directs the DoD to implement a comprehensive preventive program in ovarian cancer that includes prevention planning, implementation, and development planning. The language also specifies that eligible institutions are limited to NCI-designated Comprehensive Cancer Centers. The OCRP is currently in the planning stages, with a scheduled release of the BAA in July 1997.

CONCLUSIONS

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.

*Co-Coordinator
Medical Professionals/Persons with CFIDS/CFS
Co-Founder
The North Coast San Diego CFIDS Support Group
Cardiff, California*

Meghan-Morgan Shannon, M.S.

Thank you for inviting me to share this vital information that I have collected concerning medical professionals who are getting sick with this nebulous and mysterious disease. The U.S. Centers for Disease Control and Prevention (CDC) has called it chronic fatigue syndrome. However, as I testified before the Office of Research on Women's Health at the National Institutes of Health in Washington, D.C. on June 6, 1991, I call it acquired immune dysfunction syndrome, non-HIV. Not all medical professionals with CFIDS (MPWCs) feel comfortable with this label.

The facts indicate that health care workers are getting sick and we are being left without health care. We live under the poverty level. We are a drain on the society.

Cluster outbreaks of CFS/CFIDS/ME, etc., have been documented since 1934 and possibly earlier. The National CEBV (Chronic Epstein Barr Viral) Syndrome Association in Portland, Oregon, did an in-depth survey with Minnan, Inc., Glenview, Illinois on February 25, 1986. The results showed that health care workers were the highest risk, teachers were the second highest.

Dr. Bell, a well-respected medical doctor from Harvard University who works with children with CFS/CFIDS/ME, has been quoted as saying “health care workers are at the highest risk and, indeed, are getting sick.” In 1992, at the Albany, New York Conference for Chronic Fatigue Syndrome, Dr. Leonard Jason, et al., presented compelling evidence that health care workers were at the highest risk.

It is no accident that most support group leaders in the United States are from the health care field. When I say health care field, I include R.N.s, medical technologists, secretaries, respiratory therapists, M.D.s, etc.

As a result of my statement in 1991, Gail Dahlen, R.N., former OB/GYN lead nurse and instructor of the Long Beach OB Hospital, joined me in starting a support group for MPWCs in 1992. Since 1994, we have advertised in the *North Carolina CFIDS Support Group Journal* five or six times. We now have nearly 600 MPWCs in our data and possibly hundreds more that have not responded back to us from the first contact. This journal reaches 20,000 people. Recently, through the efforts of the editor of our newsletter (Lori Clovis), we are now online and are receiving two to three letters a day, from health care workers who are ill.

We have observed several patterns that may be of interest to the scientific community. The Hepatitis B vaccine seems to have triggered at least ten of the people in our first group of 150. When others are asked directly if they received the HEP B vaccine, we find that there’s a possibility of more persons whose CFS/CFIDS/ME started with that vaccine. Most infected individuals have worked in emergency care, or intensive care units, such as Gail and I, and became ill when a “flu” was in the community and we had treated those people. You may see our stories in the book that says “MPWCs Stories.” I have the booklet with me. It appears that the doctors at highest risk are OB/GYNs and family practitioners.

I know exactly when and where I got sick. It is well documented in my medical records as well as in *JAMA*, 1983. I was working at Children’s Hospital in San Diego in 1980 when an outbreak of an adenovirus went through the hospital and killed several children. It infected about 10 to 15 percent of the staff over the next 3 years and continues even to this day. Since then, I have learned that the leading neonatologist, Dr. Morton Cohen, who tested culture-positive as well as having high titers for the adenovirus, committed suicide in the late 1980s. He was diagnosed as “depressed.”

An R.N. named Sally worked at the hospital during the viral incident in the 1980s. She continued to work there through 1993. I have recently learned that she has also committed suicide. She was diagnosed as being addicted to Vicodin, which she was taking for severe pain and lack of energy. She was “rehabilitated” from her drug addiction in 1992. Her physical illness was never addressed. Her pain was unbearable and she killed herself.

As my friend Gail Dahlen expresses so often, “How can the very institutions to which we dedicated our lives turn their backs on us and allow us to either commit suicide or live on the meager social security benefits that put us well below the poverty line?”

Having spoken with Dr. Elaine DeFrietis, formerly of the Wistar Institute in Pennsylvania, and Dr. Garth Nicholson, of the MD Anderson Cancer Center, Houston, Texas, I agree with them that this is a multiple insult to the immunological and neurological systems of the body. Of course the health care workers are at the highest risk, not only to the viruses and the bacterias and the mycoplasmas, but also to environmental toxins that are common in a hospital environment.

I wonder, at times, if CFS/CFIDS/ME (myalgic encephalomyelitis) kicks in autoimmune responses such as lupus, multiple sclerosis, diabetes, rheumatoid arthritis, etc. Could it be that if someone studied the health care workers we might find some common threads tying all this together?

I am appalled that the United States is using the MMPI (a test for personality disorders) to diagnose this disorder. However, I do believe that once diagnosed with a physical illness such as CFS/CFIDS/ME, the MMPI can be useful in helping to treat the patient.

If health care workers are ill, how can we have a health care plan in America? Who will take care of the sick? Being ill, or disabled, is truly a political issue. As a woman who is a feminist, I now truly understand the statement that the “personal is political.”

Amanda Sherman

*President, DES Action USA
Oakland, California*

Organizational Summary for 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 persons 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 on the following subjects.

- Facts about DES, a synthetic estrogen, and numbers exposed in the United States.
- Health effects for DES daughters resulting from in utero exposure to DES.
- Previous research efforts led by the Office of Research on Women's Health, National Institutes of Health.
- Present and pressing research questions faced by DES daughters.

*Institute of Women and Ethnic Studies
New Orleans, Louisiana*

Denise O. Shervington, M.D., M.P.H.

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.

- 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 should be integrated into a holistic approach to women's health.
 - Contraception research agenda should be expanded to include more contraceptive options for men.
- 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.

PUBLIC TESTIMONY

- FDA must monitor post-marketing surveillance of drug safety and efficacy.
- A system must be developed for reporting, monitoring, and responding to consumer and/or providers' reports of side effects.
- A system must be established for safeguarding against drug misuse (by misleading marketing to consumers or inappropriate prescribing by providers).



WORKSHOP AGENDA AND PARTICIPANT ROSTER

B E Y O N D H U N T V A L L E Y :
R E S E A R C H O N W O M E N ' S H E A L T H
F O R T H E 2 1 S T C E N T U R Y

Sheraton New Orleans Hotel
New Orleans, Louisiana

June 11-13, 1997

A G E N D A

W E D N E S D A Y , J U N E 1 1 , 1 9 9 7

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

T H U R S D A Y , J U N E 1 2 , 1 9 9 7

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 H. 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

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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, and 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

F R I D A Y , J U N E 1 3 , 1 9 9 7

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 and 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

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

NEW ORLEANS, LOUISIANA
JUNE 11-13, 1997

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