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

INFLUENCES OF SEX AND GENDER ON HEALTH

Scientific Meeting and Public Hearing
Philadelphia, Pennsylvania
September 1996

4 VOLUME

NATIONAL INSTITUTES
OF HEALTH
Office of the Director

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Hosted by:
University of Pennsylvania School of Medicine
and
Allegheny University of the Health Sciences,
MCP◆Hahnemann School of Medicine

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PREFACE

In September 1991, the Office of Research on Women's Health (ORWH) of the National Institutes of Health (NIH) convened a meeting in Hunt Valley, Maryland, to assess the state of the science and to develop an agenda to guide women's health research in the coming decade. The report generated by that meeting, 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 provide 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 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 have participated in the process and continue to provide guidance and expertise to ORWH.

The information presented in this volume represents the outcome of the Philadelphia regional meeting — the scientific workshops 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 New Orleans and Santa Fe and at the national meeting in Bethesda.

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This workshop and scientific meeting, sponsored by the Office of Research on Women's Health (ORWH) of the National Institutes of Health (NIH), elicited participants' views concerning NIH's agenda for research on women's health for the 21st century.

From the excellent and informative public testimony presented at the public hearing and the recommendations received, ORWH re-examined NIH's existing agenda for women's health research. Drawing on participants' wisdom and insight and availing ourselves of scientific directives in a science-driven agenda, we worked in concert with the members of ORWH's Task Force on the NIH Women's Health Agenda for the 21st Century, the Advisory Committee on Research on Women's Health, and the Coordinating Committee on Research on Women's Health to re-examine NIH's priorities in women's health research. The goal was to direct, or redirect, NIH's future endeavors in biomedical and behavioral research, so that the knowledge that we gained in recent years and the momentum that our collective efforts generated would be used to preserve and improve the health and well being of women.

I wish to acknowledge the wonderful, sincere, and dedicated contributions of Iris Schneider, of the National Cancer Institute, to women's health research at NIH. We miss her today, as we know she would have been here to guide and inspire our efforts. Iris was instrumental in the development of our Office and its programs across NIH. With her death just a few weeks ago, she left a great void in the women's health community; we mourn for her friendship, her tireless energy, her unrelenting commitment to women's health research, and her boundless courage in the face of her own ovarian cancer.

The major charge during this workshop was to help us determine future directions for women's health research and a myriad of related issues. There is no question that research is central to providing the scientific foundation for change and improvement in women's health. There must be multidisciplinary collaboration involving multiple partners who share the responsibility to establish and disseminate new information that results from increased and enhanced research on women's health. We must also collaborate in implementing and translating the findings of research in health care delivery, and we must seek innovative strategies for influencing the behavior and health practices, not only of the scientific and medical communities, but also of individual women and their families.

We know that to bring about change in women's health research, there must be a coalition of effort that includes the scientific and health care communities, those involved in professional education, federal agencies, women's health advocacy groups, and, most importantly, women and their families and communities. History has demonstrated that when these groups work in harmony with concerted effort, significant improvements can occur.

History also demonstrates that the focus on women's health and the women's health movement are not new. The Boston Women's Health Book Collective just celebrated the 25th anniversary of the legendary tome, *Our Bodies, Ourselves: A Book by and for Women,*[1] and the National Women's Health Network and the National Black Women's Health Network, among many others, are advocacy and action groups that have been around for years — working in the "trenches," so to speak — to call attention to the need to focus our attention on women's health. In recent years, the Federal Government has recognized women's health as a priority requiring significant attention and resources. Today, thanks to the efforts of many, we are beginning to make progress.

THE PHS TASK FORCE AND THE ESTABLISMENT 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 issued 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 recommendations of the Task Force report was one which 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.*[2]

As Assistant Secretary for Health, Dr. Brandt said that he was *"committed to seeing that this report results in action that is beneficial to the women of America."* [3] This report and commitment thus launched the federal initiatives to address women's health.

HISTORY OF INCLUSION POLICIES AT THE NATIONAL INSTITUTES OF HEALTH

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by NIH has its origins in the women's health movement. Following the issuance of the report of the PHS Task Force on Women's Health Issues 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 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, at the encouragement of the Society for the Advancement of Women's Health Research, requested that the General Accounting Office (GAO) investigate the implementation by NIH of the guidelines for the inclusion of women. In 1990, this GAO report stated that the policy for the inclusion of women was implemented inconsistently across NIH.[4]

Just 3 months after the release of the GAO report, in September 1990, the Office of Research on Women's Health (ORWH) was established at NIH. In fact, the press release announcing the formation of this office was dated Monday, September 10.

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.

Since the establishment of ORWH, our responsibilities and major program efforts have increased and, in 1993, our office was legislatively mandated in the NIH Revitalization Act.

ORWH has taken the leadership in implementing policies requiring the inclusion of women and minorities in human subject research. Wanting to ensure that the policies for inclusion were firmly implemented by NIH, Congress made what had previously been policy into Public Law, through a section in the National Institutes of Health Revitalization Act of 1993, entitled, "Women and Minorities as Subjects in Clinical Research."[5]

The National Institutes of Health 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* [6] in March 1994, and they have been fully implemented.

ORWH has also convened two meetings of Institutional Review Board(s) chairs and representatives to determine potential remaining barriers to the implementation of this policy.

ORWH's mandate on inclusion also calls for the development of a tracking system to monitor the inclusion of women and minorities in clinical trials. By working in collaboration with the Office of Extramural Research, ORWH has developed a tracking system, which is now in place. For the first time, we are now able to determine the numbers of women and minorities included in human subject research. As we collect additional data, we will determine how best to interpret these figures.

ORWH also funded the Institute of Medicine study *Women and Health Research,*[7] which is an excellent report on the legal and ethical issues related to women, especially women of childbearing age, in human subject research.

To address concerns about the inclusion of women in clinical trials, ORWH held a public hearing and workshop in July 1993 on the recruitment and retention of women. The report of that study[8] is available to assist investigators who seek information to aid them in their efforts.

In June 1992, ORWH had held a public hearing and workshop on the recruitment, retention, advancement, and re-entry of women in biomedical careers.

Using the report from this meeting,[9] which identifies barriers to women entering or advancing in scientific careers, ORWH established a number of programs, including our re-entry scientists program and other initiatives, to help develop the careers of women and men scientists and to stimulate research on women's health issues. These programs include workshops on how to speak and write about science.

Under the leadership of Joyce Rudick, Senior Program Analyst, and Dr. Anne Sassaman, Cochair of our Coordinating Committee on Research on Women's Health Career Development Subcommittee, we have evaluated the re-entry program and are now looking for ways to expand this and other ORWH initiatives. Suggestions received during the public hearing and recommendations from the working group on young investigators were of great assistance to us in this endeavor.

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.

ORWH 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 reflect on our progress to date. 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 original agenda began with the report, *National Institutes of Health: Opportunities for Research on Women's Health* (referred to hereafter as the Hunt Valley Report).[10] This agenda was formulated from a public hearing and workshop held in September 1991 in Hunt Valley, Maryland. In the agenda, the parameters of women's health were expanded and redefined, and research has been redirected to provide better information on sex and gender differences between women and men in normative development, health, and disease.

The NIH agenda recognizes the full spectrum of research from clinical to basic, behavioral to epidemiological. We have also recognized the many gender issues that must be taken into account in designing clinical research studies. The agenda emphasizes the need to proceed from an expanded concept of women's health: one that crosses scientific disciplines and medical specialties to examine women's health across the life span and that focuses on outreach to populations of women and girls who have been previously excluded from scientific investigation. Including minorities, women of low socioeconomic status and diverse geographic locations, and lesbians is an integral part of ORWH's research agenda. In all of our efforts to implement our research agenda, we are pursuing active and beneficial partnerships with all NIH institutes, divisions, and centers.

The 1991 Hunt Valley meeting led to our current working research document. We believe that it is time to look "beyond Hunt Valley," to update our priorities, and go beyond research to consider how best to implement the results of such research. We found the model of broad participation in this process through public hearings and workshops with representative and voluntary participation to be most effective, and we have thus turned again to this model.

We asked working groups to:

- 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; and

- 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.).

Participants were told to keep in mind that all of our programs and initiatives should be science driven. They were asked to consider how, where, and in what manner we can best ensure implementation of the results of our advances from research. Their role was a significant and meaningful one. Our updated agenda reaffirms NIH's commitment to an integration of 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 your assistance, as we enter into the 21st century, ORWH can build on that power and maximize its efforts to improve the health of women and their families. That is ORWH's and NIH's vision for women's health in the United States and beyond, which we are trusting to you to help us ensure for the future. No single individual or group can do the job alone. The challenge — and the responsibility — must be shared by all of us.

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WORKING GROUP REPORTS

CARDIOVASCULAR DISEASE/ VASCULAR BIOLOGY

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BACKGROUND

The 1991 workshop "Opportunities for Research on Women's Health" generated a surge of new research recommendations on issues related to the cardiovascular health of women. Many more important questions still must be addressed, especially through research on the molecular, cellular, and physiological levels.

Cardiovascular disease (CVD) is the number one killer in the United States, killing more than 954,000 Americans each year, about one person every 33 seconds. The disease is also a major cause of disability. About 13.5 million Americans, including 6.6 million under age 60, now live with the effects of heart attack. In 1992, CVD accounted for 4.7 million years of potential life lost before age 75. Approximately 3.8 million Americans, more than 900,000 of whom are under age 60, suffer from the consequences of stroke, the main cause of permanent disability in the United States.[1]

More than 1 in 4 million Americans suffer from some form of CVD, at an estimated cost of $151 billion in 1996. The costs for patients with CVD are growing because we are treating the disease with expensive technology, not preventing it. Moreover, there will be even more cardiovascular disability in the future because many people who have had effective treatment for coronary artery disease (CAD) and prevention of atherosclerosis between ages 40 and 60 will develop further CVD later in life unless effective prevention methods are discovered.[1]

Cardiovascular disease is the number one killer of women in the United States, accounting for about 45 percent of deaths among women. It kills almost twice as many American women as all cancers. Heart attacks kill more than five times as many women as breast cancer. Of the more than 489,700 deaths from heart attack each year, more than 48 percent occur in women.

An important fact to consider is that the heart attack death rate for African-American women between ages 35 and 74 is about twice that of white women and three times that of women of other races. Stroke, America's number three killer, kills twice as many women as breast cancer. However, until recently, heart attack, stroke, and other CVDs in women have not been recognized as a serious problem, particularly by women themselves.

Women develop heart disease later in life than men, but, at any age, heart attack in women is more deadly. Older women who have suffered heart attacks are twice as likely as men to die from them within a few weeks. About 44 percent of women who have heart attacks die within a year, whereas only about 27 percent of men die within a year. Among women who died suddenly of coronary heart disease, 64 percent had no previous symptoms, compared to 48 percent of men.

Other CVDs are prevalent in women. More than 87,000 of fatal stroke victims are women, representing 60.6 percent of stroke fatalities. Less prevalent are cases of rheumatic heart disease, an inflammatory disease that permanently damages the heart and its valves. Again, mortality from this disease is higher for women (69.9 percent) than for men.

The procedures for clinical diagnosis of CAD in women must be improved. Research should focus on better descriptions of anginal syndromes, on enhancing the efficacy of diagnostic and screening testing in women, and on developing alternative strategies for diagnosis.

In the environment of managed care, all research, especially research on women's health, must incorporate measurements of outcomes. The Office of Research on Women's Health (ORWH) should carefully assess the therapies that are being delivered, how effectively they are being delivered, and the outcomes that women experience from the results of these therapies. Outcomes research in women's health is needed to influence health care policy. Funding is needed for research on gender differences in disease outcomes across the board.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Although progress has been made, there is still a long way to go in CVD research on women. The 1991 *Report of the National Institutes of Health: Opportunities for Research on Women's Health* ("Cardiovascular Function and Disease," pp. 171–184) made 14 recommendations that addressed the clinical and psychosocial aspects of CVD. This report focuses on the basic science of cardiovascular disease as it relates to women's health.

The Hunt Valley report identified coronary artery disease as the highest priority for research on women's health, and it identified sex hormones, particularly estrogen, as the major determinant of CAD risk in women. The Hunt Valley report made three recommendations regarding CAD:

1. The procedures for clinical diagnosis of CAD in women must be improved. Research should focus on better descriptions of anginal syndromes, enhancing the efficacy of diagnostic and screening testing in women, and developing alternative diagnosis strategies.
2. Studies should investigate the mechanisms that result in women's poorer outcomes after myocardial infarction and coronary revascularization procedures and how to correct these problems.
3. Research should examine the efficacy of components of the cardiac rehabilitation effort on outcome after myocardial infarction, including factors that affect women's success in such programs.

(Note: Portions of the remainder of this section have been adapted or excerpted from an article by Dr. Suzanne Oparil entitled "Cardiovascular Risk Reduction in Women," November 1, 1996, Journal of Women's Health, *vol. 5, with the permission of the publisher.)*

Gender differences in CVD, from clinical practice to understanding basic mechanisms, have been inadequately explored in part because of the false assumption that atherosclerosis is less prevalent and more benign in women. Gender differences appear to exist in areas ranging from risk-factor identification and modification to diagnosis and treatment.

Recent attention to the high prevalence of fatal and nonfatal cardiovascular disease in women has underscored the importance of lifestyle modification and cardiovascular risk-factor reduction in this population. Recommendations for risk-factor reduction in women are generally the same as in men, with one major and several minor exceptions. Postmenopausal hormone replacement therapy has a powerful effect on cardiovascular risk reduction, but it may be inappropriate for some women because of apparent enhanced breast cancer risk. The utility of aspirin therapy in the primary prevention of CVD in women remains to be established. Further, the benefit of, and prescription for, lipid-lowering therapy may prove to be different than men, and the benefits of antihypertensive treatment may be less. For the other risk factors, including smoking, diabetes mellitus, obesity, sedentary lifestyle, and alcohol, recommendations are the same for both sexes.

Menopause and Hormone Replacement Therapy

Meta-analyses of observational studies suggest that a benefit of a 50-percent reduction in risk for heart disease occurs among postmenopausal women taking estrogen replacement therapy. However, observational studies have the severe limitation of treatment-selection bias. Women who are taking postmenopausal hormone replacement treatment tend to be healthier, better educated, and more attentive to lifestyle-modification strategies for reducing cardiovascular risk and to have better health care.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial is a prospective, randomized, double-blind, placebo-controlled trial that is assessing differences among placebo, unopposed estrogen, and each of three estrogen/progestin regimens on selected heart disease risk factors in healthy postmenopausal women. The findings after 3 years of followup provide strong evidence that estrogen alone, or combined with progestin, has a cardioprotective effect in postmenopausal women, particularly in those women with preexisting coronary disease or those who are at high risk for developing coronary disease. Whether these beneficial effects on cardiovascular risk factors translate into a reduced incidence of heart disease and reduced cardiovascular mortality rates awaits the results of large-scale, multicenter, long-term, randomized trials, which are in progress in the Women's Health Initiative.

Meta-analyses suggest that there may be a 15- to 30-percent increase in risk of breast cancer after 10 years of postmenopausal estrogen replacement therapy. There appears to be little or no risk associated with past use or short-term (5 years or less) use of estrogen, and there is no clear evidence that breast cancer risk increases with increasing doses of estrogen or different treatment regimens. Further, the Nurses' Health Study, an observational study of 121,700 female registered nurses, reported a 30- to 45-percent increase in risk of breast cancer in participants who were taking hormone replacement therapy. The increase in risk was the same whether estrogen alone or an estrogen/progestin combination was taken. Because heart disease is so much more common than breast cancer, the impact of postmenopausal hormone replacement therapy on lives saved by decreasing fatal heart attack rates has been predicted to be greater than on lives lost by increasing breast cancer rates. It should be emphasized that all of these figures are estimates based on observational studies that have potential sources of bias, such as differences in rates of participation in mammographic screening. Accordingly, data from randomized prospective clinical trials are needed to address the balance of benefits and risks of hormone replacement therapy. Further, relative risks of cardiovascular disease versus breast cancer vary greatly among women, so decisions about postmenopausal hormone replacement therapy should be individualized.

Lipids

Low levels of high-density lipoprotein cholesterol (HDLC), particularly in association with hypertriglyceridemia, are strong predictors of coronary heart disease in women. Average levels of HDLC are higher in women than in men throughout adult life, although the gender difference is lower after middle age. It has been postulated that HDLC may partly account for the gender difference in coronary heart disease risk. Estrogens raise HDLC levels by at least two mechanisms: suppressing hepatic lipase activity, thus reducing conversion of HDL_2 to HDL_3, and increasing synthesis of apolipoprotein. Estrogens also lower low-density lipoprotein cholesterol (LDLC) by accelerating LDL catabolism, probably by increasing the density of LDL receptors. Further, estrogens increase triglyceride levels by increasing the production of large, triglyceride-rich, very-low-density lipoprotein (VLDL) particles. These large triglyceride-rich VLDL particles are thought to be cleared rapidly from the circulation and not to be atherogenic. Lipid effects have been hypothesized to account for ~50 percent of the cardioprotective action of postmenopausal hormone replacement therapy with orally administered conjugated estrogen. In contrast, transdermal estradiol has little or no effect on lipids.

In the PEPI trial, all hormone replacement regimens produced significant increases in HDL cholesterol and triglyceride levels and decreases in LDLC levels compared with placebo. Thus, estrogen alone or in combination with a progestin improves the lipid profile in postmenopausal women.

Hypertension

Elevated systolic and diastolic blood pressures are independent risk factors for acute coronary events and cardiovascular mortality in women. The prevalence of hypertension, particularly systolic hypertension, increases dramatically with age in women. Whether the menopause per se contributes to the age-related increase in blood pressure in women is controversial.

Antihypertensive treatment is effective in preventing heart attack and stroke in the general population of hypertensives, but the magnitude of the benefit is less for preventing coronary events than stroke. This is particularly true among women, in whom most reported studies have shown no decrease in the incidence of coronary heart disease with antihypertensive treatment, with the exception of women with isolated systolic hypertension.

Smoking

Cigarette smoking produces a dose-related increase in cardiovascular risk in women as well as in men. This increased risk is reversible with smoking cessation, reaching the level of risk of nonsmokers within 3 to 5 years regardless of the amount smoked, duration of smoking, or age at cessation. More vigorous efforts are needed to discourage smoking among women and to prevent smoking by girls.

Diabetes Mellitus

Diabetes is a more important risk factor for coronary disease in women than in men. The Nurses' Health Study showed that maturity onset diabetes was associated with a threefold to sevenfold increase in risk of a cardiovascular event. Further, after 45 years of age, women are twice as likely as men to develop diabetes mellitus. Although the mechanisms by which diabetes accelerates the natural history of vascular disease are poorly understood, there are clear interactions with other modifiable risk factors, such as hypertension, lipid abnormalities, obesity, and smoking.

Obesity

Overweight increases the risk of coronary heart disease twofold to fourfold in women. The magnitude of the excess risk is directly proportional to the excess body mass. This is a growing public health problem, as the prevalence of overweight (body mass more than 20 percent over the upper limit of normal) in the United States has increased from 25 to 33 percent in the past decade. The excess cardiovascular risk of adiposity is related in part to effects on lipid levels, glucose tolerance, and blood pressure and in part to other poorly understood mechanisms. The best approach to obesity is prevention.

The distribution of body fat may also be associated with risk of coronary heart disease. Excess abdominal fat appears to confer a high risk of coronary heart disease in both sexes. Among women, coronary risk is greatly increased when the waist-to-hip ratio is more than 0.8. It has been postulated that intra-abdominal fat has effects on lipid metabolism that result in hypertriglyceridemia, reduced HDL cholesterol levels, and insulin resistance. Observational studies have related abdominal adiposity in women to a number of cardiovascular risk factors, including hypertension, physical inactivity, and smoking.

Sedentary Lifestyle

The effects of exercise on coronary disease and coronary risk have been studied far more extensively in men than in women. However, preliminary evidence from small prospective and case-control studies in women and estimates derived from a meta-analysis of studies based largely on men suggest that physically active women have a 50-percent reduction in coronary disease risk compared with inactive women. Further, prospective data from the Healthy Women Study indicated that exercise had beneficial effects on important risk factors, including weight and HDL cholesterol levels, in perimenopausal women. Large, long-term prospective studies are needed to determine whether the favorable effects of exercise on cardiovascular risk factors in women translate into a reduced incidence of coronary disease.

Alcohol

Case-control studies and cohort studies have shown that moderate (one or two drinks per day) alcohol use protects against coronary heart disease in women and men, but the beneficial effects must be balanced against the health hazards of alcohol, including increased blood pressure and increased risk of hemorrhagic stroke, breast cancer, and addiction and abuse. Accordingly, alcohol is not recommended for cardioprotective purposes in women (or men) who are nondrinkers.

Aspirin

Aspirin reduces (by ~25 percent) the recurrence rate of myocardial infarction, stroke, and death from cardiovascular causes in women, as well as in men, with established coronary artery disease. In contrast, data on the efficacy of low-dose aspirin in the primary prevention of coronary heart disease in women, all derived from observational studies, are inconsistent. Studies in progress are assessing the risks and benefits of aspirin in the primary prevention of coronary heart disease and stroke in women.

Antioxidants

Antioxidant vitamins, including vitamins E and C, and beta carotene have shown inconsistent benefit and some increased risk (hemorrhagic stroke) in men. The recent evidence that antioxidant vitamins may have harmful effects, and appear not to be beneficial in some settings, underscores the need for further study before the widespread use of these agents can be recommended for heart disease prevention.

GAPS IN KNOWLEDGE

Although progress has been made in controlling CVD, there is still a long way to go in the prevention of CVD in women. In the near future, it will become necessary for research efforts on cardiovascular diseases, immunology, and infectious disease to merge. For example, information is increasing about whether or not agents, such as chlamydia, may play an intimate role in atherogenesis.

Evaluation of Chest Pain in Women

Women with CVD are generally older and sicker than men and do not respond to treatment as well as men. The reasons for this still need to be elucidated. Women report symptoms of ischemia differently than men and responses to diagnostic tests for ischemic heart disease are different between the sexes. For example, silent ischemia and silent myocardial infarctions occur commonly in women, perhaps due to the presence of diabetes, which greatly enhances CAD risk in women. Further, chest pain in the absence of identifiable disease in the epicardial coronary arteries is a major problem in women. Since diagnostic standards developed for men are generally applied to women, diagnosis of CVD is difficult for women. Additional research is needed to refine the specificity/sensitivity of diagnostic testing for CAD in women.

Atherosclerotic Process in Men and Women

There are major differences between men and women in the evolution of atherosclerosis and the risk of disease, especially at the cellular level. The need to fill the gap in knowledge and fundamental understanding of cell biology is certainly an issue in the treatment of atherosclerosis. It is highly possible that estrogen is a part of the problem, but the fact that you can treat women with estrogen much more successfully than men, regardless of dose, is an issue that should be addressed.

There is mounting evidence that atherosclerosis represents an inflammatory response to infectious agents such as chlamydia or to noninfectious agents such as oxidized low-density lipoprotein. Some inflammatory disorders are more common in women, particularly premenopausal women, than in men. For instance, in lupus arteritis, it is believed that estrogen has beneficial effects in the vessel wall. Therefore, there is a need for more knowledge about the interaction of estrogen and the inflammatory process, including inflammatory cell expression and expression of cell-adhesion molecules.

Stroke

Sixty percent of stroke fatalities are among women. Twice as many black women as white women die of stroke in all age groups. Multiple pregnancies may increase the risk of cerebrovascular disease and stroke through the mechanism of insulin resistance. Diabetes triples the risk of stroke in women. The increased risk of subarachnoid hemorrhagic and ischemic stroke in women who smoke may be reversed in 2 to 4 years after smoking ceases.

Lack of Psychosocial Support After Myocardial Infarction

Women with a diagnosis of myocardial infarction generally have poor outcomes. The psychosocial impact on these women, who usually must return home and resume the routine of running a household, is not known. For example, there is a gap in knowledge about women who suffer depression after a diagnosis of CVD. Women are four times more likely to suffer from depression than men. Depression increases mortality in women from approximately 4 percent to greater than 40 percent. Depression not only creates social problems, it can also alter chemicals in the brain.

Diabetes and Cardiovascular Disease

Insulin-dependent diabetes mellitus is an important cause of premature CVD among young men and women under 45 years of age. Cardiovascular disease is especially high among premenopausal women who have insulin-dependent diabetes mellitus and smoke cigarettes. Studies are needed to ascertain why diabetes increases the risk for CVD among premenopausal women. Data are needed on the efficacies of medical and revascularization therapy and on exercise rehabilitation for coronary heart disease failure and stroke.

The interaction between diabetes, estrogen therapy, and CAD in women is not known. It is unclear whether estrogen replacement therapy effectively protects postmenopausal diabetic women from developing CVD. More clinical data are needed, as well as more basic information about the effects of estrogen on the biology of the diabetic blood vessel.

Lipid Profiles and Obesity

The major risk factors for coronary heart disease and stroke are similar for men and women. These include high levels of LDLC, low levels of HDLC, smoking, high blood pressure, diabetes, obesity, and physical inactivity. The gender differences appear to be in the magnitude of the increased risk for disease at similar risk-factor levels. Estrogens have direct effects on the arterial wall and appear to enhance the activity of LDL receptors, resulting in lower levels of LDLC among premenopausal women. As the estrogen level and ovarian function decline, postmenopausal women develop higher LDLC levels. This increase in LDLC in older women contributes to the increase in atherosclerosis and coronary heart disease.

Weight gain is common in American women between the ages of 30 and 50 years. The distribution of body fat is different in women than in men.

For example, central obesity is more common in African-American women than in white women, but in one study, the body mass index and waist-to-hip ratio were predictors of cardiovascular death only for white women.

Vascular Effects of Estrogens

Large gaps persist in the knowledge about the vascular effects of estrogens. There is evidence that various estrogen preparations (natural versus synthetic, orally versus percutaneously administered) have different vascular effects. The mechanisms of their differences should be studied further. It is important to do research that will close the gap of knowledge about whether hormone replacement therapy increases the risk for breast cancer while decreasing risk for CVD. Women, in general, see coronary disease as a problem of very old age, but they see breast cancer as a disease that affects women at younger ages.

RESEARCH RECOMMENDATIONS

The consensus of the working group was that an overall recommendation should be made for gender-specific evaluation in all areas of CVD discussed in this report. Also, for certain CVDs, a longitudinal study should be conducted that is specific to certain racial or ethnic groups. Because women communicate their symptoms differently, it is important that all cardiovascular research outcomes identify gender-specific diagnoses and treatments.

Coronary Artery Disease

- Study the cellular aspects of coronary artery disease in men and women to determine if this is really a different disease in women than in men.

- Determine the basic mechanism of action of both endogenous and exogenous reproductive hormones in the development of atherosclerosis.

- Determine if differences in hormonal measures, dietary factors, and genetic characteristics influence the changes in risk factors and the progression of atherosclerosis.

- Design studies to determine the qualitative aspects of angina in women and men.

- Determine if women have subtle asymptomatic limitations in coronary reserve.

- Determine how response to diet modification is affected by age, status, hormone replacement therapy, and baseline lipid lipoprotein levels.

- Determine the outcomes of antihypertensive therapy by gender.

Cerebrovascular Disease

- Research should incorporate outcomes measurement in research. Scientists should carefully assess existing therapies, how effectively they are being delivered, and the outcomes that women are experiencing from these therapies.

- Determine why stroke occurs in African-American women at an earlier age than in white women.

- Identify other potentially reversible stroke risk factors in addition to smoking.

- Determine why there is a later onset of stroke, other CVD, and CHD in women than in men.

- Determine the extent of various venous disorders seen predominantly in women, and whether these can be prevented.

Chest Pain and Arrhythmias in Women

- Define the mechanisms of chest pain in the absence of epicardial CAD in women.

- Improve methods for diagnosing ischemia in women.

Prevention and Education Strategies

- Expand research to include strong behavioral models. Encourage medical schools to expand their curricula by fostering research in this area.
- Educate health care providers about the symptoms of CVD in women. Provide disease-by-disease information on prevention and education.
- Educate the public that heart disease is the major killer of women.
- Educate the public on the hazards of smoking as it relates to cardiovascular disease.
- Develop educational strategies aimed at health care providers, especially nurse practitioners.
- Provide information on the large numbers of women who do not report heart palpitations to their health care providers.
- Focus on prevention strategies, particularly nutrition and body weight.
- Educate physicians, nurses, and the public about the nature of CAD in women and its unrecognized importance.

Vascular Mechanisms with Hormone Replacement Therapy

- Study hormonal impact on endothelial function both in pre- and perimenopausal women.
- Develop a replicate mechanism for hormone therapy for women as well as for men.
- Define a good animal model for testing hormone therapy.
- Look at the interaction between diabetes and CAD in women. Develop research programs to determine if estrogens protect diabetic women against the prospect of atherosclerosis or other vascular defects.
- Compare the different estrogens (both human and nonhuman) to determine whether there is an advantage of one over the other.
- Study what effect estrogen has in molecular biology.
- Develop research programs to study whether different vascular beds respond differently to estrogen therapy from a vascular biology standpoint.
- Revisit the question, “Do the risks of breast cancer outweigh the risk of heart disease when administering hormone replacement therapy in women?”
- Increase the understanding of the various types of hormones used for basic therapy.
- Determine if estrogen and estrogen-progestin combinations alter the risk of coronary heart disease.
- Determine the relation of estrogen to other risk factors on vasoregulation and other atherosclerotic processes.
- Determine the metabolic effects of estrogen replacement therapy or hormone replacement therapy on patients with other metabolic abnormalities.
- Determine the efficacy of hormone replacement therapy in preventing CVD in postmenopausal women.
- Determine why HDLC levels are higher in women after puberty compared with men. Are they determined solely by sex-steroid metabolism?
- Determine if hormonal or psychosocial factors explain why childless women have a higher risk of sudden death.

- Identify the effect of estrogen therapy on the reversal and progression of stroke and peripheral vascular disease.

Comparative Atherosclerosis in Men and Women

- Conduct research to determine if the rise in the LDLC level and the development of atherosclerosis in women can be prevented.

Gender-specific Secondary Analysis in Hypertension

- Develop better knowledge and criteria for studying hypertension in women.

Prevalence and Clinical Manifestations of Peripheral Vascular Disease

- Conduct research to determine what level of blood pressure should be considered normal (140/90 or 120/80).

- Obtain more information about the different categories of active hypertensive medications and in which groups these medications might be most effective.

- Develop better methods to identify those patients who would benefit from heart transplants.

- Conduct prevalence and clinical manifestation studies for peripheral vascular disease. Determine if there are gender differences in peripheral vascular disease.

Comparative Etiology of Heart Failure in Men and Women

- Conduct studies to determine if the etiologies of heart failure are different for women and for men.

- Determine if progress has been made in understanding why women diagnosed with myocardial infarctions have poor outcomes.

- Determine what changes occur in risk factors during the peri- and postmenopausal periods in nonwhite populations.

- Determine how the patterns of obesity and fat deposition relate to CVD in women.

- Identify the determinants of weight gain in women.

- Identify the most effective approaches to preventing obesity among minorities.

- Determine if there is an association between number of pregnancies and weight gain.

NEUROSCIENCE, BEHAVIOR, AND THE HEALTH OF WOMEN ACROSS THE LIFE SPAN

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BACKGROUND

In recent years, advances in basic and clinical neuroscience have enhanced the ability of researchers and clinicians to understand the neurobiology underlying diseases and conditions such as Alzheimer's disease, anxiety disorders, chronic pain, depression, epilepsy, multiple sclerosis, Parkinson's disease, schizophrenia, and stroke. Such advances have occurred, in part, as a result of improvements in the tools and technologies now available to study and map the brain and its functioning in health and disease. Understanding brain disorders has also benefited from an increased focus on the role of estrogen, progesterone, dopamine, serotonin, and other naturally occurring chemical substances in cognition and emotion.

Through the use of positron emission tomography (PET), single photon emission computerized tomography (SPECT), magnetic resonance imaging (MRI) and spectroscopy (MRS), functional MRI (fMRI), and similar methods, neuroscientists have begun to examine in vivo the physiology, neurochemistry, and anatomy of the human brain. With the increased attention given to research on women's health, and gender differences in health and disease, studies have begun to focus on sex and gender differences in brain structure and function that may contribute to differences in cognitive and emotional processing.[1] Studies have also identified sex differences in the manifestation of brain disorders and the influence of reproductive endocrine disorders in women and men suffering from such diseases as epilepsy.[2,3] Research has also begun to focus on the influence of hormonal states on cognition and affect in health and disease.[4]

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Sex Differences in Cognition and Effects of Hormones

Scientific evidence on the effects of sex hormones on adult cognition has emerged since the 1991 meeting organized by ORWH in Hunt Valley, Maryland. Through basic science and clinical research, it is now known that varying estrogen and progesterone levels, across the menstrual cycle and across the life span, can influence an individual's performance on a number of cognitive tasks.

Estrogens have been shown to have numerous effects on the brain, beginning at gestation and continuing into adulthood. Many of these effects implicate areas of the brain that are involved in memory processes and their alterations over the life span in healthy people, and this is important for understanding the pathophysiology and consequences of neurodegenerative diseases.[5] Preliminary studies conducted in recent years have shown that the decline of estrogen/progesterone levels at menopause is associated with diminished cognition, but that estrogen replacement therapy (ERT) in postmenopausal women can enhance performance of cognitive functions.[6] In addition, there is now evidence that ERT can prevent or delay the onset of Alzheimer's disease and stroke by affecting nerve-growth-factor systems, particularly cholinergic neurons in the basal forebrain.[7]

Recent research on animal and human subjects is challenging the long-held assumption that the adult brain does not undergo changes in its structure, particularly in relation to the actions of circulating hormones. It is now clear that estradiol and progesterone have important effects on adult brain structure and function. Animal studies have documented how the density of dendritic spines on hippocampal CA1 pyramidal cells is dependent on circulating estradiol and progesterone and fluctuates naturally during the 5-day estrous cycle of the adult rat.[8] In one of these studies, increased spine numbers were accompanied by increased numbers of synapses on spines. Changes of synaptic density in the hypothalamus are responsible, at least in part, for the cyclicity of sexual behavior,[9] while the cyclicity of synapses in the hippocampus may influence spatial reasoning and memory.[10]

In humans, such cyclic fluctuations in gonadal hormones are associated with cyclic changes in performance on a variety of cognitive and motor tasks.[11] Other research, conducted in recent years, suggests that estrogen and progesterone modification of dendritic spines in the CA1 region of the hippocampus may contribute to cognitive changes during menopause, as well as temporal lobe epilepsy associated with polycystic ovaries or hypogonadotrophic hypogonadism.[12]

Sex Differences in Manifestations of Brain Disorders

Several observers of the effects of brain disorders have documented sex differences in the frequency and severity of several brain disorders (e.g., stroke, depression, schizophrenia). However, more recent work indicates that such differences are ubiquitous and may help shed light on the pathophysiology. Several examples may help illustrate how such research can have both theoretical and clinical implications.

Sex differences were noted in a prospective Finnish study that examined diabetes mellitus as a risk factor for death from stroke, with women being at a higher risk than men. Similarly, women with myocardial infarction, treated with thrombolytic therapy, have a higher incidence of hemorrhagic stroke. This may relate to increased rates of cerebral blood flow in healthy women compared to men.

Sex differences have also been documented in the manifestations of Alzheimer's disease (AD). Women are at a higher risk for late-onset familial AD, and this might be related to gender differences in apolipoprotein E epsilon4 (EPOE) heterozygous genotype, which is more common in women. Women with AD perform worse than men with AD on measures of semantic memory and language, whereas healthy women perform better than healthy men on these tasks. Neuropsychiatric manifestations in AD are also more severe in women, which is consistent with the greater frequency and severity of depression experienced by women.

In contrast, schizophrenia manifests itself less severely in women than in men. The symptoms occur later in life for women than for men, are less severe, have a milder course, and show a better outcome. It is noteworthy that this difference may be age related since elderly women with schizophrenia have more severe symptoms than elderly men. These differences have been linked to sex differences in neurobiological measures and their correlations with disease factors.

Sex Differences in Response to Treatment of Diseases

The increased recognition of sex differences in health and brain disease has implications for examining sex differences in response to treatment. The literature is limited, however, since most studies were conducted with only men or were not evaluated for sex differences. Integrating research that examines sex differences in treatment with research on sex differences in disease presentation is essential. Some preliminary studies are noteworthy.

Studies suggest that the effectiveness of treatment for chronic pain may be different for women and men. Basic research on pain has shown that estrogen appears to induce analgesia through a different pathway in female mice than in male mice. Thus, drugs developed in studies with male research models, and tested in males, may not be as effective in relieving pain in females.[13]

Other studies using animal models and humans have demonstrated that pregnancy and parturition are associated with elevated pain thresholds in the mother.[14] During hormone-simulated pregnancy, an opioid-mediated maternal analgesia involving the spinal chord dynophin/kappa-opioid system attenuates the pain associated with late pregnancy and labor.[15] Such research could lead to the development of new interventions that are more effective in mitigating pain in both women and men.

Animal work suggests that the development of drugs for the treatment of stroke, for example, should evaluate potential sex differences very carefully. In the rat, N-methyl-D-aspartate antagonists have been reported to induce greater age-associated neuronal necrosis in females than males.

Methodological Developments

The number of studies in which sex and gender differences are included as study variables has increased since 1991. These range from studies focusing on the differences in the structure and functioning of the brain in males and females to research on the effects of hormones on the brain, the central and sympathetic nervous systems, and brain disease manifestation and treatment in women and men. There is convergence of both basic and clinical neuroscience methodology that enables examination of sexual dimorphism developmentally.

Animal work provides the foundation for integrative research on neuroanatomy, neurochemistry, neuroendocrine function, and neurophysiology. The developmental perspective examines sex differences across these variables in relation to brain development and maturation. In clinical neuroscience, the availability of neuroimaging techniques for quantitative measurement of brain anatomy and function (physiology, neuroreceptors) provides an opportunity to spell out the major brain parameters that show sex differences. These measures, when taken concomitantly with clinical and neurocognitive assessment, can yield a powerful tool that will help in identifying the mechanisms for sex differences in healthy brain function and in specific disease states. Perhaps as important, these technologies can offer and test hypotheses that have implications for intervention.

GAPS IN KNOWLEDGE

While encouraging progress has been made in recognizing that sex differences in brain function exist both in health and disease, the scientific base is still at the very beginning and the gaps in knowledge are wide. Many questions remain about sex differences in the normal and abnormal development and functioning of the nervous system, and there is a need for research that focuses on sex differences in brain function and cognition across the life span. Such research must be more than merely descriptive, and for that it has to be interdisciplinary and focus on health and pathology. Further studies are also needed to address genetic regulation of neural functioning in both sexes, as well as to determine hormonal influences on brain development and plasticity.

CHANGE IN QUESTIONS SINCE HUNT VALLEY

Over the past decade, the number of studies focusing on sex and gender differences in brain health and disease have increased. More recently in the neurosciences, there has been a major shift away from descriptive questions and studies of sex differences in normal and abnormal brain function and a movement toward questions and studies aimed at determining underlying mechanisms that influence brain function. This shift reflects both an increase in understanding that sex and gender differences exist and improvements in the tools now available to researchers for documenting brain function.

At the same time, investigators have enlarged the scope of studies, moving away from questions and studies confined to a single discipline and toward those that integrate the study of cognition, emotion, endocrinology, and immunology. Such integrative, multidisciplinary approaches allow researchers to determine how biological mechanisms may be tied to changes in cognition and affect over the life span. Such work is germane for insight into mechanisms and consequences of brain disorders, and how sex-related factors may modulate their effects on cognitive and behavioral changes.

To better understand normal brain development and function across the entire life span, researchers have therefore begun to focus increasingly on the study of healthy brain functioning in women and men at different life stages. This reflects a larger trend in the neurosciences and in biomedical science to exert greater efforts in documenting and understanding the range of healthy variability as a means of sharpening the sensitivity of diagnostic tools to the effects of brain pathology.

RESEARCH RECOMMENDATIONS

Working group participants made the following recommendations for research on sex and gender in neuroscience and behavior:

- Undertake multidisciplinary studies of healthy women across the life span to determine sex differences in normal development as these affect:
    - the brain and neural development;
    - brain function; and
    - cognition and emotion.
- Study the effects of hormones on cognition and emotion within different phases of the menstrual cycle and at different reproductive stages (especially perimenopause).
- Study sex differences across brain health problems (e.g., epilepsy, multiple sclerosis, Alzheimer's, depression, sleep disorders, schizophrenia), including:
    - presentation, course, and prognosis;
    - compensatory mechanisms; and
    - response to treatment, including hormones and other therapeutics (e.g., drug interactions).
- Study sex differences in brain plasticity and development, including implications for rehabilitation and strategies for learning.
- Undertake studies to establish sex differences at the molecular level (e.g., preclinical investigations of novel ligands for estrogen receptors).
- Study the neurogenetics of sex differences as expressed in brain function, pathology, and complex behaviors (e.g., non-Mendelian expression of X-chromosome effects such as imprinting).
- Develop appropriate methodologies to advance the research agenda through:
    - longitudinal designs (e.g., within and across the menstrual cycle in the same women);
    - modification of instruments that measure symptoms and function and that take into account variability across the menstrual cycle and reproductive stages;

- multidisciplinary assessments of individual patients that take into account medical, environmental, sociological, and psychological variables; and

- movement away from difference/deficit models of brain function and behavior to models of variability.

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IMMUNOLOGY

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BACKGROUND

At the Opportunities for Research on Women's Health workshop — sponsored by the Office of Research on Women's Health (ORWH) and convened in Hunt Valley, Maryland, in September 1991 — participants emphasized the importance of intensified research on immunologic diseases. Since then, many discoveries have been made about the intricate functioning of the body's immune system, making the past 5 years an exciting time in the field of immunology. The new understanding of the immune system will lead scientists to develop techniques to turn on the immune response to protect against infectious diseases and to turn off the immune response to protect against the allergic and autoimmune diseases. Many advances have already been made in the clinical diagnosis of and therapies for the immunologic diseases, and many more are on the horizon.

Even more importantly, recent basic science research has shown that immune mechanisms appear to complicate many diseases, although their primary cause has nothing to do with the immune response. Thus, the scope of immunology has expanded far beyond a study of the immunologic diseases to include a study of atherosclerosis and cancer, the two leading causes of death in the United States for women and men.

Nevertheless, many gaps remain, among the biggest of which is the lack of understanding of the causes of the autoimmune diseases and of why they affect women disproportionately (see Table 1). However, like the Chinese, who use the same ideogram to express the concepts of both crisis and opportunity, immunologists recognize that the many gaps now existing in immunology present great opportunities for making further advances in basic science and clinical intervention. Many immunologists in academia and in pharmaceutical and biotechnology industries believe that most of these issues will be significantly better understood in the coming years.

Participants in the Working Group on Immunology discussed the advances in immunologic research since ORWH was established in 1990 and made several recommendations for further research in those areas where gaps remain.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Since the Hunt Valley workshop, the understanding of the processes of the immune system has advanced greatly. Many of these advances have already led to more effective clinical interventions for the immunologic diseases. Advances have also been made in the understanding of the epidemiology and natural history of several diseases and in the impact of behavior and education on prognosis and response to therapy.

Technological Advances

Many of the advances in immunology in the last 5 years are the result of new technologies, such as the genetic manipulation of mice and other animals and the use of molecular biology techniques to identify disease-susceptibility genes.

TABLE 1 Estimated Number of U.S. Residents with Selected Autoimmune Diseases in 1996, by Gender*

	Female	Male	Total
Addison's	12,335	1,000	13,335
Chronic active hepatitis	1,020	136	1,156
Glomerulonephritis (primary)	33,408	72,494	105,902
Graves/hyperthyroidism	2,678,449	370,187	3,048,636
Insulin-dependent diabetes¥	70,320	76,572	146,892
Multiple sclerosis	99,122	55,156	154,278
Myasthenia gravis	9,880	3,709	13,589
Pernicious anemia	266,303	133,152	399,455
Polymyositis/dermatomyositis	8,983	4,480	13,462
Primary biliary cirrhosis	8,189	1,043	9,232
Reiter's syndrome	28,036	1,401,784	1,429,820
Rheumatoid arthritis§	1,297,978	438,120	1,736,099
Scleroderma§	3,527	298	3,825
Sjögren's syndrome	35,726	2,382	38,108
Systemic lupus erythematosus	55,585	7,467	63,052
Thyroiditis/hypothyroidism¶	1,410,554	79,817	1,490,371
Uveitis	2,319	2,319	4,637
Vitiligo	554,488	505,072	1,059,560
Total**	**6,745,909**	**3,190,660**	**9,936,568**

* In a population of 264,755,000 unless otherwise indicated.
¥ In a population of 76,494,000 individuals <20 years of age.
§ In a population of 202,939,000 individuals >16 years of age.
¶ In a population of 188,557,000 individuals >19 years of age.
** Totals may vary due to rounding.

Source: Jacobson, D.L., et al. *Epidemiology and population burden of selected autoimmune diseases in the United States*. Baltimore: Johns Hopkins University.[1]

The development of techniques for the genetic manipulation of mice and other animals has greatly increased understanding of how the immune system works. Since at least 99 percent of the genes in mice and humans are the same and serve quite similar purposes, much of what has been learned about the various molecules and interactions in the mouse can now be tested in human beings.

Mario R. Capecchi and others at the University of Utah recently developed the technology for “knocking out,” or completely inactivating, a particular gene in mouse embryos to determine the function of the gene. For example, if the researcher knocks out in the mouse embryos a particular gene involved in making antibodies, the researcher can then examine the immune response of the newborn mice in the absence of antibody production. The technique also makes possible targeted mutation by which researchers can insert a mutated copy of a selected cellular gene into cells. This technology can lead to mouse mutations, such as those that exist in certain diseases, and permits “clinical” trials in a mouse-disease model. This technology also allows scientists to determine whether a mutant gene can cause the disease.[2]

The use of molecular biology techniques has also provided a great deal of information on the mechanisms of the immune responses. Using these techniques, scientists are able to develop specific vaccines against microorganisms that cause illness by identifying them and isolating the protein, or series of proteins, that give rise to a protective immune response. Once the protein and the gene encoding it have been isolated, protein- or DNA-based vaccines can be developed to expose individuals to the specific element rather than to the entire, potentially pathogenic organism. This technology is now being applied to the identification of self proteins that are targeted in autoimmune disease and to allergenic proteins that lead to asthma and other allergic diseases.

Advances in Etiology and Pathogenesis

With the help of the new technologies, various initiatives have been developed in the last 5 years to elucidate the etiology and pathogenesis of immune diseases.[3] These initiatives have had important ramifications for a number of diseases — asthma, autoimmune diseases, infectious diseases, and even cancer and arteriosclerosis. Some of the areas in which major strides have been made are the following:

Histocompatibility Complex (MHC) Molecules. As a result of the new understanding of MHC molecules, a class of proteins essential for generating T-cell responses, scientists are now able to obtain a killer T-cell response to invading pathogens by giving a specific vaccine or by injecting DNA that encodes a foreign protein. Understanding the structure of the MHC molecules could lead to the development of molecules that will block unwanted immune responses. Peter C. Doherty and Rolf M. Zinkernagel won the 1996 Nobel Prize in Medicine for their pioneering work on MHC molecules.[4]

Mucosal Immunity. The new understanding of mucosal immunity has helped researchers understand how the oral administration of antigens leads to immune responses that differ from responses to antigens administered in other ways. Understanding the body's tolerance of oral antigens has important implications for the treatment of various diseases, such as multiple sclerosis, and is leading to new vaccines against infectious diseases and new therapies against autoimmune and allergic diseases.[5]

Mechanisms of Immunologically Mediated Tissue Injury. The susceptibility of targeted organs to immune-mediated tissue injury varies among people. Consequently, some people with autoreactivity develop autoimmune diseases, while other people do not. Genetic studies are beginning to reveal the basis for target-organ susceptibility in different diseases.[6]

Interaction Between Immune System and Extracellular Matrix. Tim Springer's pioneering studies on a family with an immunodeficiency syndrome led to the identification of adhesion molecules, integrins and selectins, on all cell surfaces. Understanding how these molecules are regulated, and how the cell matrix differs in health and disease, has led to new information on the movement of immune cells to sites of infection or tissue injury.[7]

Cell Signaling Cascades. When a T cell finds a matching antigen on an antigen-presenting cell that offers the appropriate signals, or when a B cell encounters antigen in the presence of T-cell help, tryosine kinase enzymes are activated, initiating a cascade of other chemical changes as the T cell (1) enlarges and divides, thereby increasing the number of cells that react to the antigen, and (2) secretes lymphokines to inhibit the pathogen or to recruit other cells to join in the immune response. Multiple molecular components of signaling cascades have been identified, and molecules capable of blocking these cascades have been found or engineered.[8]

T- or B-Cell Tolerance. Immunologists have long known that two of the mechanisms that prevent T or B cells from attacking the body's healthy tissues are (1) clonal deletion, the physical elimination of lymphocytes that recognize the body's molecules during their development, and (2) immunoregulation, the generation of regulatory cells that weaken harmful or inappropriate lymphocyte responses. Recently, immunologists have identified a third mechanism, anergy, which shuts down specific sets of T or B cells to prevent them from attacking, absent the appropriate signals.[9]

Cytokines. Researchers have found that the cytokines — including such proteins as the interferons, interleukins, and tumor necrosis factor (TNF), which the body produces in response to viral and bacterial infections — are critical in determining the outcome of an immune response. Researchers also have found that cytokines differ between male and female mice and in female mice at different phases of their reproductive cycles. For example, one study found that the immune response of pregnant mice differed from that of nonpregnant mice, suggesting that shifts in cytokines strongly influence outcomes of infections during pregnancy.[10]

Antigen Processing. Researchers have found that antigen processing, which enables the immune system to recognize infectious agents, is tied to the mechanisms that synthesize and recycle all proteins inside cells and transport them between intracellular compartments. A major part of this new knowledge is the understanding of how an enzymatic complex called the proteasome is involved in the transportation of the peptides by the genes TAP (for *T*ransporter associated with *A*ntigen *P*rocessing). The greater understanding of antigen processing has helped clarify what is occurring at a molecular level inside both diseased and healthy cells and has aided in vaccine development.[11]

Relationship Between Immune System and Neurological and Endocrine Systems. The discoveries of the many relationships between the immune system and the neurological and endocrine systems has legitimatized neuropsychoimmunology as a field of study. Estrogen receptors have been located on macrophages and on a B-cell subset, allowing researchers for the first time to determine what is the direct effect of estrogen and what is an effect mediated through a cellular cascade. Estrogen-response elements have been located in genes important in immune regulation, such as the gene encoding of interferons. This knowledge will also enable researchers to understand in detail how hormones work to activate or depress different pathways in the immune system. Researchers have found that lymphoid cells also have receptors for neurotransmitters and even make some neurotransmitters, thus allowing mental health and emotional states to affect the immune system.[12]

Clinical Intervention Advances

Many of the increases in basic knowledge in the past 5 years have already been translated into diagnostics and therapeutics.

Genetic and Other Markers of Human Disease. The recent development of technologies for the identification of genes conferring susceptibility to a number of diseases will permit clinicians to tailor therapy to particular diseases according to an individual's prognosis. For example, physicians can now identify individuals with human lymphocyte antigens (HLA) haplotytes, which predispose an individual to severe disease, and can now identify serologic and cellular markers of diabetes in patients before they need insulin therapy. Physicians are also beginning to test interventions that might prevent the full expression of diabetes.

Transplantation. The understanding of the development of cells within the immune system has revolutionized the medical management of patients undergoing chemotherapy and transplantation. For example, in bone marrow transplantation, scientists are growing small amounts of marrow cells in the laboratory so that the patient can be given both stem cells and mature cells, thus eliminating the period during which the transplant recipient is at risk from infections.[13]

Treatment of Multiple Sclerosis. As a result of the better understanding of cytokine regulation of the immune response, the treatment of multiple sclerosis has been enhanced by the introduction of three new drugs: Betaseron, Copaxone, and Avonex. (To date, only Betaseron has been tested.)

Treatment of Osteoporosis. Big advances have been made in the clinical intervention in bone metabolism, which is useful in treating osteoporosis. Accelerated osteoporosis is a major side effect of steroid therapy used to treat many autoimmune and allergic conditions. A new class of drugs, phosphatose inhibitors, are now in clinical use to prevent bone resorption. In addition, estrogen replacement therapy is now routinely used to prevent osteoporosis.

Treatment of Lupus. A clinical trial known as SELENA (Safety of Estrogen in Lupus Erythematosus National Assessment) is now addressing questions about the use of estrogen as an oral contraceptive and estrogen replacement therapy in postmenopausal women with lupus.[14]

Asthma. Recent research on the immunologic basis of asthma, and the identification of the inciting antigens in asthma, and other allergic conditions has enabled the medical community to better treat asthma patients and to develop strategies for desensitizing patients.

Advances in Epidemiology/Natural History

Advances have also been made in understanding the epidemiology and natural history of many immunologic diseases.

- The National Institute on Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has been working with the Centers for Disease Control and Prevention and the National Center for Health

Statistics on a major paper updating information on all the major immune diseases and osteoarthritis.[15]

- Several studies have focused on whether ethnic differences affect natural history and outcome. For example, studies have shown how the genetic risk factors for lupus differ for Caucasians, blacks, and Hispanics and that socioeconomic variables also constitute important risk factors.[16] Also, a study of the HLA haplotypes predisposing Caucasians, blacks, and Hispanics to rheumatoid arthritis found that different haplotypes may associate with rheumatoid arthritis in different ethnic populations.
- The use of meta-analysis has facilitated the gathering of precise epidemiologic data. Meta-analysis is a method of summing the results of multiple studies of a phenomenon, which increases the statistical power brought to bear on the research question and thus greatly enhances the precision of estimates of effect. This approach has been applied in studies on such diseases as lupus and rheumatoid arthritis and on the use of estrogen and oral contraceptives.[17]
- Better tissue banks, blood banks, and other repositories have been developed to facilitate basic epidemiologic and clinical therapeutic research.

Advances in Behavior and Education

Physicians have learned the importance of empowering patients to take better control of their diseases, which results in more effective therapy. Various studies have shown that patients who see themselves as having control over their lives have diminished disease, compared with those who believe that they have no control.[18]

GAPS IN KNOWLEDGE

In spite of the tremendous advances that have been made in the past 5 years, many gaps remain. Scientists are still unable to explain what causes the autoimmune diseases, for example, or why these diseases predominantly strike women.

Basic Science Gaps

Although gene-targeting technology has created opportunities to manipulate the mammalian genome in ways that were unimaginable even a few years ago, scientists still have a great deal to learn. Additional studies are needed on risk factors and immunologically mediated tissue injury and on the role of environmental factors in immune responses.

With good definitions of a specific disease and of the population being studied, the powerful sib-pair technology should yield a great deal of information about which genes constitute risk factors in specific populations. Sib-pair technology compares the genes of two siblings having the same disease with the genes of other siblings, relatives, and others to determine the specific genes involved in the disease. Similar approaches will facilitate the understanding of the mechanisms of immunologically mediated tissue injury, which would help researchers determine why some autoreactivity leads to disease and some does not, and why it leads to disease in some people but not in others.

A major gap exists in knowledge about the role of environmental factors in immune responses, whether intercurrent infections, pollution, stress, or nutrition are all separate issues. An advance has been that researchers understand the legitimacy of these fields of investigation, but they know little about how environmental factors work.

More studies are needed of the various autoimmune diseases. After reviewing the medical literature for incidence and prevalence rates of 25 autoimmune diseases, researchers at Johns Hopkins University found that epidemiologists have done little research on many of the autoimmune diseases. They found that although some autoimmune diseases had been frequently studied, such as multiple sclerosis (64 studies), rheumatoid arthritis (21 studies), and systemic lupus erythematosus (16 studies), many diseases had been the subject of only two studies each (Addison's disease, polymyositis/dermatomyositis, Sjögren's, uveitis, and vitiligo), and others had been the subject of only one study each (chronic active hepatitis, Graves/hyperthyroidism, and pernicious anemia), and some had never been the subject of a study (autoimmune hemolytic anemia, strep, pemphigus, and rheumatic heart disease). The researchers emphasized the urgent need for further studies to increase scientific knowledge about the prevalence and incidence of autoimmune disorders, in light of their medical and public health impact and of their cost to the U.S. health system.[1]

Gaps in Knowledge About Gender Differences

Although researchers now have some information about how immune responses differ in women and men and how they differ in women at different phases of their reproductive cycles, they still have much to learn about gender differences.

- Researchers know little about whether gender differences lead to greater susceptibility to infection or to an altered response to vaccination.
- Many times researchers find no statistically significant difference between women and men because the standard deviation for women is far greater than for men. The increased variability of the immune response in women is a significant finding and should be pursued further.
- Scientists know little about which differences between males and females are sex-determined and which are hormonally regulated, or which are the result of other factors, such as body mass and body weight. To a large extent, sex differences have been assumed to be hormonally mediated differences. Yet, one study found that the incidence of the onset of diabetes in girls and boys was 3:1 before puberty, and 2:1 after puberty. This finding indicates that the greater susceptibility of females to diabetes is due to more than just sex hormones.
- Most of the basic research has been done in rodents, which have a different reproductive cycle from that of humans. Consequently, issues of how the menstrual system affects immune responses, for example, cannot be determined by a study of rodents. Nevertheless, the current availability of new laboratory mice allows researchers to begin addressing the question of gender differences for many immune functions.
- Scientists still know little about how to apply basic molecular knowledge to the treatment of women. They do not know if therapies for women should differ from those for men, if women's therapies should take into account the menstrual cycle, or if the therapies have different side effects in women than they have in men.
- Studies are also needed on why some autoimmune diseases, such as Reiter's syndrome and ankylosing spondylitis, are more common in men than in women, to determine what the mechanisms are that make men more susceptible and women less susceptible to those diseases.
- Scientists are still unsure about whether cell signaling differs between men and women and between those who are predisposed to certain diseases and those who are not predisposed.
- Few studies have focused on gender differences. More studies are needed on such questions as the effect of the woman's phase of development on her immune system. For example, clinical trials for estrogen studies seldom include women who have never been pregnant, even though the effect of pregnancy on the woman's immune system is important.

- Although NIH requires that all data be analyzed by comparing genders, journals seldom publish studies where no differences were found because they consider this fact uninteresting.

Clinical Intervention Gaps

Many of the recent advances in basic science have yet to be translated into better diagnostic and therapeutic tools. Although one reason is that pharmaceutical companies are sometimes little interested in many of the immunologic diseases that affect women because of the relatively small market, the most important barrier is that scientists have yet to determine how to make the translation. The following are some of the major areas where translations to clinical interventions need to be made.

Apoptosis. With a better understanding of the mechanisms of cell death through apoptosis, scientists might develop the ability to push pathogenic cells into an apoptotic pathway, which could result in better treatments for such varied disorders as cancer and rheumatoid arthritis.

Anergy. A better understanding of anergy could prove useful in preventing the rejection of transplanted organs and for treating patients with autoimmune diseases.

Mucosal Immunity. The new understanding of mucosal immunity in the mouse could lead to a better understanding of mucosal immunity in human beings so that therapies can be developed to excite immunity in a particular mucosal system (the eye, mouth, gut, or vagina), in order to combat various diseases, such as cervical cancer, or to make the immune system tolerate particular antigens, in order to combat diseases like multiple sclerosis.

Antigen Processing. The benefits of the work on antigen processing and presentation could eventually result in better treatments for many illnesses, from infections to cancer. The understanding of the existence of two types of antigens — agonist, which turn on immune responses, and antagonist, which turn off immune responses — could lead to vaccines that will turn on an antigen-specific response in an infectious disease or block an antigen-specific response in an autoimmune disease.

Gender-based Differences for New Therapies. More clinical trials are needed to test new therapies for immunologic diseases, including analyses of whether the efficacy and side effects of these new therapies differ in men and women. For example, methatrexate for rheumatoid arthritis may pose no threat to men but can cause cervical cancer in women.

Vaccines. Researchers are close to identifying protective epitopes or immunogenic epitopes in many infectious diseases. This information will help researchers develop better vaccines and help them determine how the effectiveness of vaccines varies with gender and with age and when is the best time for giving vaccines. In 1995, the Centers for Disease Control and Prevention recommended flu immunization of pregnant women for the first time. However, no one knows whether the immunizations have different efficiencies in the various trimesters.

Impact of Hormones and Life Changes. Studies are needed on the effect of hormones on the different parts of the immune system. In rat models, the antibodies in the vagina and uterus will have different responses to the administration of hormones. This fact has life-threatening implications for women trying to balance fertility with protection against disease. The failure to consider both of these concerns simultaneously is an urgent issue in much of the world today. Systematic studies are needed on how the changes associated with pregnancy, menarche, and menopause affect the outcomes of immunologic diseases or the impact of the use of oral contraceptives and hormone replacement therapy.

Different Susceptibility to Autoreactivity. Researchers need to understand why the same immune response can have different outcomes in different people. For example, some people with kidney disease will have anti-DNA antibodies, and some will not; some people with thyroid disease will have anti-thyroid antibodies, and some will not. Scientists need to understand more about what makes a target organ susceptible to immune injury. They also need to understand why outcomes differ in general, how they differ in men and women, and how they differ over the woman's life span.

Neuropsychoimmunology. A better understanding of how the manifestations of depression vary in men and women suffering from chronic diseases is fundamental to developing gender-sensitive immune therapies to prevent these manifestations. Also, the psychological and sociological aspects of immune disorders that occur disproportionately in women, such as fibromyalgia and the chronic fatigue syndrome, should be examined.

Gaps in Epidemiology and Natural History

Two of the major gaps in epidemiology and natural history are the lack of a comprehensive immunological database and of multidisciplinary research. Although the NIH Office of Rare Diseases is now setting up a database for clinical trials, it will exclude the projects being supported by private companies. Generating improved databases would help researchers do more informative research and more targeted clinical trials. These databases might also provide the opportunity for assessing the risk factors of rare diseases, such as lupus, and of widespread diseases, such as osteoporosis.

Many repositories exist — DNA repositories and serum repositories, for example — that researchers probably do not know about. For example, NIH has given numerous grants that support databases that are theoretically open to researchers outside the institutions. Researchers need information on what databases have been created. Clinical researchers looking at a particular virus or bacteria that they think may play a part in the autoimmune disease should have access to the findings of other researchers who are studying the same agent.

More multidisciplinary research is also needed, especially in light of the fact that infectious agents and toxins trigger certain autoimmune diseases. Closer collaborations should be fostered among immunologists, microbiologists, protein chemists, toxicologists, pathologists, epidemiologists, behavioral scientists, and clinicians.

Gaps in Behavior and Education

Generalists need better training on when to refer patients to a specialist in immunologic diseases. Too often, doctors tell their patients with undiagnosed autoimmune diseases that they are imagining their symptoms. Many patients have to see four or five doctors before getting a correct diagnosis. This situation may be a factor in some women's turning to alternative medicines and may be exacerbated if health care systems restrict access to specialists.

Physicians also need to become aware of the importance of a family history of immunologic disease. At present, physicians will routinely ask about a family history of cancer or high blood pressure, but they rarely ask about a family history of immunologic disorders. Both the physicians and the general public need to be made more aware that immunologic diseases tend to run in families.

Public awareness of autoimmune diseases would encourage people to offer information to their physicians, which might help the physicians detect the disease earlier than they otherwise might. However, public information campaigns have been most effective when they are based on preventive measures that people can take, for example, exercising or eating vegetables. At present, too little is known about the risk factors of many autoimmune diseases to recommend particular behaviors.

SPECIAL ISSUES

The participants in the Working Group on Immunology discussed their concerns about two special issues: (1) the underrepresentation of minority populations in clinical studies of various diseases, and (2) the potential threat that the new managed care system poses to continued progress in immunologic research.

Minority Populations

- Women cannot be treated as one homogeneous group. Disease and clinical intervention must be studied in all ethnic and racial groups.
- One of the problems in dealing with minorities is that researchers are using social definitions to ask biological questions. Either the social definitions should be made more stringent, or researchers should find a way to correlate biological definitions with social definitions.
- Classifying various ethnic and racial groups together as “Native American” or “Hispanic,” as researchers often do, results in erroneous data. For example, many studies have been based on data on Mexican participants, the largest Hispanic population in the United States, and then extrapolated to Hispanics from other countries, although vast differences exist among the various Hispanic groups.
- Because of their different cultural and linguistic backgrounds, Native Americans, Hispanics, and other minority groups sometimes vary in their interpretations of questions that researchers ask them, which results in incorrect survey data. Researchers should identify minority populations appropriately, tailoring their questions to specific ethnic groups.
- One of the barriers to doing research on Native American populations is that tribal groups often require that researchers seek their permission to work with the tribe, a process that sometimes takes years. Another barrier is that many tribes regard research with disfavor because in the past they have felt exploited by researchers; however, this attitude is changing as more Native Americans are being trained to do research. In general, it is important that researchers communicate well with individuals of different ethnic and cultural backgrounds in order to dispel any distrust of the research community that may exist.

Managed Care

The new managed care system could enhance immunologic research in many ways. For example, the new system will likely generate larger, more centralized databases. As more data become available, researchers may be able to determine whether a problem correlates more with a woman’s racial or ethnic background or with her socioeconomic status. Finding such information is difficult today because study participants are often uninsured, or the insurers are unwilling to share the data. However, the new system could also present some problems.

- Managed care companies may be unwilling to collect the type of information that public health care professionals need, or they may be unaware of the need for such information. For example, for a study of mortality birthweight, it is not enough to know that the mothers are Hispanic; rather it is necessary to know whether they are Dominican, Cuban, Mexican, and so on. The lack of detailed information will limit researchers’ ability to eventually do clinical trials because managed care companies may be less willing to try new therapies.
- Physicians will have an incentive for overlooking the possibility that a patient’s symptoms indicate the presence of an immunologic disease, in order to avoid referring the patient to a specialist.

- Information on epidemiology and natural history, or on which clinical interventions are effective and which are not, may become less accessible to researchers because they will have limited access to patient populations. Researchers should remind NIH and the U.S. Department of Health and Human Services that these are issues that need to be considered as major issues as the new health management system is established. The public health function may not be funded in the new role of managed care; there may be no set-aside for these kinds of surveillance and research activities.

- Managed care companies often do not allow patients to participate in clinical trials.

- Managed care may pose a special problem for immunologic diseases in terms of the training of physicians. The limited access to patients and consequent limited remuneration may discourage people from specializing in rheumatology, allergy, and other immunologic diseases. Women physicians, especially, will find it harder to compete in the new managed care environment because the concern about the bottom line will discourage companies from allowing women the flexibility they have had in the past 10 years to combine career and family.

- A recent study by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the potential outcomes for patients with chronic diseases, rheumatoid arthritis, and lupus in the managed care environment found that the patients requiring care with chronic diseases tend to be poor, do badly, and should do even worse in a managed care system.[19]

RESEARCH RECOMMENDATIONS

The Working Group on Immunology made the following recommendations to improve future research:

- More studies of immune modulation and response, target organs, cell signaling, and other basic phenomena should be conducted. Until researchers have more basic knowledge in these areas, they will be unable to translate their knowledge into clinical interventions.

- Gender-based differences should be fully explored in immunologic functioning. Researchers should analyze their data by gender, unless scientifically justified not to do so.

- The effect of the hormonal environment, as defined by puberty, pregnancy, and menopause, should be carefully examined.

- The role of external pressures, including the environment, in immunologic diseases should be studied.

- The investigation of mucosal immunity should be expanded in order to provide a better understanding of the body's tolerance of orally administered antigens in the treatment of various diseases.

- Researchers should try to translate the animal-based data they have in some meaningful way to human beings.

- More multidisciplinary research should be done.

- NIH should establish a central source of information about the many databases that exist — patient registries, cell banks, DNA banks, serum banks, and brain banks. NIH should work with such local organizations as local chapters of the Lupus Foundation, Arthritis Foundation, Multiple Sclerosis Society, and Office of Crohn's Disease in establishing this comprehensive database. Also, researchers should be trained to get informed consent for the use of their samples for later research projects. They should also be instructed on the proper preservation of their samples.

- Steps should be taken to ensure that an adequate number of immunologists will be trained under the new managed care system, with special emphasis on encouraging the training of women in clinical and basic immunology.
- Better education should be provided to the general physician and to the public on the diagnosis and treatment of immunologic diseases.

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INFECTIOUS DISEASES AND EMERGING INFECTIONS

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BACKGROUND

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

It was not possible for this working group to cover all infectious diseases of particular importance to women. Time was, of course, a consideration; however, the expertise of the working group, as well as evidence of the increasing scope of the epidemics, led to a focus on sexually transmitted diseases (STDs) and HIV/AIDS, with limited discussion of a significant number of other infectious diseases. For instance, the group did not discuss urologic diseases of women because none of the group's members were experts in this area. Therefore, the four sections that follow will focus on STDs and HIV, with passing references to other infectious diseases from which women suffer disproportionately. Discussion within each section of this report is divided into basic science, epidemiology, clinical practice, and behavior and education.

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

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Advances in Basic Science

Basic research progress in the fields of HIV and STDs in the past 5 years is evidenced in the many new studies being undertaken and in the significant increase over the past several years in research funding. The ambitious research and program agendas of the National Institutes of Health and the Centers for Disease Control and Prevention have included an increase in funding by the National Institute of Allergy and Infectious Diseases of STD centers that are focusing on an examination of the vaginal ecosystem. Other projects have begun to characterize the endogenous defense systems of the vagina and cervix. Grant-funded research is currently focusing on vaginal immunology and physiology, and is examining normal and abnormal vaginal ecosystem responses to preventive and therapeutic agents. Examples of basic scientific progress include the development of single-dose azithromycin for treatment of chlamydia and research on mucosal factors in relation to STDs.

The medical literature has reported new advances in basic science research on HIV/AIDS. For example, the recent findings of the AIDS Clinical Trial Group 076 showed that in pregnant women with HIV, antepartum and intrapartum zidovudine (AZT) treatment of the mother, followed by short-term treatment of the baby, reduced the risk of vertical transmission of HIV infection from approximately 24 to 8 percent. New antiviral drugs have been studied and approved for treatment of HIV-infected persons, including protease inhibitors, which are an entirely new class of antiviral drugs. People who elect antiviral therapy can now take a combination regimen that results in sustained suppression of virus production, increased CD4 cell counts, and improved quality of life. Specifically with regard to women's health, recent advances in basic research on HIV include, in addition to the focus on perinatal transmission of the virus, research on the natural history of the virus and its disease progression in women. The case definition for AIDS in women has been expanded to include new diagnostic criteria for HIV-positive persons (including invasive cervical cancer); this has resulted in improved identification of previously unsuspected HIV infection in women.

Epidemiologic Advances

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

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

Natural history studies of HIV in women have helped determine how HIV is acquired and the appropriate clinical utility and prognostic significance of viral load and CD4 counts. The gynecologic manifestations of HIV are also being defined. More accurate and more timely diagnoses of HIV in women have resulted from the broadening of the case definition for AIDS, which includes increasing the range of symptoms that defines the presence of HIV in women, as well as the increasing recognition by clinicians that women are at risk for HIV infection. The risk factors for heterosexual transmission of HIV are now better defined.

Advances in Clinical Practice

Clinical and therapeutic triumphs in the past 5 years are evident in the availability of new diagnostic tests and new drugs, including antiretrovirals (especially protease inhibitors). The findings of the AIDS Clinical Trial Group 076 showed that when AZT was given to pregnant women during pregnancy and delivery, and to infants in the first 6 weeks of life, the risk of vertical transmission of HIV was reduced substantially (25.5 percent to 8.3 percent). Single-dose therapies, such as azithromycin for treatment of chlamydia, show great promise in large part because ongoing patient compliance is not required. Better diagnostic methods have been developed, such as polymerase chain reaction (PCR) and liquid chain reaction techniques using urine-based (and therefore noninvasive) sampling for the diagnosis of chlamydia infection; multiplex PCR for congenital ulcer disease; and home-based tests for HIV. Other clinical progress includes earlier diagnosis of infections such as chlamydia and HIV that allows the prevention of complications of disease, and the development of the second-generation hepatitis B vaccine and the improved acellular pertussis vaccine.

Advances in Behavior and Education

Epidemiologic data have helped to describe the occurrences and transmission of STDs and have helped bring about an increased sensitivity to the importance of behavior as an area that should be studied and addressed. For example, documentation of the increasing numbers of women diagnosed with HIV has led to growing awareness that the HIV epidemic is not limited to the homosexual male population. This awareness has prompted more diverse educational messages about HIV, resulting in significantly increased awareness that women may be at risk for HIV infection; with counseling, voluntary testing for HIV infection has increased. In some settings, condom use has increased substantially; the Thailand prostitute study indicated that consistent condom use can substantially reduce STD transmission.

Advances in Scientific Perspective

What has begun to underlie the scientific progress described above is progress in the conceptual perspective about research on women's health. No longer is the vagina viewed, in research terms, merely as a repository for semen and a vessel for fetal and/or microbial growth, but rather as a complex ecosystem that should be studied in this context in order to advance biomedical knowledge about the infectious diseases that afflict women.

GAPS IN KNOWLEDGE

Gaps in Basic Science

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

Gaps in basic science knowledge of HIV infection range from understanding the precise mechanisms of transmission to delineating the pathogenesis of full-blown AIDS in women. Gaps in knowledge about transmission and initial infection include how to quantitate the infectious viral load in genital secretions; how infection is established (what is the first cell that gets infected?); the in vivo role of peptides that inactivate HIV and other organisms and viruses in test tubes; and the effectiveness of natural defense mechanisms such as pH level and the presence of lacto-bacilli. Gaps in knowledge about HIV, pregnancy, and hormones include the role of the placenta as a viral barrier, since

75 percent of infants born to an infected mother are not themselves infected; whether pregnancy increases susceptibility to HIV infection; the role of HIV in adverse outcomes of pregnancy; hormonal influences on viral expression; and the safety of antiretroviral drug treatment during pregnancy. Additional gaps include the biologic interaction of STDs and HIV, particularly with regard to effects on the regulation of HIV expression, oral markers for HIV infection, vaginal yeast infections as early markers, and HIV strain differences regarding susceptibility to and progression of infection.

Epidemiologic Gaps

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

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

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

Gaps in Clinical Practice

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

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

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

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

Gaps in Behavior and Education

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

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

CHANGE IN QUESTIONS SINCE HUNT VALLEY

The working group felt that, in the 5 years since the Hunt Valley Report, a conceptual paradigm shift has occurred regarding research on women's health. Because society and the health professions are now less likely to view women as mere reproductive beings, the concept of "women's health" has expanded beyond reproductive health issues; serious attention is being paid to the great variety of morbidity and mortality health issues affecting women.

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

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

- *Emphasize prevention.* Research should focus on a continuum of prevention methods to avoid infections and their complications:
  - **primary:** prevention of infection;
  - **secondary:** prevention of disease; and
  - **tertiary:** prevention of disease complications.
- *Consider the changing context throughout women's life cycles.* Research on women's health should take into account the full biological life cycle of the woman and the concomitant physical, mental, and emotional changes that occur. Easily identifiable stages in a woman's life are childhood, puberty, age of reproduction, and menopause. For example, research should elucidate the impact of the given life stage of the individual on the progression of infectious disease from exposure to asymptomatic carriage to full-blown disease. In addition, there may be significant differences in the acceptance

and efficacy of vaccines and therapy due to the effects of hormonal variations that occur throughout the menstrual cycle.

- *Address the full continuum from the health of the individual to the health of the community.* Research studies should be undertaken that will affect not only an individual woman's health but also the health of her family and the communities within which the woman lives and works. Different infectious diseases impact certain communities to varying degrees; the reasons for this, and the influence of community on the diagnosis and treatment of the individual, must be better understood.

RESEARCH RECOMMENDATIONS

Basic Science

The Vagina. STD research should focus on the human vagina. Research is needed to increase knowledge about the vaginal ecosystem: the "normal" state, alterations caused or enhanced by exogenous factors; effects of the menstrual cycle on disease; effects of the frequency of intercourse, both with single and with multiple partners, on disease; and changes in the vaginal ecosystem across the life span.

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

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

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

Therapeutics for Adverse Outcomes of Pregnancy. Continue and increase research to prevent the myriad of adverse outcomes of pregnancy caused by STDs and HIV. Conduct research on infertility, its causes, and methods to reverse it.

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

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

Epidemiology

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

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

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

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

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

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

Microbiologic Tools. Develop microbiologic tools to facilitate epidemiologic research.

Clinical Practice

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

Clinical Trials. Enroll more women in efficacy and safety trials. This recommendation has two implications: (1) conduct more clinical trials on women's health issues, and (2) enroll more women in clinical trials in which men have previously prevailed in numbers. Specifically, clinical trials on microbicides and other barrier methods are needed to define the efficacy, the safety, and the long-term sequelae of STD and HIV therapy not only on the "typical" patient but also on pregnancy and neonatal outcome. Researchers will need access to clinical trials and treatment for women with HIV and women who are pregnant; both groups have often been excluded from studies in the past. In addition, studies should be conducted on patients with multiple infections.

Cures and Vaccines. Continue research to find cures for viral STDs and HIV, to develop methods to combat microbial resistance, and to develop treatments and vaccines to prevent or eradicate these infections entirely. Train dental personnel to recognize oral lesions as a sign of HIV infection.

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

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

Behavior and Education

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

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

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

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

Other Research Recommendations

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

- *Urinary tract infections.* Morbidity associated with urinary tract infections encompasses such problems as "honeymoon cystitis" and incontinence.
- *Tuberculosis.* After adolescence, a woman's risk of disease progression after exposure to tuberculosis is significantly higher than a man's risk. An understanding of the factors contributing to this increased susceptibility to disease, such as hormones, pregnancy, contraceptives, or lifestyle, is needed.

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

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

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

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

Other infectious disease issues for women's health research include bacterial vaginosis and other nonsexually transmitted vaginal diseases, hepatitis C, H. pylori, infectious etiologies of rheumatoid diseases, toxic shock syndrome, and the long-term immunologic sequelae of rubella vaccinations.

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

RECOMMENDATION FOR DEVELOPING A FULL AGENDA

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

HIV

- David Ho's *Viral Dynamics;*

- Rosenthal, "Changing Face of the HIV Epidemic" in a 1995 edition of *Science;*

- Monthly statistics from the *MMWRs;*

- Quinn, on the global HIV epidemic, in *Lancet;*

- Scott Holmberg (from CDC) in the *American Journal of Public Health*, on calculating HIV infection rates in 58 metropolitan centers; and

- Jeff Kelly article (from Penny Hitchcock) on what has worked in HIV prevention.

HPV

- Ho and Burke, "Natural History of HPV," in *Cancer*; and

- Pulaski articles.

Herpes

- Brown, *Natural History and Pregnancy;* and

- Use of PCR for diagnosis.

MENTAL AND ADDICTIVE DISORDERS

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BACKGROUND

Although mental and addictive disorders were not formal topics for discussion at the 1991 Hunt Valley conference, many recent findings indicate body and mind cannot be separated. Inclusion and equal status at the "Beyond Hunt Valley" symposia is a significant change that represents progress for these areas of research, placing mental and addictive disorders on a par with physical disorders. The integration of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH) into the National Institutes of Health (NIH) has given national impetus for mental and addictive disorders, represented by these institutes, to be placed on a par with physical diseases, disorders, and conditions. While mental and addictive disorders were included on the list of priorities of the Office of Research on Women's Health (ORWH) from its inception, the integration of the Institutes supporting research on these important women's health concerns ensures systematic attention to these disorders.

The biological and sociological roles of gender have been recognized as powerful factors in the causes, correlates, and treatment of mental and addictive disorders. With new awareness about how the differences between men and women affect wellness, it is critical to present, study, evaluate, and implement changes based on gender-based research to positively impact the treatment of mental health and addictions in women. Concerns about mental and addictive disorders must be addressed on a multi-tiered level; clinicians and researchers must be willing and able to work even more closely together to promote wellness in mental health for women in the 21st century.

Mental Disorders

Taken as a group, mental disorders affect both sexes with equal frequency; however, important gender differences exist in the prevalence, symptoms, and treatment responses of specific disorders. For example, major depression and dysthymia (a less severe, more chronic form of depression) affect approximately twice as many women as men. An estimated 21 percent of U.S. women experience a major depression during their lifetime, compared with 12.7 percent of men; and additional 8 percent of women have dysthymia. Women are two to three times more likely to have anxiety, panic, and phobic disorders. The eating disorders anorexia nervosa and bulimia nervosa affect women at an eight to ten times greater frequency then in men. While schizophrenia and manic-depressive illness are equally prevalent among men and women, they also appear to be marked by gender differences in age of onset, pattern of symptoms, treatment response, and natural course.

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

Simply studying a group termed "women" is not enough. Multiple variables, in addition to gender, affect research and treatment: age, physical health, stage of menses, ethnicity and race, marital status, parental status, education, income, occupation, sexual orientation, labor force participation, and geographic location; other differences exist in accessibility of services, and administration of services. Furthermore, study groups that often are not identified by gender, such as studies on children and animals, need to be recorded and analyzed by gender in the future in order to understand the biological processes and developmental course of gender-related risk and protective factors.

Addictive Disorders

Alcohol Abuse. Alcohol remains the drug of choice among Americans today. According to the 1992 National Longitudinal Alcohol Epidemiological Survey (NLAES) one-third of women age 18 and older are current drinkers, 21 percent are former drinkers, and nearly 4 million women (4.1 percent) were found to be alcohol abusers or alcohol dependent according to *Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)* criteria.

Fewer women than men drink alcohol, and women who drink consume less alcohol and have fewer alcohol-related problems and dependence symptoms than men. However, among the heavier drinkers, women equal or surpass men in the number of problems that result from their drinking. Studies of alcohol-dependent women in treatment suggest that they often experience greater physiological impairment earlier in their drinking careers, despite having consumed less alcohol than men. The interval between onset of drinking-related problems and entry into treatment appears to be shorter for women than for men. Women become intoxicated after drinking smaller quantities of alcohol than are required to produce intoxication in men. Female alcoholics have premature death rates 50 to 100 percent higher than those of male alcoholics. Women develop alcoholic liver disease, heart muscle damage (alcoholic cardiomyopathy), and brain damage with lower daily alcohol intake and at an earlier time in their drinking careers. Proportionately, more alcoholic women die from cirrhosis than do alcoholic men.

Drug Abuse. The 1994 National Household Survey on Drug Abuse indicates that females comprise 45 percent of those who reported ever using illicit drugs in their lifetime, and 37 percent of individuals reporting use in the prior month. The survey also found that more women than men reported having taken prescription drugs for nonmedical purposes during the past month. The National Pregnancy and Health Survey, conducted by the National Institute on Drug Abuse, reported that in 1992, among women who gave birth in the United States, an estimated 221,000 used illicit drugs while they were pregnant. The National Comorbidity Survey, conducted between 1990 and 1992, estimated that 6 percent of all women 15 to 54 years of age have met the criteria for lifetime drug dependence.

Women frequently have predisposing psychiatric disorders prior to their drug abuse. Research on antecedents of crack cocaine abuse has found pre-existing psychiatric problems, particularly depression, to be a major co-factor. Additionally, drug-abusing women have been reported to have conflicting relationships with, and less attachment to, their mothers. Women who have been victims of crime, also, appear to have increased vulnerability to substance abuse.

A high correlation exists between eating disorders and substance abuse. Moreover, research indicates that the more severely a woman diets and engages in binge eating the more likely she is to meet the criteria for substance abuse or dependencies and the more likely she is to experience negative consequences from drinking alcohol and using drugs.

Women present a unique set of physical, social, and psychological problems that require specific interventions to meet their needs. Many women at risk for drug use/abuse have low self esteem, are single mothers (often with limited parenting skills), come from minority communities, are often school dropouts and therefore have few marketable job skills, and have had at least one sexually transmitted disease. Women look to men for protection and support but, unfortunately, many of those men are themselves involved in drugs and influence the woman to become drug involved also.

There is growing evidence that the effects of drug abuse and addiction do not always affect men and women in the same manner. For example, data indicate that for illicit drugs, women may proceed more rapidly to drug dependence than do men. There is also evidence that nicotine dependence in females, relative to males, is controlled less by the nicotine itself and more by psychosocial factors, including the use of cigarettes as a "nicotine delivery system" for use in weight loss.

One of the most devastating consequences of drug use for females is the risk of HIV/AIDS. AIDS is now the fourth leading cause of death among women 15 to 44 years of age. In the United States, over 78,000 cumulative cases of AIDS were reported in women and female adolescents by mid-1996 and 64 percent of the AIDS cases among women are related to injection drug use. Injection drug use and heterosexual sex with an injecting drug user (IDU) play a major role in AIDS for women. Seventy to 80 percent of AIDS cases ascribed to heterosexual contact in the United States have been in women, most of them in young women who use crack cocaine and who trade sex for money or more drugs. Forty-six percent of AIDS cases in women are attributed to injection drug use and 18 percent to heterosexual contacts with IDUs; in comparison, 22 percent of AIDS cases in men are related to injection drug use, and one percent to heterosexual contacts with IDUs. Additionally, among the total cases of pediatric AIDS in the United States, 54 percent are related either to the mother's injection drug use or to the mother having had sex with an IDU.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Recommendations from 1991 Hunt Valley Report

In the 1991 Hunt Valley Report, the Working Group on Mental and Addictive Disorders recommended attention to the following:

- Comorbidity among mental illness, substance use, and physical illness — the identification of certain subgroups of women at risk (genetically, by psychosocial history, chronic stress) for comorbid illness could prove useful for preventive treatment efforts.

- Genetic and environmental factors contributing to mental and addictive disorders through genetic epidemiology — in order to develop promising prevention strategies.

- Significant gender differences in prevalence of mood, anxiety, and personality disorder.

- Biological and psychosocial gender-related variables related to the development, onset, course, treatment, and relapse of mental and addictive disorder, including early developmental history — the role of sexual and physical abuse.

- Gender differences in cognitive and/or personality variables that may influence onset or recurrence of disorders.

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

- Gender differences in grief reactions and depression following bereavement.

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

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

Progress in the 5 years since the establishment of ORWH includes the following:

Mental Disorders in Women — Progress

The latest data from epidemiological studies continue to show that depression, anxiety disorders, and eating disorders affect women more often than men. While some progress has been made in the search for the causes of this gender-based disparity, investigators are generating novel hypotheses that are now propelling research forward. For example, preliminary data raises the possibility that estrogen's interactions with the circadian pacemaker may somehow be involved in seasonal affective disorder and rapid-cycling bipolar disorder, illnesses that affect women more than men.

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

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

Depression and Related Disorders. Out of the recent wealth of mental health related clinical and epidemiological data, gender emerges strongly and consistently as a major risk factor for depression, with depressive disorders affecting more than twice as many women as men. Yet despite the robustness of this finding, much less is known about specific etiologic factors that underlie this association. Further complexity stems from the reality that the mood disorders represent a broad spectrum ranging from those that arise primarily in reaction to environmental stressors to those related more strongly to endogenous factors. The role and relative weight of various gender-specific factors may differ across this spectrum, and may also influence symptom patterns, comorbidity, course, treatment response, and outcome.

Community and clinical samples have indicated that gender-specific risk for mood disorders varies with the specific type of mood subtype. Men and women differ little in rates of bipolar disorder, but have been shown to vary strikingly in the broader spectrum of unipolar disorders. Nonetheless, there is evidence that men and women with bipolar disorder may differ in clinically significant ways in phenomenology, comorbidity, and course. Recent research indicates that the course of bipolar illness in women is characterized by more depressive and fewer manic episodes, and that women are more likely to develop the rapid-cycling form of the illness. Gender differences in prevalence are more pronounced in unipolar depressive illness, with some early evidence that differences may be greater in the less severe forms. Clinical studies have found that women predominate in seasonal affective and rapid cycling bipolar disorders and in dysphoric mania.

The differential actions and beliefs of socializing agents — parents and teachers holding different expectations and behavioral norms for boys and girls — combined with the impact of differences in how boys and girls construct gender identities may cause girls, more than boys, to exhibit high levels of self-evaluative concerns that increase their later vulnerability to depression. Gender stereotypes and socialization processes may lead males and females to feel differently about themselves and to attach different importance to meeting evaluative standards imposed by parents, teachers, and other people important in a child's life.

An NIMH-funded longitudinal study of social development in young children found evidence supporting the idea that girls (but not boys) as young as age 4 have lower scores on measures of perceived competence, self confidence, and self esteem, and have more negative feelings following failure, and that these correlated with higher scores (more depressed feelings) on the Children's Depression Inventory. Scores on the depression inventory move toward normal as the girls move through the first 4 years of school, suggesting that girls are more vulnerable during periods of transition — entering school and entering puberty — than during times of stability. If future longitudinal research finds that these observations are reliable developmental markers, then it may be possible to take steps to help at-risk girls and women through transition periods and thus reduce their vulnerability for depression.

Anxiety Disorders and Posttraumatic Stress Disorders. Phobias, a type of anxiety disorder, are extremely common in the general population. Two to three times as many women as men are affected by phobias, making research on these disorders a particularly important issue for women's mental health. Data suggest that even simple phobias predispose to more serious anxiety and depressive disorder in late life.

Posttraumatic stress disorder (PTSD) is an anxiety disorder first characterized in male combat veterans, but soon was found also to affect female victims of trauma. Core symptoms of PTSD include:

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

Although many forms of intervention exist for rape-related PTSD symptoms, only a few well-controlled studies have been conducted to systematically evaluate the treatment response of women who have been the victims of sexual assault. Overall, cognitive-behavioral interventions for rape-related PTSD, with single or multiple treatment components, have been found to produce a decrease or remission of posttrauma problems when compared to no treatment. Cognitive desensitization, in which the victim practices relaxation techniques in a safe environment while mentally reliving the trauma, weakens the fear response triggered by these terrible memories. Few women receive such therapy, however, since the most common professional intervention for rape victims is the limited crisis intervention counseling offered in rape crisis centers. Recent data show, however, that such limited therapy is not enough to help many women overcome PTSD following sexual assault, suggesting that the nation's rape counseling network can be significantly enhanced.

Studies of women victims of violent crimes have shown that cognitive-behavioral interventions can reduce posttrauma problems that plague these women and help them escape the fear-induced anxiety that can limit their daily activities. Unfortunately, few women receive such therapy, pointing out the need to increase outreach and educational efforts aimed at women and women's health centers.

Eating Disorders. The eating disorders anorexia nervosa and bulimia are primarily seen in women. People with anorexia starve themselves into extreme weight loss, a behavior that is associated with an irrational fear of becoming obese and severe body-image disturbance of near psychotic proportions. Those with bulimia engage in repeated binge-eating episodes followed by self-induced vomiting, fasting, or using laxatives or diuretics. It is not uncommon for the two disorders to occur together.

It is well established that individuals with bulimia recover more often than do those with anorexia or both disorders. However, a recent NIMH-funded survey of women with anorexia found that nearly half the anorexic and mixed subjects no longer met full diagnostic criteria for at least 8 consecutive weeks during the first year after completing psychotherapy for the disorder. Total recovery at 1 year — no symptoms of the disorder — was seen in 56 percent of bulimia patients, compared to 18 percent of women with both anorexia and bulimia and 10 percent of women with anorexia alone. It is not known how many of these "recovered" patients stay symptom free beyond 1 year, suggesting that a long-term monitoring effort is needed to gain a better understanding of the prognosis for these disorders.

Though little is known about the central nervous system mechanisms involved in these eating disorders, researchers are focusing currently on cholecystokinin (CCK), a neuroactive peptide that exists in high concentration in the gut and in regions of the brain associated with satiety. Measurements of CCK in the cerebrospinal fluid of women diagnosed with bulimia and in healthy volunteers found that bulimia sufferers had significantly lower levels of this peptide.

Mental Health and AIDS

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

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

- Successful behavioral interventions developed to address the risk factors of specific groups with increasing rates of HIV transmission, including women and people with severe mental illness.
- Methods refined for the early detection of cognitive impairment in people infected with HIV who have no other medical symptoms.
- Scientific understanding of the biochemical events that take place in the brain and central nervous system during various stages of HIV infection.
- Animal models developed that permit closer investigation of different aspects of HIV infection of the central nervous system.

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

Addictive Disorders in Women: Alcohol Dependence — Progress

At least three factors have been found to account for differential susceptibility of women to alcohol. First, women have less total body water than men of comparable height and weight. After ingestion, alcohol diffuses uniformly into all body water, both intra- and extracellular. Because of their smaller amount of body water, women achieve higher blood alcohol concentrations (BAC) than men after consuming identical amounts of alcohol. Second, research indicates that diminished activity of gastric alcohol dehydrogenase (ADH) in women may contribute to the gender-related differences in BAC as well as heightened vulnerability to the physiological consequences of drinking among women. First-pass metabolism (when alcohol is metabolized in the stomach by gastric ADH) decreases the availability of alcohol to the body. Due to decreased activity of gastric ADH, first-pass metabolism is decreased in women relative to men, and is virtually nonexistent in alcoholic women. Third, fluctuations in gonadal hormone levels during the menstrual cycle may affect the rate of alcohol metabolism, according to recent studies, making women more susceptible to elevated BACs at different points in the cycle.

The relationship between alcohol consumption and bone density/calcium metabolism is a complicated one. Male alcoholics are known to be at markedly increased risk for osteoporosis; however, in postmenopausal women, low levels of alcohol consumption appear to contribute to increased bone density. Now a recent study raises questions about the long-term health consequences of drinking even a small amount of alcohol while taking estrogen replacement therapy. The study found that when postmenopausal women on oral estrogen therapy drank half a drink, the levels of estrogen circulating in their blood nearly doubled. After three drinks, estrogen levels tripled. Recently, many large epidemiologic studies have indicated that alcohol consumption, even at levels as low as one to three drinks per week, is associated with a moderately increased risk of breast cancer. Since alcohol consumption has been shown to elevate estrogen levels, this is a possible mechanism for causing breast cancer.

Recent treatment research indicates that women do as well as men in top-quality alcoholism treatment. However, more research is needed to determine if outcomes for women in treatment can be optimized by using gender-specific modalities.

Addictive Disorders in Women: Drug Abuse — Progress

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

In human studies, the progression or developmental stages of drug involvement appear to differ according to gender. In the progression from legal drug use to illicit drug use, for example, cigarettes seem to play a major role for girls; for boys, alcohol alone is sufficient. Women's initiation into drug use also differs from that of men. A study on gender differences in cocaine initiation and abuse indicated that approximately 90 percent of women reported that men played some role in their involvement with crack cocaine; by contrast, only 17 percent of men reported that women were involved in their initiating or maintaining the use of crack cocaine. Women were more likely to begin or maintain cocaine use in order to develop more intimate relationships, while men were more likely to use the drug with male friends and in relation to the drug trade. Since current unisex drug abuse prevention efforts may be neglecting the primary issues of females, the necessity of a female-specific program needs further investigating.

Childhood sexual abuse has been associated with drug abuse in women in several studies. For example, a study of women in drug abuse treatment found that 70 percent of the women reported histories of physical and sexual abuse, with victimization beginning before 11 years of age and continuing on a serial basis. Additionally, a risk-reduction study found that 74 percent of the women interviewed reported sexual or physical abuse at some time in their lives (childhood, adolescence, or adulthood) and that 15 percent were abused at all three periods in their life. Women who were physically or sexually abused as adults reported engaging in more drug use than women who had not been abused in adulthood. Although, there is a growing literature on violence against women and its relationship to substance abuse, the path by which substance abuse develops following childhood sexual abuse experiences in women is unclear. Further research is needed to understand the etiology of this strong correlational finding and address its implications for prevention and treatment efforts for women.

Women who abuse drugs may be more vulnerable to crime victimization than men. A recent study of homicide in New York City found that 59 percent of white women and 72 percent of African-American women had been using cocaine prior to their death, compared with 38 percent of white men and 44 percent of African-American men. Although cocaine is used by more men than women, this study suggests that its use is a far greater risk factor for victimization for women than for men. In another study, conducted among a population of women in residential or outpatient drug treatment programs, 80 percent had been crime victims. Female crime victims were more likely to have major drug and alcohol problems than nonvictims, and female crime victims who suffered from PTSD were almost ten times more likely to have major alcohol problems and 17 times more likely to have major drug abuse problems than nonvictims. Numerous studies have shown PTSD to be a strong predictor of substance abuse.

The long history of making pregnant women the exclusive focus of drug abuse has shifted; the focus is now on all females, regardless of their age or reproductive status. This new focus applies to all areas of drug abuse research from determining women's vulnerability to substance abuse to determining specific treatments for women. Researchers are also beginning to examine drug effects affected by the menstrual cycle, including the possible need to time cessation with a woman's body rhythms. Other studies are examining the hormonal status of the subject, acknowledging that the presence of estrogen, for example, affects response.

There is general acknowledgment that, due to a variety of barriers, female drug abusers have difficulty accessing treatment and successfully completing a course of treatment. Barriers have been identified in treatment entry, engagement in treatment, and long-term recovery. Examples of such barriers have been shown to be:

- lack of economic resources, referral networks, and woman-oriented services;
- conflicting child-related responsibilities;
- models of drug treatment that are primarily male oriented; and
- lack of treatment modalities that address the specific treatment needs of women.

In past research on drug abuse, human and animal subjects have been almost exclusively male; as a result, little data has been available on women. Recently, however, gender differences have gained attention in the field of drug abuse research, and preliminary data indicate that the biological mechanisms involved in drug abuse and dependence vary considerably between men and women. For example, a study examining gender and menstrual cycle difference in response to acute intranasal cocaine reported that mean peak cocaine plasma levels in women were higher in the follicular phase than in the luteal. This study also found that, overall, male subjects achieved the highest mean peak plasma cocaine levels, detected cocaine effects significantly faster than females, and experienced a greater number of episodes of euphoria.

Studies on Comorbid and Addictive Disorders

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

Additionally, a high correlation appears to exist between eating disorders and substance abuse. For example, recent research reported that as many as 55 percent of bulimic patients have drug and alcohol use problems. Conversely, 15 to 40 percent of females with drug abuse or alcohol problems were reported to have eating disorder syndromes, usually involving binge eating.

OPPORTUNITIES TO ADVANCE KNOWLEDGE

Research Across the Life Span

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

Ethnic Minority Females

Knowledge about ethnic minority women's mental health and use of addictive substances is limited in terms of understanding the etiology and prevalence, the clinical course, intervention effectiveness, and service use related to these disorders. The meaning of ethnic identity as it pertains to acculturation, social class, and sex-role socialization requires careful refinement when considering associations with psychopathology. Differences in response to high blood pressure medications among men of different ethnic groups suggest that there may be possible differences in the pharmacokinetics and pharmacodynamics of psychotherapeutic drugs among ethnic groups of women. Outreach to ethnic communities is needed in order to fashion research that addresses these concerns.

Impact of Violence

Overwhelmingly, women are the more likely victims of violent abuse. A study of a representative national sample of women indicated almost 13 percent of women (about 12 million) have been raped and 11 percent more have been the target of aggravated assault at least once. Evidence indicates that there is more drug abuse among women with a history of child abuse. There is a possible association between a history of sexual trauma and chronic gastrointestinal symptoms. Long-term studies are necessary to determine the psychological and biological consequences of sexual assault and other abuses. It is critical that the factors involved in the relationship between drug abuse and physical and sexual victimization (including partner violence) be identified and understood.

HIV/AIDS in Women

Women's unique HIV transmission contexts and behaviors, including the link between drug dependence and risky sex and the potential for vertical transmission, have implications for the development of targeted, gender-specific risk reduction interventions, including programs for pregnant women. The following provide direction for future gender-specific, HIV/AIDS-related intervention research:

- An obvious gender difference is biological, with HIV-infected women having the potential to transmit the virus to their infants. Pregnancy and childbearing (and childrearing) also create experiential differences between men and women and may have the effect of isolating women from participation in HIV risk-reduction interventions.
- Other experiential differences between men and women include interpersonal power differentials and the experience of physical or emotional violence. Being in an abusive relationship may negatively affect a woman's ability to adopt protective behaviors such as using condoms. Studies show that women with abusive partners practice more HIV-risk behaviors than nonabused women and are less likely to seek drug treatment, or disclose their HIV status to their partners.
- Economic strategies are sometimes different between men and women. Studies show that drug- dependent women are more likely men to engage in sex trade, raising the risk of HIV infection (women are also more likely to engage in other high-risk sex practices).

- Men and women sometimes have differential access to other resources, such as a greater number of drug treatment slots available for men than women.

- Cultural norms and gender-based role expectations may affect women's HIV risks relative to men's; for example, a recent study of IDU networks shows that in multiperson drug injection scenes, men were more likely to start an injection sequence and women were more likely to use a needle that had been previously used by someone else.

- Differences in psychosocial development may result in different communication styles for men and women and their interpretations of HIV risk-reduction messages.

Gender Differences in Pharmacology

Epidemiologic surveys indicate that women comprise 45 percent of those who report having used an illicit drug in their lifetime, they are prescribed and use psychotropic medication at twice the rate of men, yet large gaps remain in the knowledge base of gender differences in pharmacology. Historically, this difference is due, in part, to the exclusion of women of childbearing age from drug-development trials because of fear of unintended birth defects. In addition, men have been considered less complicated research participants because their levels of sex hormones were assumed to remain relatively constant, thus reducing the chance of confounding results. By excluding women, researchers have not had to concern themselves with questions about the effects of the menstrual cycle, or whether the women were pre-, peri-, or postmenopausal or on hormone medications. This research strategy has not furthered the understanding of gender differences in pharmacokinetics and pharmacodynamics of psychotherapeutic drugs. Research should be undertaken to study the effects of psychotropic drugs and hormones over time, because millions of women take antidepressant drugs and hormone replacement medications regularly.

Drug Abuse

In addition to the above issues related to drug abuse, studies are also needed to examine:

- the nature and extent of drug abuse in females of all ages, ethnic backgrounds, SES groups, and sexual orientations;

- the role of the menstrual cycle in modulating drug use and drug effects;

- gender-specific behavioral, biological, and medical effects of drug abuse; and

- gender-specific biological and behavioral mechanisms that underlie drug abuse and addiction.

Prevention research should be expanded to include interventions based on female-specific antecedents, pathways, and risk and protective factors.

Gender-focused drug abuse research is needed to study the role of dieting and eating disorders in drug abuse etiology, the relationship between affective and anxiety disorders and drug abuse, and the role of PTSD as a risk factor in drug abuse. Additionally, gender-based research is needed to examine the factors that result in over-prescription and abuse of psychotherapeutic agents.

The development of well-designed, theoretically based drug treatment models that address female-specific issues is necessary if treatment is to be effective. The models should be broad based and comprehensive; include pharmacological, psychotherapeutic, behavioral, and psychosocial treatment modalities; and address co-existing psychiatric disorders (especially depression, anxiety, PTSD, and eating disorders). These models must also address service needs including child care, transportation, assertiveness training, and vocational training. Such services, by themselves, do not constitute treatment. However, if they are not provided, women are likely to experience barriers to accessing treatment and/or to remaining drug free. Within the context of treatment, there is also a need to examine, from the perspective of gender, the complex issues involved in relapse.

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

Alcohol Dependence

Research is currently lacking on:

- gender differences in alcohol metabolism;
- differential susceptibility of women to alcoholic organ damage;
- effects of alcohol consumption on bone density and osteoporosis;
- long-term consequences of alcohol use while on estrogen replacement therapy;
- the relationship between alcohol use and breast cancer; and
- determination of optimal treatment methodologies for women alcoholics.

Integration of Mental and Addictive Disorders into Primary Care and Community Settings

The primary care setting presents an ideal opportunity for screening for mental and addictive disorders. This opportunity is lost, however, if clinicians are either not adequately trained or, because of the stigma attached to these disorders and difficulties associated with reimbursement, are unwilling to address them. Primary care clinicians are uniquely positioned to screen, diagnose, treat, and refer. Their ability and willingness to provide the full range of services is essential if mental and addictive disorders are to be integrated throughout the health care delivery system.

Research Environment

Research is not user friendly to the average person, in part because patient and researcher often do not speak the same "language." The actual service setting is an important variable: a person's comfort level determines whether she will return, will be honest, or will benefit optimally from care. The community could be an important source of information to aid treatment; therefore, outreach to the community, religious institutions, and into the home should be considered important adjuncts to treatment regimens.

CHANGE IN QUESTIONS SINCE HUNT VALLEY

In addition to the questions that fine-tune the focus on studies of disorders most prevalent in women, there are now questions that address variation among women. Learning more about the roles of ethnicity, age, sexual orientation, genetically and biologically based variation, and social and economic resources in the etiology, course, and outcomes of mental and addictive disorders among women will lead to more effective treatment efforts. Examples of new questions include:

- What are the roles of specific (e.g., pregnancy, divorce) and chronic stressors (e.g., single parenthood, caring for a dependent family member) across the life span with regard to risk and course of mental and addictive disorders? What factors compound the stressors to produce greater risks (e.g., genotype, limited social and financial resources), and what factors can protect against negative effects of these stressors?
- Less severe symptoms may cause as much, if not more, impairment across the population due to great prevalence as more severe clinical disorders among fewer people. This may be particularly the case for minor depression, with women assumed to have higher rates than men. What is the prevalence of minor depression? What is its functional impact on work and relationships? And what are some

promising clues to prevention and treatment of minor depression among both women and men?

- How does variation in a women's physiological response to drugs, possibly due to menstrual cycle or estrogen medication, affect treatment approaches to both mental disorders (e.g., dosing antidepressants) and interventions aimed at substance use (e.g., nicotine addiction)?
- What are the factors that contribute to more user-friendly preventive approaches for women at risk for mental or addictive disorders, and similarly, more user-friendly intervention strategies for women already suffering from these disorders?
- What are the best treatment approaches to address the more common comorbid disorders, such as depression and nicotine addiction, depression and anxiety, or PTSD and depression, for certain subgroups of women?

RESEARCH RECOMMENDATIONS

Summary Recommendations

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

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

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

Neuroactive Peptides in Women with Bulimia. Further explore the findings that levels of neuroactive peptides, such as cholecystokinin (CCK), may be altered in women with bulimia and that lower levels of this peptide also correlate with higher scores on measures of anxiety and anger. Attempt to link these findings with studies showing that CCK interacts with serotonergic neurons, which have been implicated in the etiology of bulimia.

Long-term Effects of Violence and Victimization. Encourage and support research on (1) psychological and biological effects of sexual assault in childhood, and (2) intervention research designed to prevent and/or treat the long-term mental health effects of experiencing abuse and violence.

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

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

Co-existence with Mental Disorders. Conduct research on the co-existence of drug dependence with psychiatric disorders, especially depression, PTSD, anxiety disorders, and eating disorders.

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

Women and Alcohol. More research is needed to:

- Ascertain mechanisms of gender differences in alcohol metabolism;
- Determine the causes and mechanisms of differential susceptibility of women to alcohol organ damage;
- Explain and quantify the relationship between alcohol consumption and bone density and osteoporosis;
- Examine the long-term consequences of consuming alcohol while on estrogen replacement therapy;
- Determine if the relationship between alcohol consumption and breast cancer is causal and, if so, by what mechanisms(s); and
- Determine optimal treatment methodologies for women alcoholics.

Address Diversity in All Research Studies. Many measurement tools used today were normed on white male reference groups. These tools need to be re-examined and validated for use with female and diverse ethnic groups. Similarly, there is need for female-centered models of treatment. In developing these models, researchers need to be cognizant of the variables important in women's mental health, including racial, religious, socioeconomic status, and sexual orientation.

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

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REPRODUCTIVE HEALTH

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BACKGROUND

The discussions of the Working Group on Reproductive Health built on a foundation of three components: (1) the changing status of reproductive health in women's health research, (2) the Hunt Valley Report, and (3) an outline of topics developed by the cochairs as a framework for discussion.

As an area of research, the female reproductive system has fallen in and out of favor with the biomedical establishment. Historically, "women's health research" was limited to the study of obstetrics and gynecology. In the 1970s, however, societal shifts including, most notably, feminist concerns about women's interactions with the medical system, resulted in broadening the research agenda to encompass a more comprehensive definition of women's health. This agenda drew attention to the lack of research on the major causes of morbidity and mortality in women, including cardiovascular disease and cancer (especially breast cancer), and to the problem of ineffective or inappropriate treatment of diseases and conditions. As the agenda broadened, the focus on women's reproductive capacity was seen as a form of medical reductionism, and research on female reproduction fell out of the mainstream.

Not until the late 1980s through the early 1990s, in the context of increased government attention to and funding of women's health research,[1] did the female reproductive system begin to make its way back onto the research agenda. The Hunt Valley Report, produced during this period, reflected this renewed interest in the papers of working groups that examined the current issues in women's health from two perspectives: (1) from a developmental perspective, looking at women's health throughout the life span; and (2) from a basic science perspective, looking at women's health in terms of the state of current biological knowledge.

The Hunt Valley Report set out a series of questions intended to guide the women's health research agenda. The questions about female reproduction encompassed basic biology and clinical practice. The report emphasized the need for research on the physiology of the female reproductive system; on the links between sex hormones and human behavior; and on the etiology and treatment of a number of reproductive abnormalities including preterm labor, polycystic ovary syndrome (PCOS), premenstrual syndrome (PMS), endometriosis, and uterine fibroids. From a developmental perspective, the report called for research on sexually transmitted diseases (STDs) and contraception (particularly pertinent to adolescent and young adult women) and for attention to menopause issues including, most prominently, hormone replacement therapy (HRT). In addition, the Hunt Valley Report emphasized the need for interdisciplinary work to study the effect of social context on women's health.[2]

The present Working Group on Reproductive Health (the change in terminology reflects the intent to broaden the perspective of the field) has built directly upon the foci and recommendations of the Hunt Valley Report. Using the report, the cochairs developed a framework to help the working group participants structure their discussions. The framework delineates content areas (i.e., reproductive health, reproductive disorders, and special populations) and research strategies (i.e., basic biology, clinical research, and social and behavioral approaches). Working within the matrix formed by content and strategy, the working group addressed the agenda — progress, gaps in knowledge, change in questions, and research recommendations — set by NIH's Office of Research on Women's Health (ORWH).

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

Pregnancy

Progress has occurred in four major areas of research on pregnancy. First, knowledge has advanced about infectious diseases during pregnancy. Recent research has identified several infections — for example, bacterial vaginosis, chlamydia, and trichomoniasis — in the etiology of preterm labor. In the interests of preventing poor birth outcomes, attention has focused on finding accurate methods to diagnose such infections and effective treatments that may be administered during pregnancy. Continuing research on HIV/AIDS has led to the finding that the use of antepartum and intrapartum zidovudine (AZT) appears to reduce the risk of perinatal transmission of the virus.

Second, knowledge has advanced about the prevention of fetal malformations. Improvements in genetic testing and prenatal diagnosis have provided parents with better information for making choices about whether to continue a pregnancy of a malformed fetus. There is greater understanding of the role of maternal nutritional factors in the development of fetal malformations. Recent research on the role of folic acid (a B vitamin) in preventing neural tube defects (spina bifida and anencephaly) has led to the recommendation that all women of childbearing age consume 0.4 mg of folate per day and that folate be added as a supplement to bread and other grain products.

The third area of progress has been in identifying risk factors for preterm labor. Screening for the presence of fetal fibronectin in the vagina or cervix of a pregnant woman seems to hold promise as a predictor of preterm labor. The presence of fetal fibronectin also appears to be a good indicator of upper reproductive tract infection in pregnant women. The link between vaginal infections and preterm delivery suggests that screening and, if necessary, treatment of high-risk women might have potential in preventing poor birth outcomes. Data have improved on the disparities in preterm delivery rates among racial and ethnic groups. Preterm delivery rates may be higher among African-American women because they have higher rates of reproductive tract infection. The new research confirms a likely heterogeneity in the etiology of preterm labor.

Fourth, in the social and behavioral realm, there has been progress in understanding and promoting measures to improve the health of women during pregnancy. Recognition of the safety and benefits of exercise, increased awareness (among health care providers and pregnant women) of the detrimental effects of alcohol consumption during pregnancy, legislation prohibiting smoking in public places, improved management of ectopic gestation, and new methods of medical abortion have all improved the health of the pregnant woman.

Contraception

Progress has been made in several areas of research on contraception: the development of new methods (and the reintroduction of some old ones), research on the safety of existing methods, and recognition of the need for a new generation of contraceptive technologies.

Since Hunt Valley, Norplant (levonorgestrel subdermal implants), Depo-Provera (medroxy-progesterone acetate injection), and the female condom have all been introduced to women in the United States. The innovative delivery systems used in Norplant and Depo-Provera seem particularly promising for adolescent women. The female condom has met with problems — cost, ease of use, provider resistance — but has been shown to be popular among women who have received good health education and support. The concerns about HIV/AIDS that prompted the development of the female condom have led to a resurgence in the use of the male condom. Recently, women and providers also have taken a new look at the intrauterine device. Finally, progress has been made in the area of emergency contraception. The Food and Drug Administration issued an advisory regarding off-label use of mifepristone (RU 486) and oral contraceptives for postcoital contraception ("morning after pill").

Perhaps most important is the increased awareness on the part of researchers and clinicians of the need for new methods. This awareness derives from research showing the ambivalence of certain racial/ethnic groups about using some methods and, more broadly, the recognition that women need different contraceptive choices at different periods of their lives. The worldwide epidemic of STDs has led to calls for the development of new microbicides and microbicide/spermicide combinations. Early research on these combination methods looks promising. In addition, some progress has been made in developing a new male contraceptive — a hormonal injection being tested by international researchers.

Infertility

Substantial progress has occurred in the treatment of infertility and understanding of the many etiologies of the condition. Technological advances have included many new (or improved) assisted reproductive technologies: in vitro fertilization, embryo transfer, the use of donor eggs, and intracytoplasmic sperm injection; laser surgery for the treatment of pelvic inflammatory disease; the use of GnRH analogs in ovulation induction; and improved provider expertise at using these technologies. In addition, the recent expansion in knowledge about ovarian physiology and conception (e.g., the timing of intercourse relative to the LH surge and the importance of egg quality) promises to result in new clinical applications.

Advances also were made in understanding the etiologies of infertility. The evidence does not support the suggestion that video display terminals are a cause of recurrent spontaneous abortion. Research on the part played by STDs in causing infertility has led to the development of a screening test (urine PCR) for chlamydial infection. Early detection of chlamydial infection can reduce the development of pelvic inflammatory disease, thus preventing later problems with infertility. A provocative new area of research is the role played by cell-mediated immunity in male and female infertility.

Progress has been made in the psychosocial and policy areas relevant to infertility treatment. There has been an increased awareness of the trend toward women's delaying first birth[3] and the necessity for quick, appropriate treatment in those cases. Policy and science have interacted in the field: science has influenced policy (e.g., institution of screening for chlamydia) and policy has influenced science (e.g., development of quality-control guidelines for infertility clinics).

Ectopic Gestation

Diagnosis and treatment of ectopic gestation have improved, thus reducing associated morbidity and mortality. Specifically, transvaginal ultrasound and the timely measurement of serial hCG have improved diagnosis. New treatments, including methotrexate, have improved medical management and reduced the need for surgical intervention.

Ovarian Failure

Much of the progress in ovarian disorders has been in increased awareness of their definition and prevalence. Conceptually, the recent distinction made between ovarian failure and "premature menopause" has been extremely important. In some cases, premature ovarian failure can remit, with return of cyclic menses and ovulation. There has been a recognition of iatrogenic ovarian failure. Clinicians and researchers have determined the inefficacy of estrogen and ovulation induction to treat the condition.

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS), which involves absent or disturbed ovulation and excessive androgen secretion, is a leading cause of female infertility and is difficult to treat. There has been a new awareness of the occurrence of PCOS in adolescent and middle-aged women. Research has shown a link between PCOS and increased risk for diabetes, cardiovascular disease, and breast cancer. The role of insulin resistance in the etiology of PCOS has been recognized, and researchers are looking at the use of insulin sensitizers and a follicle-stimulating hormone for treatment.

Endometriosis

Awareness of endometriosis has increased, and health care providers and researchers are more likely to take it seriously. Retrograde menstruation now is recognized to be a background condition, not a sole cause. Laser treatment to remove endometrial masses is not thought to be efficacious, but infertility caused by endometriosis may be successfully corrected through assisted reproductive technologies. An exciting area of research is the role of abnormal cell-cell adhesion molecules in endometriosis. Realization that biological activity of this disease may not correlate well with the appearance of lesions, has cast doubt on the usefulness of the current classification scheme.

Myoma

Researchers have begun to make progress in determining the etiology of myoma. Active research is seeking to elucidate the roles played by gap junction proteins and the extracellular matrix. Among providers, there is a decreased concern about malignancy and a trend toward more conservative management (i.e., treating for symptoms, not presence). There has been some progress in treatment — an improved radiographic technique for assessing presence and severity, laparoscopy for removal, and the use of GnRH analogs for the treatment of anemia before surgical removal.

Abnormal Uterine Bleeding

There is an increased awareness among clinicians and researchers of abnormal uterine bleeding. Progress has been made in understanding the differences between normal menstrual shedding and abnormal bleeding. Research is focusing on the endometrium itself and the control of uterine vasculature.

Pelvic Floor Relaxation

Researchers have begun to recognize the neuromuscular etiology of pelvic floor relaxation. In addition, surgical methods to treat it have improved, resulting in less morbidity.

Pelvic Pain

Pelvic pain has been recognized as a condition, but it has not yet been well defined. Researchers have presented preliminary findings suggesting a myofascial etiology. Most progress, perhaps, has been in the recognition of the psychosocial ramifications of this condition among women and their families.

Premenstrual Syndrome

Awareness has increased of the variability of definition and presentation of premenstrual syndrome, as well as of its multifactorial etiology. There is more knowledge about which treatments are not effective (e.g., vitamin B-6, evening primrose oil). Promise exists in the seeming efficacy of GnRH analogs for the suppression of ovulation and in the use of sophisticated imaging technologies to describe the neurological and endocrine pathways involved in the condition.

General Issues

While progress in specific strategic areas has been uneven, there was a consensus that awareness of all conditions has improved and that such awareness could help serve as a blueprint for the future. A general theme in the working group's discussion of progress was the idea that even negative results in research, that is, results that do not support the hypothesis of the research, represent an advance in that they narrow the specific avenues of inquiry. As one participant noted, "We know a lot more about what we do not know."

GAPS IN KNOWLEDGE

Pregnancy

There are gaps in all areas of knowledge about pregnancy. Research is needed on the basic biology of preterm labor, growth restriction, preeclampsia, and spontaneous abortion. Better data are required on the sociodemographic correlates of pregnancy outcomes, including data on the effects of race/ethnicity, poverty, abuse/battering, housing instability, and immigration. Little is known about postpartum depression or the use of alternative therapies during pregnancy. In addition, there is a need for technology assessment and outcomes research on many of the medical interventions related to pregnancy care (e.g., home uterine monitoring, cesarean section, prenatal care). Such outcomes research should look at both short-term and longitudinal outcomes of treatment and use multidimensional measures for assessment. Researchers should begin to look at the pharmacodynamics and pharmacokinetics of drug therapies during pregnancy. Finally, more work needs to be done to determine the effects of pregnancy (or of never being pregnant) on women's health throughout the life span.

Contraception

Three major topics related to contraception are priorities for research. First, research is needed to determine the long-term effects of currently available methods — in particular, the metabolic and long-term effects of hormonal methods and the possible role of the intrauterine device in causing primary tubal infertility. Second, options for contraception should be expanded through the development of new methods. Research should focus on immunologic methods, on a reversible method for men, on new microbicide/spermicides (as well as on microbicides that are not spermicides), and on new materials for barrier contraceptives. Recent research points to a need for better provider knowledge of certain methods — the IUD and the female condom. Finally, there is a tremendous dearth of knowledge of the psychosocial context in which women (and men) choose and use (or do not use) contraceptives, especially about decisionmaking related to contraceptive choice and the determinants of early, unprotected intercourse.

Infertility

There are gaps in current knowledge about almost all aspects of infertility. Questions remain about the epidemiology of infertility, about the role of environmental and occupational exposures in the etiology of some types of infertility, about the psychosocial aspects of infertility (e.g., the social/psychological effects of anonymous egg donation), and about male infertility. Too little is known about the effectiveness of specific treatments in specific populations, the quality of infertility treatment, and the cost effectiveness of currently available treatments. In addition, there is a lack of knowledge about the long-term effects of certain treatments for infertility (e.g., the possibility of a link between ovulation induction and later development of ovarian cancer). Many questions remain about recurrent spontaneous abortion — etiology (including the role played by environmental and occupational exposures), epidemiology, the immunology and endocrinology of the condition, and management (e.g., the effectiveness of bed rest). Finally, there is a gap between the advances in basic science and the clinical application of this knowledge.

Ectopic Gestation

Research is needed to determine the epidemiology of ectopic gestation. More needs to be learned about the role of local effectors, biochemical stimuli, cytokines, douching, and other factors in the etiology of the condition. Research also is needed to determine the long-term effects (for example, on fertility) of using medical instead of surgical treatment.

Ovarian Failure

A multitude of questions remain about disorders of ovulation. In contrast to the relative ease of treating infertility due to hypothalamic or pituitary hormone deficiency, premature ovarian failure is extremely difficult to treat. Gaps in knowledge exist about almost every aspect: connections between epidemiology and etiology (e.g., the possible role of smoking and occupational/environmental exposures in ovarian failure); pathophysiology; markers of reversibility or remission; and somatic, psychosocial, and functional effects of ovarian dysfunction.

Polycystic Ovary Syndrome

Polycystic ovary syndrome is now recognized as an important cause of infertility and of morbidity even in women not trying to conceive. More work is needed on the complex hormonal interactions involved in the etiology and pathogenesis of this common and distressing condition. In this way, improved treatments can be devised based on a foundation of scientific knowledge.

Endometriosis

Little is known about the epidemiology and etiology of endometriosis and how to treat it effectively. The pathway by which the condition causes infertility remains unclear. Research is needed to establish the impact of the condition on women's quality of life and economic functioning. Perhaps the greatest need is for noninvasive markers to aid early identification of these conditions. Such markers would facilitate identification of risk factors, early diagnosis, and better monitoring of treatment. It is expected that this would make conservative management more viable, and thus more attractive to both providers and patients, reducing the use of hysterectomy.

Myoma

Studies of the epidemiology and etiology of myoma are needed. Technology assessment of laparoscopic and other treatments (including alternative therapies) must be performed to provide better management. Questions remain about the implications of large fibroids and pregnancy, about hormone replacement therapy and regrowth of fibroids in postmenopausal women, and about the use of GnRH analog treatment. New combination or low-dose therapies need to be developed that will control myoma symptoms yet avoid the somatic effects of estrogen deficiency seen with present regimens. There is a need for education of the public and professionals on the issue of treating intolerable symptoms, not simply presence of myomas.

Abnormal Uterine Bleeding

Research is needed to determine treatment effectiveness and to look at the long-term effects of treatments currently in use (e.g., endometrial ablation).

Pelvic Floor Relaxation

Little is known about the etiology or pathophysiology of pelvic floor relaxation. More attention should be paid to finding effective treatments with minimal complications. Questions remain about the effectiveness of physical therapy, Kegel exercises, and biofeedback in ameliorating the condition. Perhaps most important, research should look at how management of labor and delivery might be changed to prevent its occurrence.

Pelvic Pain

Very little is known about pelvic pain. A clear definition and effective management strategies are needed. In addition, research is needed on the psychosocial issues involved (e.g., the link between sexual abuse and pelvic pain).

Premenstrual Syndrome

Work is needed to better define PMS and to explore what it can teach us about the connection between hormones and behavior. Too little is known about the quality of life issues for women who suffer from the condition. Research on treatment should look at the use of antidepressant medications and the role that complementary therapies might play in ameliorating symptoms.

Special Populations

No rigorous data exist on reproductive health in women with disabilities. Too little is known about issues of access to care for reproductive health services in underserved populations (e.g., adolescents and minority women) and the phenomenon of differential treatment for women from different socioeconomic groups. In addition, more attention should be paid to understanding the cultural aspects of reproductive health (e.g., acculturation and favorable birth outcomes among ethnic subpopulations and immigrant groups; female genital mutilation).

General Issues

Two themes recurred in the working group's discussion of gaps in knowledge. The first theme was the impact of new systems of reimbursement on medical research and practice. Because the effects of managed care on quality of care have yet to be determined and because of the new emphasis on cost in the medical setting, the working group saw a great need for studies in the areas of outcomes research and cost-effectiveness assessment. Although aware that such research traditionally has not fallen under the NIH research mandate, the working group suggested that the increased importance of such issues might argue for more flexibility. The second theme was the difficulty of acquiring funds for research on conditions such as pelvic pain and PMS. Because such newly recognized conditions are believed to have psychogenic components, it is unclear which NIH institute has purview over them. This point led to a more general observation: many health concerns of women cut across various aspects of their lives, such as physical, emotional, and social; however, the NIH structure is organized by disciplines and organ systems. This mismatch makes it difficult to institute the multidisciplinary approaches best suited to studying women's health.

CHANGE IN QUESTIONS SINCE HUNT VALLEY

The managed care environment is prompting researchers and clinicians to ask questions about outcomes and the cost effectiveness of current and new treatments. Outcomes are being conceptualized broadly, encompassing multidimensional measures (e.g., quality of life) and longitudinal designs. Perceived problems with the new reimbursement systems are prompting questions about access to care for underserved populations and quality of care for all patients. A related change is the need for better education of generalists (because they function as gatekeepers) to increase their awareness of reproductive health issues and to improve their competence in treating these conditions, including when to refer to a specialist.

While discussing progress made in understanding pregnancy and improving pregnancy care, the working group noted that although many of the advances were directed at improving the health of the fetus, attention recently has shifted to a concern for the woman during pregnancy. Many of the interventions to improve maternal health are social, directed at lifestyle, rather than biological.

In contraception research, only recently has attention turned to the man's role in contraception. New questions are being asked about contraceptive technologies that serve women's and men's broader needs across the life span. In infertility research the importance of psychosocial issues has come to be understood. The demographic shift — women delaying their first pregnancy until well into their 30s — has driven the demand for infertility services. That demographic shift is prompting researchers and clinicians to ask new questions about when to begin to treat infertility, about how far treatment should go, and about the meaning of infertility in women's and men's lives.

Changes in policy and technology also have shaped the questions being asked about women's reproductive health. NIH's policy guidelines requiring the inclusion of women in clinical trials[4] will give researchers an opportunity to look at the pharmacodynamics, pharmacokinetics, and pharmacoeconomics of drugs in women of reproductive age. Advances in computerization technology have improved data collection, thus expanding the kinds of research questions that may be pursued.

A final change — a paradigm shift in the field of reproductive health — has been the recognition of heterogeneity: women are different from one another, and individuals vary across the life span. The integration of this paradigm of heterogeneity into the reproductive health research agenda promises to fulfill the expectation implicit in the term "reproductive health" and to change the scientific questions.

RESEARCH RECOMMENDATIONS

Pregnancy

The working group's research recommendations reflect its assessment of the two most pressing problems in this area — preterm labor and maternal health — and the need for continuing to emphasize the social context of reproductive health. The working group recommends:

- research on the basic biology of preterm labor and the role of social factors; and
- research on the effects of external factors — lifestyle, pharmacology, and environmental and occupational exposures — on the health of pregnant women.

Contraception

These recommendations reflect the increased concern with understanding the psychosocial factors involved in contraception. They also focus on the serious problem of STDs among women of reproductive age, particularly adolescent women. The working group recommends:

- research on contraceptive-use behavior (decisionmaking and compliance);
- research leading to the development of contraceptive options appropriate under different circumstances and for different populations; and
- research on interactions between contraceptives and STDs.

Infertility

The working group's recommendations emphasize the importance of conceptualizing infertility as the problem of a couple and also of developing more specific and efficacious management strategies. The recommendations call for:

- recognition that infertility is a problem of the couple in which the male factor must not be neglected; and
- efficacy research on management strategies for more focused treatment selection based on the biomedical and psychological needs of each couple.

The research recommendations for the following reproductive disorders reflect the very preliminary stage of current knowledge about the biology and management of these conditions.

Ectopic Gestation

The working group recommends research on the etiology and risk factors of ectopic gestation and on the efficacy and long-term effects of current and evolving management of this condition. Data are needed on whether maintaining tubal integrity through conservative management results in preservation of fertility potential and a decrease in repeat ectopic gestation.

The HPO Axis (Polycystic Ovary Syndrome, Anovulation, and Ovarian Failure)

The working group recommends research on the etiology and pathophysiology of ovarian dysfunction, on the amelioration of infertility, and on the long-term effects of these conditions and their treatments on general health.

Endometriosis, Myoma, and Abnormal Uterine Bleeding

The working group recommends:

- research to find noninvasive markers of disease activity (endometriosis) to establish prevalence and risk factors; and
- recognition of the inadequacy of current therapies and the need for an understanding of pathophysiology to develop new and better treatment options.

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CANCER

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BACKGROUND

Although the death rates for many cancers have decreased over the last 20 years, cancer remains the leading cause of death for women 35 to 74 years old. In 1997, an estimated 596,600 women will be diagnosed with cancer, and 265,900 women will die from the disease.[1] Lung cancer now surpasses breast cancer as the leading cause of cancer deaths for women, followed by cancers of the breast, colon, and rectum. Cancer remains a major public health problem, causing untold anxiety and suffering for patients and their families, as well as generating a substantial part of the nation's health care expenditures.

SCIENTIFIC PROGRESS SINCE ESTABLISHMENT OF ORWH

The major event since Hunt Valley in 1991 is the decrease in the U.S. cancer mortality for the first time. In addition, the field of genetics has advanced the scientific understanding of cancer significantly. The genetic loci for some hereditary cancers of the breast, colon, endometrium and the ovary have been identified. Already, inherited susceptibility to cancer accounts for 5 to 10 percent of these cancers. This number is likely to increase as other genetic factors are identified. Further, the genetic pathways responsible for the loss of normal cellular-control mechanisms may lead to an understanding of the process of carcinogenesis in sporadic (or nonfamilial) cancers. Furthermore, research has demonstrated similar changes in oncogenes and tumor-suppressor genes across many cancers, suggesting common mechanisms of loss of cell cycle control.

The links between infectious agents and some cancers have also been clarified since 1991. These include the association between H. Pylori and gastric cancer, specific human papilloma viruses and cancers of the cervix and vulva, the Epstein-Barr virus and Burkitt's lymphoma, nasopharyngeal carcinomas and leiomyosarcomas, and human herpes virus 8 (HHV8) and Kaposi's sarcoma. The observation that integration of the viral genome into the host DNA is necessary for carcinogenesis suggests a mechanism for viral carcinogenesis in cancer etiology.

Broad population-based studies have documented the impact of diet and lifestyle in the development of cancers of the head and neck, esophagus, stomach, and colon. These observations have fostered the design of intervention trials; attempts to change diet or habits to reduce the incidence cancer. The fall in cancer mortality underscores the importance of research into diet and environmental factors in carcinogenesis, as well as screening and more effective treatments.

Since Hunt Valley, differences in response to carcinogens, drug metabolism, and response to treatment have been observed between women and men, between different racial and ethnic groups, and between older and younger individuals. For example, compared to men, women develop lung cancer after lower doses and shorter intervals of cigarette smoking. Research has begun to describe the interplay of genetic, environmental, socioeconomic, and other factors which determine whether an individual will develop cancer and whether that cancer responds to treatment.

Since 1991, important advances have occurred in cancer therapy. These include chemotherapeutic agents with novel mechanisms of action, such as paclitaxel and topotecan. 5 FU and leucovorin have been shown to be effective in preventing recurrences in patients with stage 3 colon cancer. The use of minimal access surgery, which has the potential to decrease morbidity and improve quality of life for cancer patients, has become much more common. Multi-modal, organ-sparing therapy has been proven effective in treating breast, laryngeal, and rectal cancers.

In the years since Hunt Valley, consumer and patient advocates have strengthened. These groups have helped focus the nation's attention on a variety of critical cancer issues, including laboratory research, prevention, education, screening, treatment, and survivorship. They have helped set priorities for research and have become involved in the design and conduct of prevention, screening, and treatment trials. Consumer groups and cancer investigators have also strengthened research on quality-of-life issues for those undergoing treatment for cancer and for cancer survivors who have completed primary treatment.

Since 1991, major changes have occurred in health care delivery. Enrollment in health maintenance organizations and other managed-care organizations has increased dramatically. Many cancer patients have reported difficulties in gaining referrals to the appropriate cancer specialists, as well as in gaining access to NCI-sponsored cancer trials and treatment at NCI-designated cancer centers. Changes in reimbursement have limited investigator time and institutional monies available to support basic and clinical research. These changes, together with the persistence of a major portion of the population without health insurance, have had a major impact on the conduct of basic and clinical cancer research.

CHANGE IN QUESTIONS SINCE HUNT VALLEY

The areas of scientific progress and societal change since 1991 have also expanded the questions considered critical in cancer research. For example, genetic advances in cancer required addressing the medical, social, ethical, and legal issues of screening for genetic abnormalities. Knowledge about the heterogeneous etiology of cancer, including genetics, diet, cigarette smoking, and hormonal and environmental influences, has led to small- and large-scale cancer prevention trials. These have included evaluation of retinoids in the prevention of secondary lung and head and neck cancers, as well as of tamoxifen in the prevention of secondary breast cancers and breast cancer recurrences. Consumer and patient advocate groups have appropriately encouraged a closer look at quality-of-life issues during and after cancer treatment.

In this report, the working group addresses gaps in knowledge about the most common malignancies affecting women, including cancers of the lung, breast, colorectum, uterine corpus, cervix, and ovary. General research and policy recommendations are presented below.

GAPS IN KNOWLEDGE

Lung Cancer

In 1992, lung cancer was the cause of death for 54,348 American women. The American Cancer Society (ACS) estimates that 64,000 women died of lung cancer in 1996,[2] 25 percent of all cancer deaths among women. The incidence of lung cancer varies by gender and ethnicity, representing historical patterns of cigarette smoking. In 1990, for example, the incidence of lung cancer per 100,000 individuals was 78.6 for white men, compared to 41.5 for white women, 116 for black men, and 45.3 for black women.[3] Among women, the number of adenocarcinomas of the lung, a type of lung cancer less associated with tobacco smoke, is rising.

Recent molecular evidence definitely links tobacco smoke with cancer causation. Men and women appear to respond differently to the carcinogens found in tobacco smoke. Compared to men, women develop lung cancer after smoking fewer cigarettes over a shorter period of time. There is some evidence that vitamins A, C, E, selenium, and other micronutrients may be beneficial in preventing lung cancer.[4] Diets rich in fruits and vegetables appear to lower the risk of lung cancer by up to 50 percent. Epidemiology studies of lung cancer may help identify other potential chemopreventive agents, as well as the etiologic agents for pulmonary adenocarcinomas.

Smoking cigarettes has been identified as a risk factor not only for lung cancer, but also for cancers of the mouth, larynx, pancreas, bladder, kidney, cervix, and vulva. Prevention of smoking onset, therefore, would decrease the risk of lung and other cancers and chronic lung disease. Since 90 percent of all smokers report that they began smoking during their teens, the key to primary prevention is to prevent smoking among adolescents and young adults. Unfortunately, smoking rates, which had previously been falling among adults, are now increasing. In 1994, 48 million adults reported smoking, compared to 46 million in 1993. Twenty-eight percent of men smoke, and 23 percent of women smoke. Almost three-quarters (71 percent) of high school students have tried cigarettes.[5]

Smoking Average Among High School Students

	White	Black	Hispanic
Boys	37%	28%	35%
Girls	40%	12%	33%

The most urgent research priority must be focused on optimizing prevention efforts targeted to children and adolescents. Education about the health hazards of smoking, beginning in early childhood and repeated into adolescence, may be effective. Recognition of the role of peer pressure and the urge to rebel against adult authority must be incorporated into educational strategies.

Messages should be nuanced to address a variety of ethnic, racial, and socioeconomic groups, and to counteract the pro-tobacco messages promulgated by cigarette advertising and promotions. Advertising aimed at adolescents and young adults, which connects smoking with slenderness, social activity, and popularity, exercises a powerful impact on adolescent girls. Specific advertising campaigns aimed at black and Hispanic young women, which may have sparked recent increased usage among these groups, must be challenged in the public forum. Research must determine the optimal forum of oppositional advertising. Self-esteem issues such as weight, peer pressure, mood, and depression also play a role in the decision of many young girls to smoke. Researchers should focus on these factors to develop effective anti-smoking messages for this age group.

Nicotine, a stimulant which can ameliorate negative emotions such as depression, may be particularly important to women who have higher rates of depression and, as a group, take more mood-modifying medications than do men. Research should examine the interactions among gender, mood modulation, and smoking patterns and their relevance to prevention and cessation interventions.

Ongoing research into optimal strategies for smoking cessation should focus on the many influences in smoking behavior from peer groups, school, work site, and the community institutions in which women participate. Clinical and research findings suggest that social support can play a significant role in successful smoking cessation, particularly for women. Additional research on the role of social support in smoking cessation is recommended.

Smokers whose parents have had lung cancer are twice as likely to develop lung cancer as the general population of smokers. Research to address genetic and metabolic risks for lung cancer, as well as cessation approaches and supports for this more vulnerable population, is also important.

Phase I, II, and III chemopreventive trials are needed to prevent first and second primary lung cancers. Large-scale screening approaches for people at risk could have a major impact on death rates. The National Cancer Institute is supporting a randomized study of screening with chest radiography as part of the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO). Development of reliable biomarkers and imaging technologies are urgently needed to improve the early detection of lung cancer.

Advances in cancer treatment are urgently needed, since only 16 percent of individuals with lung cancer are alive 5 years after diagnosis.[6] The timely completion of randomized clinical trials evaluating surgery, chemotherapy, and radiation therapy are critical to progress in the treatment of lung cancer. These studies should be large enough to address the interaction issues of gender and race/ethnicity with treatment. All Americans must have access to the appropriate cancer specialists, as well as to lung cancer prevention programs, screening, and treatment trials.

Breast Cancer

The incidence of breast cancer per 100,000 women rose dramatically between 1980 and 1987, from 85 to 112, but it appears to have leveled off in 1990 with a rate of 109 per 100,000 women.[7] In 1996, the National Cancer Institute (NCI) estimates that 184,300 women were diagnosed with breast cancer, and 44,300 died of the disease. For the first time, the mortality rate appears to be falling, particularly for premenopausal women.

Understanding the etiology of breast cancer is critical to developing new prevention, diagnosis, and treatment strategies. Research priorities include the basic biology of the breast, mechanisms of carcinogenesis, and genetic, hormonal, reproductive, environmental, and other factors. For example, changes in the dose or schedules of hormonal contraception and hormonal replacement therapy might reduce the risk for breast cancer and significantly lower the incidence of breast cancer. Study of plant-based phyto-estrogens could prove useful. As the development of breast cancer is better understood, detection of precancerous lesions may become more accurate. New imaging modalities may help to identify persons at high risk for developing breast cancer, as well as identify smaller cancers before metastasis has occurred.

Prevention trials have been initiated. The Breast Cancer Prevention Trial, which is evaluating tamoxifen versus placebo for 5 years in women at high risk for breast cancer, will complete its accrual of 13,000 women shortly. Phase I, II, and III trials of new preventive strategies, particularly important for women at high familial risk for breast cancer, should continue.

Data continue to support the use of routine screening mammography for detecting breast cancer. Between 1983 and 1990, the incidence of detection of in situ cancers rose.[8]

Detection of In Situ Cancer Cases in 1990 Compared to 1983

	Aged < 50 Years (Percent)	Aged > 50 Years (Percent)
Black	131	150
White	82	157

Black women continue to have a lower survival rate than white women. The 5-year survival rate for white women diagnosed between 1986 and 1991 was 84 percent, whereas it was only 69 percent for black women.[9] A recent study suggests that 75 percent of the difference in survival between black and white women may be explained by late diagnosis, tumor characteristics, concomitant illness, and social and demographic factors.[10]

Data from the 1992 National Health Interview Survey indicate that only 30 percent of women age 50 or older had a mammogram during the previous year. Poverty and lack of insurance are the chief factors associated with low utilization. Improved access to screening and education to increase utilization rates for all ages and racial/ethnic groups would be a major priority.

Major progress has been made in the identification of genetic loci responsible for many cases of familial breast and ovarian cancer. In 1994, two of the most common genetic loci, BRCA1 and BRCA2, were isolated. Fifty percent of women with mutations in BRCA1 and a strong family history will develop breast cancer by age 50 and 85 percent by age 70.[11] These discoveries, however, introduce new questions. Tests for mutations in BRCA1 and BRCA2 are now commercially available. The ethical, legal, and social implications of such testing deserve study. Under what conditions are these tests most helpful and least harmful to women and their families?

Treatment issues remain of great importance. Developmental diagnostics may help better define which women with breast cancer may be safely treated with surgery alone, and which would benefit from adjuvant chemotherapy or radiotherapy. The activity of new drugs, such as paclitaxel and taxotere, in breast cancer suggests that we can improve adjuvant and salvage chemotherapeutic regimes. The effectiveness of tamoxifen in reducing the risk of recurrent or contralateral breast cancer supports further investigation of endocrine therapy for both prevention and treatment. The efficacy of high-dose chemotherapy, coupled with hematologic support (stem cell transplant), is currently under evaluation in randomized, controlled clinical trials. Finally, an area for active study is how to improve the quality of life after treatment for breast cancer; for example, ways to restore a positive body image and sexuality, ensure fertility after adjuvant chemotherapy, and prevent osteoporosis after surgical or natural menopause.

Cancer of the Reproductive System

Corpus Uteri. A projection based on SEER data is that 34,000 women will be diagnosed with cancer of the uterus in 1996; 6,000 will die of the disease. Most of these cancers arise in the endometrial lining of the uterus (endometrial adenocarcinoma); the remainder arise in the muscle wall at the uterus (uterine sarcomas and carcinosarcomas).

Risk factors for endometrial adenocarcinoma include anovulation, obesity, diabetes, and estrogen unopposed by progesterone. Elevated estrogen levels may be endogenous (associated with obesity or certain ovarian tumors), or exogenous (from estrogen replacement therapy or tamoxifen). Protective factors include pregnancy, lactation, and oral contraceptives. Atypical endometrial hyperplasia is a precancerous lesion.

Research on the basic biology of endometrial cancers, uterine sarcomas, and carcinosarcomas is critical to develop effective prevention and treatment programs.

Clinical trials aimed at preventing endometrial cancer should be encouraged, particularly for obese or anovulatory women or women on tamoxifen or unopposed estrogens.

Eighty percent of women with endometrial cancer develop abnormal vaginal bleeding, prompting early evaluation and treatment, usually hysterectomy. The role of ultrasound in screening for endometrial cancer deserves further evaluation.

Mortality from endometrial cancer is higher for black women (6.0 per 100,000) than for white women (3.3 per 100,000).[12] Although the time from onset of symptoms to treatment appears similar for black and white women, the incidence of carcinomas associated with normal estrogen levels is higher among black women. These tumors are associated with higher stage at diagnosis, greater propensity to metastasis, and worse survival. A better understanding of the biology of endometrial cancer may facilitate development of prevention and treatment strategies for endometrial cancers.

The association of many cases of endometrial cancer with elevated estrogen levels, however, suggests that progesterone might be an effective prevention for women with atypical endometrial hyperplasia, thus sparing some women a hysterectomy. Other clinical trials might evaluate the role of laproscopic surgery, adjuvant radiotherapy, and chemotherapy, as well as systemic chemotherapy for patients with metastatic disease.

Cervical Cancer. The estimated number of American women with a new diagnosis of cervical cancer in 1996 was 15,700; some 4,900 women are estimated to have died of the disease.[13] Worldwide, cervical cancer is second only to breast cancer in incidence and mortality from cancer. More than 471,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing and industrialized nations.

Invasive cervical cancers and precursor lesions have been firmly associated with the presence of specific strains of sexually transmitted human papilloma virus (HPV). Studies have demonstrated that the HPV genes E6 and E7 are integrated into the host genome and inactivate P53 and Rb, thus resulting in malignancy. The prevalence of infection decreases with increasing age suggesting that most infections resolve over time through host-immune responses. Cigarette smoking is a co-factor in humans. Other factors under study include use of oral contraceptives, number of live births, age at first intercourse, co-infection with other sexually transmitted diseases, and immune response including growth factors, cytokines, and humoral and cellular immunity. Immunosuppressed women, whether due to corticosteroids or HIV infection, are at increased risk for precursor cervical lesions and cervical cancer.

Primary prevention of HPV infection will require (1) directing education efforts toward adolescents and health care providers regarding the strong causal link between the acquisition of HPV as a sexually transmitted disease and the development of cervical cancer; (2) encouraging delayed onset of sexual intercourse; and (3) developing effective vaginal microbicides. Secondary preventive efforts must focus on the development of effective antiviral agents to treat HPV and/or prevent transformation by E6/E7 and of therapeutic vaccines to prevent HPV progression.

Squamous cell cervical cancer is an ideal disease for screening because of the typically long preclinical phase, which provides the opportunity for early detection. Use of the Pap smear is effective in reducing morbidity and mortality from cervical cancer. Despite the recognized benefits of Pap smear screening, many American women have not been screened or are not screened at regular intervals. One-half of women with newly diagnosed invasive cervical carcinoma have never had a Pap smear, and another 10 percent have not had a Pap smear in the past 5 years. The inadequately screened populations include older women, the uninsured, ethnic minorities (especially Hispanics and elderly blacks), and poor women, particularly those in rural areas. Data from the 1992 Health Interview Survey indicate that one-half of all women 60 years old and older have not had a Pap smear in the past 3 years.[14] Older women are screened less frequently, despite the same number of recent physician visits as younger women, indicating the need to educate older women and their health care providers about the importance of Pap smear screening. Reasons for nonparticipation in screening should be identified and appropriate interventions studied.

Research to improve current screening technology should be encouraged. Liquid-based specimen collection methods are currently under study. Automated instruments for screening smears, recently approved by the Food and Drug Administration, need further evaluation in routine primary screening and in subsequent screening. Their cost effectiveness should be evaluated.

Optimal management of patients with certain precursor lesions, atypical cells of undetermined significance, and low-grade squamous intra-epithilial lesion is not established. A large NCI clinical trial is currently evaluating the different ways to manage these patients.

Strategies to develop more accurate imaging studies would better define the extent of disease at presentation as well as to plan radiation therapy. Currently, no category of cervical adenocarcinoma, which could be treated conservatively to preserve fertility, can be identified. Clinical trials should define the benefit of neoadjuvant chemotherapy. Progress in developmental diagnostics may identify which patients with disease confined to the cervix might benefit from adjuvant therapy after hysterectomy. The optimal adjuvant regimen for patients with disease confined to the pelvis, whether radiation, chemotherapy, or both, has not yet been defined. Clinical trials are also needed to define the role, if any, of prophylactic or therapeutic para-aortic node radiation.

Defining any impact of P53 status and HPV subtypes may allow customizing of treatment strategies. Dose-response relationship, time-dose relationship, improvements in technical instrumentation, and optimization of brachytherapy techniques should be further studied. Predictive assays for tumor and/or normal tissue radiation sensitivity might allow individualization of radiation prescriptives. Strategies to reverse anemia and tissue hypoxia could improve the radiation responsiveness of the tumor. The optimal management of HIV-positive women with precursor lesions and cervical cancer remains to be determined.

Ovarian Cancer. Ovarian cancer accounts for about 4 percent of all cancers in women and 6.7 percent of all cancer deaths. In 1996, about 26,700 new cases of ovarian cancer will be diagnosed in the United States, and 19,800 women will die of ovarian cancer. Known risk factors include BRCA1 and BRCA2 abnormalities; advancing age; nulliparity; North American or Northern European descent; a personal history of endometrial, colon, or breast cancer; and a family history of ovarian cancer. Protective factors include pregnancy, lactation, and the use of oral contraceptives. A better understanding of the epidemiology, genetics, and biology of ovarian cancer is critical.

Based on current data on the etiology of ovarian cancer, prevention trials are problematic. Nonetheless, the population-based data on the protective effect of birth control pills, as well as some preliminary data on retinoids, suggests that prevention trials can be designed for high-risk individuals. Data on the incidence of ovarian cancer in women with BRCA1 mutations who undergo prophylactic oophorectomy are critical.

There is no effective screening test or combination of tests for ovarian cancer.[15] Screening tests currently in use include serum, gynecologic exams, CA-125, and transvaginal ultrasound. Even when used together, the sensitivity, specificity, and positive predictive value are inadequate to warrant their use in the general population. NCI's PLCO trial is currently evaluating the combination of transvaginal ultrasound and CA-125 screening for ovarian cancer. Other strategies should be evaluated.

A recent study showed that only 14 percent of women with early-stage ovarian cancer received the recommended surgical staging and treatment. In 40 percent of cases reviewed, no pathologic grade was assigned to the cancers removed.

Women should be informed of the need to have doctors with the appropriate expertise in gynecologic cancer surgery and pathology available at the time of their surgery. In patients with advanced disease, optimal surgical debulking followed by appropriate paclitaxel and platinum-based chemotherapy prolongs survival. More effective adjuvant therapy is required. Intraperitoneal therapy, immunotherapy, radiotherapy, and high-dose chemotherapy with hematologic support are current research strategies. The current Phase III trial of high-dose chemotherapy versus standard consolidation therapy should be promoted. New regimens for women with recurrent or persistent ovarian cancer should be constructed and evaluated with survival and quality of life as the major end points.

Colorectal Cancer

In 1997, an estimated 65,900 women will be diagnosed with cancer of the colon or rectum and 24,300 will die of the disease. Familial adenomatous polyposis coli and familial non-polyposis colon cancer (Lynch II) are the most common familial syndromes. Since the Hunt Valley conference, multiple genetic loci for these syndromes have been identified.

Factors decreasing colon cancer risk include exercise; a low-calorie, low-fat, high-fiber diet; estrogen replacement therapy; aspirin; and nonsteroidal anti-inflammatory agents. Prospective, randomized prevention trials should evaluate these and other agents.

Keys to early detection include an annual digital rectal examination after age 40, and yearly stool tests for occult blood and a baseline sigmoidoscopy after age 50. The role of screening colonoscopy remains controversial. A more accurate screening method than fecal screening for occult blood is needed. Imaging techniques which could augment or replace signoidoscopy/colonoscopy merit study. Recent studies have shown that women are not being screened for colon cancer. Secondary prevention efforts must include evaluation of new strategies to educate both women and their physicians about the benefits of screening for colon cancer.

Many treatment-related questions remain unanswered. The current intergroup phase III trial is evaluating minimal access surgery in early colon cancer. After primary surgery in patients with Stage 3 colon cancer, the combination of 5FU and leucovorin is effective in reducing recurrences and death from colon cancer; 6 months of therapy rather than 12 months appears adequate. Since Hunt Valley, several new drugs have demonstrated activity in colon cancer. New agents and combinations need to be evaluated to improve adjuvant therapy. Local approaches such as cryotherapy should be evaluated for women with colon cancer metastatic to the liver.

Neoadjuvant chemoradiation has been effective in preserving normal rectal sphincter function in patients with rectal cancer. Improvements in chemotherapy and radiation therapy may improve long-term survival in patients with locally advanced rectal cancer.

RESEARCH RECOMMENDATIONS

- While a major recent focus in cancer research has been on genetic factors in carcinogenesis, the federal research portfolio should be balanced with substantial funding for epidemiology, prevention, screening, treatment, and quality of life as well as other aspects of molecular and tumor biology.
- Research on genetic factors in familial cancer has produced new commercially available tests, which may allow individuals from affected families to assess their personal risk. The social, ethical, legal, and economic effects of the availability of these tests must continue to be carefully studied.
- Research on how to communicate risks and how to encourage health-promoting behavior remains a high priority. Communicating the risks of smoking and preventing the initiation of smoking by children and adolescents remains our only effective strategy in lung cancer. We need to communicate the risks of early sexual activity, and of multiple sexual partners (or of sexual partners who have had multiple partners), and to encourage appropriate behavioral changes to decrease the transmission of human papilloma virus, HIV, and thus the risk of cervical cancer, and HIV-associated lymphoma and Kaposi's sarcoma.
- Emerging patterns in tumor incidence, such as the increased incidence of pancreatic cancers, melanoma, and brain tumors, as well as of adenocarcinomas of the lung, esophagus, and cervix, may define new etiology factors.

- The ethical and legal implications of research on tissues stored in repositories must be carefully assessed, particularly involving issues of consent and confidentiality.

- Epidemiologic studies need to evaluate the interaction between genetic factors and environmental and endogenous carcinogens in cancer causation.

- Managed care has transformed the delivery and economics of health care, increasing stresses on academic medical centers and hampering education, research, and sometimes patient care. Access of all Americans to optimal cancer treatment and representation of women and minorities in clinical trials are high priorities. Barriers to participation in cancer screening and prevention programs, and access to appropriate specialists, clinical trials, and treatment in cancer centers, are unethical and shortsighted.

- Forty-one million U.S. citizens are without health insurance. Many more are inadequately insured. Uninsured individuals often do not have access to prevention or screening programs. Therefore, precancerous lesions and early cancers may go undiagnosed and untreated. They may finally seek medical care when treatment is no longer effective. The medical research community must work with policy makers to ensure that adequate access to health care is viewed as a basic human right and that health promotion becomes part of the activities of daily living.

- To facilitate evidence-based medical practice, we must support coordination of information and research results on clinical trials.

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RESEARCH DESIGNS: MULTIDISCIPLINARY PERSPECTIVES

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How can synergy between scientific disciplines be achieved through a multidisciplinary perspective that incorporates biomedical, psychosocial, and socioeconomic approaches to women's health research?

Research aimed ultimately at improving the health of women and subpopulations of women across the life span focuses on a broad spectrum of factors. Investigations may examine basic, molecular, genetic, immunologic, and other mechanisms in the etiology and pathogenesis of disease, thus contributing to the biomedical knowledge base or to the development of innovative therapies. At the same time, psychosocial research seeks to improve understanding of the cultural, lifestyle, personality, cognitive, affective, motivational, social support, and other factors associated with women's decisions to adopt or maintain healthy behaviors, or seek health care services. In addition, socioeconomic research seeks to better understand the effects of such variables as employment status and income on women's health.

Much of the research on women's health conducted in the past, and even today, addresses questions from a specific, singular perspective rather than from a range of biomedical, psychosocial, and socioeconomic points of view. Research projects involving investigators from multiple disciplines are not usually the norm. However, as available research dollars shrink, innovative integration of expertise from various disciplines may become an increasingly important strategy for maximizing funding potential. During the past several years, a growing number of funding opportunities, made available through the National Institutes of Health (NIH), have specifically encouraged or called for multidisciplinary research teams.

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

Despite the desire to encourage multidisciplinary research on women's health issues, there continue to be barriers to conducting this type of research. For example, academic systems typically have fewer means of rewarding or recognizing multidisciplinary efforts. Furthermore, there are still few funding mechanisms that focus on multidisciplinary research. Also important is the fact that researchers have limited firsthand experience or training in building and working as part of multidisciplinary teams. This inexperience is sometimes also reflected in the evaluation of study sections. Clearly, some changes within NIH and academic institutions are required if synergy between disciplines is to be achieved. Overarching issues and specific recommendations that would encourage multidisciplinary research on women's health are discussed below.

THE STRUCTURE OF NIH FUNDING SHOULD ENCOURAGE MULTIDISCIPLINARY RESEARCH

Women's health provides a unique, crosscutting research realm in that it is multidisciplinary by definition, offering important opportunities for simultaneous study of biomedical, psychosocial, and socioeconomic variables. While opportunities for multidisciplinary research with NIH funding do exist and are expanding, further progress in this area should be encouraged. In addition, coordination among NIH institutes and centers (ICs) should be heightened in support of multidisciplinary research activities, and NIH communication about these opportunities should be enhanced. The following recommendations are proposed in support of these goals.

Identify Multi-institute Issues

Issues that cut across research disciplines and across the missions of the NIH ICs should be identified, and funding for multidisciplinary research should be made more readily available.

Encourage Inter- and Intra-institute Multidisciplinary Research

NIH should encourage the promotion and development of multidisciplinary research, both within individual ICs and across ICs. Program offices within the Office of the NIH Director and directors of individual ICs can play a vital role in stimulating crosscutting research by promoting research policies and funding in support of mechanisms for multidisciplinary research. The Office of Research on Women's Health (ORWH), the NIH Office on Minority Health, and NIH Office of Behavioral and Social Sciences Research are already engaged in working closely with all of the NIH ICs to enhance their respective portfolios in behavioral and social sciences research and to identify research opportunities that foster trans-NIH collaborations.

Use RFA/RFP Mechanisms To Support Multidisciplinary Research

Despite philosophical support, NIH-funded multidisciplinary research will not be enhanced unless funding mechanisms are made available for such research. Requests for application (RFA) and requests for proposals (RFP) should be developed that specifically seek multidisciplinary women's health-related investigations. Furthermore, the time lines for application submissions must take into account the complexities of developing collaborations among researchers from different backgrounds and perspectives.

Establish ORWH as a Broker

NIH ORWH is in a unique position to function as a "broker" and advocate for funding multidisciplinary women's health research across NIH ICs. This broker/advocate role would be in keeping with ORWH's mandate "to strengthen and enhance research related to diseases, disorders, and conditions that affect women and to ensure that research conducted and supported by NIH adequately addresses issues regarding women's health." By taking a leadership role, ORWH could provide a pivotal point for communication among the ICs regarding multidisciplinary research on women's health and could proactively develop multidisciplinary research opportunities. In addition, ORWH could serve as a resource for investigators wishing to explore or develop linkages with other investigators and research programs concerned with similar research topics.

ORWH Funding Priorities Should Explicitly Encourage Multidisciplinary Research

Today, ORWH vigorously implements its mandate to strengthen and enhance research on women's health, in part by providing co-funding to ongoing NIH grants and special initiatives that have gender-specific research objectives. In planning for the 21st century, ORWH should identify as a priority, research that cuts across disciplines, and then should emphasize co-funding of investigations that cut across biomedical, psychosocial, and sociocultural perspectives.

Establish Multidisciplinary Coordinating Groups

Communication across NIH ICs and within the extramural research community is vital to increasing opportunities for multidisciplinary research and to building multidisciplinary teams of investigators. Coordinating groups, committees, and task forces comprising program-level IC staff with common interests should be established to identify shared goals and act upon priority women's health research areas. For example, the Coordinating Committee on Research on Women's Health, coordinated by ORWH, brings together representatives of NIH ICs to discuss directions for research on women's health and provide direction to the ORWH director. Similar groups could be established to discuss multidisciplinary research addressing specific disease topics that affect women, such as HIV/AIDS, autoimmune diseases, or heart disease.

Convene Multidisciplinary Conferences

Conferences, workshops, and symposia should be convened to discuss research topics on women's health from multidisciplinary perspectives. Such meetings are important in examining current knowledge, as well as theoretical and methodological issues. The Women's Health Seminar Series, sponsored annually by ORWH, serves as a model for such conferences, with topics addressing such issues as genetic testing, hormone replacement therapy, breast cancer, and domestic violence. The series is planned and implemented in conjunction with the NIH Coordinating Committee on Research on Women's Health, ensuring that numerous perspectives are addressed.

Create Core Centers

The funding of "core centers" for research on women's health could be a method to encourage close cooperation, communication, and collaboration among investigators with similar interests who are conducting individual research projects. The core center serves as an identifiable organizational focal point within a single university medical center or among a consortium of cooperating institutions. This concept fosters interdisciplinary cooperation and the sharing of resources, such as instrumentation or assays, thus enabling more efficient and productive work. Core centers for research on women's health would not supplant investigator capabilities but would enhance investigators' opportunities to learn and advance. Core centers may also provide funding for seminars, visiting scientists, or other program-enrichment activities.

MULTIDISCIPLINARY RESEARCH SHOULD BE REWARDED WITHIN ACADEMIC INSTITUTIONS

NIH and academic institutions should collaborate to increase the amount of multidisciplinary research conducted on women's health issues. Institutions should provide both philosophical support and advancement opportunities for those who build bridges across biomedical, psychosocial, and socioeconomic research domains. In addition, academic structure should follow, not dictate, research needs. Matrices that match the multidisciplinary interests and expertise of individual faculty members provide one model for encouraging crosscutting research within academic institutions. The following recommendations may assist institutions and faculty members in shifting toward a new way of thinking.

Encourage Promotion Criteria that Stimulate Multidisciplinary Research

Professional advancement in academic settings today generally hinges on success in one's discipline. However, especially as federal research resources constrict, the academic environment should not discourage but should reward faculty investigators who seek out and develop multidisciplinary research programs. Promotion criteria should incorporate faculty members' initiative and success in this regard.

Encourage Scientists to Learn How to "Package" Multidisciplinary Careers

If efforts related to research on women's health are to be successful, investigators need to increase their willingness to cross academic and disciplinary boundaries. Individual investigators need to learn to channel their research to fit current models and should draw on their multidisciplinary research abilities in developing their careers.

Encourage NIH-funding Mechanisms that Support Multidisciplinary Research and Training at Academic Institutions

Academic institutions are more likely to encourage multidisciplinary research on women's health if NIH supports such research. Therefore, NIH-funding mechanisms should encourage multidisciplinary research and investigator training. Furthermore, NIH training and career development grants should also emphasize the importance of applications proposing multidisciplinary work.

TRAINING SHOULD BE MULTIDISCIPLINARY

The environment in which researchers are trained is critical in influencing and is often a determining factor in the professional directions and interests of scientists. In the past, students of medicine, nursing, and other professional disciplines participated in core courses together, providing opportunities to share ideas and develop an awareness of varied perspectives. Today, the academic environment may often segregate the disciplines, thereby creating barriers to the cross-pollination of ideas. In addition, NIH research training and career development programs tend to be discipline specific and organ specific. Training mechanisms, some believe, are equal to or more important than funding mechanisms in determining the amount of multidisciplinary research that is conducted. The following steps are recommended to enhance the integration of disciplines during the crucial training years of scientists, as well as during the course of their research careers.

Establish Multidisciplinary Training Programs

First, there is a need to establish or reestablish professional training programs that require or encourage cross-disciplinary study. Such programs would shift the learning process away from professional separatism and toward broad-based learning. Cross-disciplinary study would encourage students to consider the spectrum of biomedical, psychosocial, and socioeconomic concerns that may interact to affect women's health.

Publicize Effective Individual and Institutional Role Models

Individuals and academic institutions that serve as exceptionally effective models for multidisciplinary training in the field of research on women's health should be recognized and publicized. Information about model training initiatives that cross disciplinary and departmental boundaries within medicine and other disciplines should be disseminated widely through professional meetings, journals, professional organization publications, the Internet, and other print and electronic media.

Publish and Publicize the Process of Putting Together Multidisciplinary Teams

The process of building successful multidisciplinary teams for research on women's health should be documented and disseminated to encourage and teach others to follow suit. Only through the sharing of ideas about the team development process will these programs effectively serve as models. Information should be disseminated widely at professional meetings, in journals and the publications of professional organizations, on the Internet, and in other print and electronic media.

Recognize Mentors

Mentors play a vital role in the career development of professionals in any field. This role is even more crucial in the relatively new field of women's health. Mentors who successfully build collaborative teams and are involved in multidisciplinary training and research efforts should be recognized and rewarded.

Encourage and Provide Funding Mechanisms for Continuing Education in Fields Other Than One's Area of Primary Expertise

Scientists wishing to pursue research careers in women's health that traverse scientific and disciplinary boundaries must possess a practical understanding of the concerns, science, and methodologies of fields other than their own. Continuing education provides a formal means of developing this understanding, although funding mechanisms are needed to encourage and support researchers who wish to maximize their capabilities in conducting multidisciplinary research. NIH training and career development grants specifically designed for researchers wishing to study outside of their traditional disciplinary realms may be one mechanism to provide such support.

Encourage NIH Institutes To Fund Multidisciplinary Training

To maintain a cadre of well-trained investigators in research on women's health, NIH ICs should be encouraged to fund research training and career development efforts that go beyond specific disciplines. Investigators-in-training, with interests in crosscutting research, should be considered for support through National Research Service Awards, whether individual or institutional, career development awards, and fellowships.

Develop Inter-institute Review Processes and Funding for Training Awards

The process of reviewing and funding applications for research training and career development often fosters single-discipline and single-organ system approaches. If investigators-in-training in the field of women's health are to develop interests in multidisciplinary work, then application review policies and procedures should ensure review by appropriate multidisciplinary review groups that are also representative of multiple NIH ICs.

MULTIDISCIPLINARY RESEARCH PROPOSALS ARE OFTEN REVIEWED BY SINGLE-DISCIPLINE INDIVIDUALS

There has been a noticeable increase in the number of NIH funding opportunities that invite or require multidisciplinary research. However, there is also a belief within the research community that application review committees evaluate applications for multidisciplinary projects from single-discipline perspectives and represent the review committee's purview. Anecdotal accounts indicate that, in some instances, there has been a lack of understanding on the part of reviewers that multidisciplinary projects can truly represent high-quality science, especially if the projects are innovative and methodologically sound. Therefore, the NIH review committee structure should be examined for its ability to ensure that multidisciplinary research applications are evaluated by individuals who possess a clear understanding of the disciplines and concerns involved in multidisciplinary research projects. This issue may be addressed through the following recommendations.

Expand Use of Ad Hoc Reviewers on Standing Committees

For most applications, the initial or first level of review involves panels of experts established according to scientific disciplines or medical specialty areas. The function of these scientific peer review groups is to evaluate the scientific merit of grant applications. Expanding the use of ad hoc reviewers who represent the behavioral and social disciplines on these standing research review committees would help to ensure that high-quality, multidisciplinary research projects on women's health are evaluated appropriately.

Use Ad Hoc Review Committees

Ad hoc review committees should also be considered for the review of multidisciplinary grant applications. Such committees would comprise representatives of multiple disciplines that cut across the biomedical, behavioral, and social sciences, depending on the application topic.

Solicit Reviewers with Appropriate Multidisciplinary Expertise

Selection of reviewers sitting on scientific peer review groups is based in part on their expertise, experience, and knowledge of specific disciplines. Individuals with multidisciplinary expertise should be identified and made known to those scientific review administrators who determine the composition of review committees.

Inform Applicants of How To Use Existing Review Structures

NIH grant applicants must learn as much about the grant application and review process as possible. Increased communication with applicants regarding the existing review structures could be accomplished through the NIH Division of Research Grants home page or by other means.

Identify and Publicize Successful Models

Research review committee structures that serve as successful models for the review of multidisciplinary grant applications should be identified and their successes publicized so that they might be emulated within the NIH review structure.

RACIAL, ETHNIC, AND CULTURAL DIVERSITY IN CLINICAL RESEARCH

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BACKGROUND

American women come from and continue to live in diverse racial, ethnic, cultural, and socioeconomic backgrounds. A growing number belong to groups commonly referred to as minorities — African American, American Indian, Alaskan Native, Asian, Pacific Islander, and Hispanic. To a large extent, a woman's health status may depend on the group or subgroup to which she belongs, as is apparent in the following statistics:

- In 1993, life expectancy at birth was 79.5 years for white women and 73.7 years for black women.[1]

- In every year from 1970 to 1993, heart disease was the leading cause of death for all women living in the United States. However, between 1970 and 1980 the age-adjusted death rate for heart disease was about 50 percent higher for black women than for white women. Between 1980 and 1993, the heart disease mortality differential between white and black women widened to 67 percent, due to a more rapid decline in heart disease death rates for white women (26 percent) than for black women (18 percent).[2]

- In 1993, the age-adjusted death rate from heart disease was 24 percent lower for American Indian and Alaskan Native women and 43 percent lower for Asian and Pacific Islander women than for white women (99.3 per 100,000), and the rate was 29 percent lower for Hispanic women than for non-Hispanic white women.[3]

- In 1993, black women were 28 percent more likely to die of breast cancer than were white women.[4]

- Since 1973, the age-adjusted incidence rate for ovarian cancer, the most common female reproductive malignancy after breast cancer, has been more than 50 percent higher among white women than among black women.[5]

- Most of the women diagnosed with AIDS during the 12 months ending June 30, 1995, were black or Hispanic women (59 and 17 percent, respectively).[6]

- Between 1988 and 1991, the age-adjusted prevalence of hypertension was higher for non-Hispanic black women (31 percent) than for non-Hispanic white women (21 percent) or Mexican-American women (22 percent).[7]

- Between 1988 and 1991, being overweight was more common among women whose family incomes were below the poverty line than among those with higher incomes. Among all women 20 years of age and over, the age-adjusted prevalence of overweight was 47 percent for women below the poverty line and 32 percent for those at or above the poverty level.[8]

- In 1992-93, women were 6.6 times as likely as men to experience violent crimes by a spouse, ex-spouse, or partner. However, the rate of violent attacks by intimates among women in families with annual incomes of less than $10,000 was 19.9 per

1,000 women, compared with 4.5 per 1,000 women among those with annual incomes of $50,000 or more.[9]

- In 1993, women below the poverty line were 3.2 times as likely to be uninsured as women above the poverty line (36 and 11 percent, respectively).[10]
- In 1993, women who lived below the poverty line were 57 percent more likely to lack a regular source of medical care than women whose family income was at or above the poverty line (16 and 10 percent, age adjusted). [11]
- For women admitted to substance abuse treatment in 1993, the type of substance abuse correlated with race and ethnicity. Alcohol, and alcohol combined with another drug, were the primary substances of abuse among non-Hispanic white women, while cocaine was the predominant substance of abuse among non-Hispanic black women, and heroin among Hispanic women.[12]

Despite these and other statistics that clearly indicate the disparities in health status among various subpopulations of women, clinical research that has included women at all has focused on white, middle-class, heterosexual, able-bodied women. This focus on the majority group retards the advance of biomedical information about minority groups, who make up over 25 percent of the population in the United States (see Table 1), and who are different not only in biological factors but also in cultural and behavioral factors that are associated with health. The percentage of minority groups in the population is increasing, and the disparity between the health status of the majority group and that of minority groups is widening.[13]

TABLE 1 Detailed Race and Hispanic Origin of U.S. Women 1980 and 1990-1993 *(Numbers in Thousands)*

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

Source: National Center for Health Statistics. 1996. *Health, United States, 1995.* Hyattsville, MD: Public Health Service.

To develop the knowledge base that will yield benefits for minority women, enabling them to access the remarkable advances in medicine and health care, population diversity must be ensured in all aspects of research, including training minority researchers, awarding grants for research that includes diverse populations, designing research models to evaluate the differences among population groups, retaining study participants from diverse populations, and publishing results so that the appropriate caretakers have access to the information.

The study of the health problems in diverse subgroups could also increase the knowledge base about how to prevent and survive disease, with applications for the entire population. Research models that study the assets on resiliencies of specific groups and individuals might reveal the adaptive mechanisms that make them healthy despite adverse environments. For example, the study of heart disease among Asian-American women, who have a much lower incidence of heart disease than women from any other racial or ethnic group, might provide insight into the resiliency factors and behaviors that protect from heart disease. An examination of beneficial dietary or exercise patterns might suggest preventive strategies for all women.

NIH Guidelines on Inclusion of Women and Minorities in Clinical Studies

In the past 5 years, the National Institutes of Health (NIH) has taken several steps to increase the participation of women from minorities in clinical studies. Most notably, early in 1994, the agency published its *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*, which require that researchers receiving NIH support include women and members of minority groups and their subpopulations, when appropriate, in biomedical and behavioral research projects involving human subjects.[14] NIH issued these guidelines in response to the NIH Revitalization Act of 1993 (P.L. 103-43), which directed that "the Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in projects of clinical research." The goal of this requirement is to increase the opportunities for obtaining critically important information with which to enhance health and treat disease among all Americans, and to detect and account for significant differences between genders or racial and ethnic groups where they exist.

The guidelines also strengthened the previous policies published in the *NIH Guide for Grants and Contracts, 1990,* which required that NIH staff and peer advisory groups "ensure that applications/proposals for extramural support for clinical research studies involving human subjects include appropriate representation of women and minorities, unless a compelling justification is made for their exclusion or inadequate representation."[15] The guidelines required NIH to take three additional actions: (1) ensure that women and minorities and their subpopulations are included in phase III clinical trials in a way that differences in intervention effect can be analyzed, (2) reject cost as an acceptable reason for excluding these groups, and (3) initiate programs and support for outreach efforts to recruit these groups into clinical studies.

Ethical Issues for Institutions and IRBs to Consider

The importance of including women and minority groups in health research must be balanced against the right of individuals to refuse to participate in research. To facilitate that process, in 1994, NIH's Office of Protection from Research Risks issued a report outlining the responsibilities of institutions and institutional review boards (IRBs) that are responsible for protecting the rights of study participants in their consideration of ethical issues surrounding the inclusion of women and minorities in research.[16] The report lists seven key responsibilities:

1. To provide investigators with written guidance clearly delineating expectations for inclusion of both genders and minorities in the design and conduct of research.

2. To specify that, when scientifically appropriate, investigators show how the research will address any difference in the way a health situation or intervention in the proposed research may affect one gender or minority group. Investigators should be prepared to describe the extent to which both genders and minority groups have been involved in similar research.

3. To review the extent to which investigators are collaborating with researchers at other institutions to ensure representation and sufficient involvement of participants of both genders from the various minority groups. The review of such information is particularly important in phase III clinical trials.

4. To consider whether cash or material reimbursements are appropriate to the educational level and socioeconomic status of the study participants and to ensure that these reimbursements do not promote coercion or undue influence to participate or remain in the study.

5. To ensure that consent documents have been translated appropriately or that translators are available when the study participants include speakers of foreign languages or those who are illiterate.

6. To include women and members of minority groups on the IRB, especially if the nature and volume of the research to be conducted at the institution routinely includes these populations. IRBs should also consider consulting ad hoc advisors who could help with understanding the perspectives of various groups. Also, institutions and IRBs can encourage investigators to seek out

such perspectives during the planning of research protocols.

7. To require that NIH-supported investigators specify the gender and racial or ethnic composition of the subject population, as well as their criteria for including or excluding any subpopulation, or to provide a clear rationale for excluding such information from the background data for the protocol.

Training of Minority Researchers

The diverse views that women and minorities could bring to bear on the research agenda have been significantly absent. Diverse populations pose diverse and challenging issues that can be better researched and understood only by a creative variety of research approaches. Researchers who are homogenous in culture and experience are less likely to generate rich and varied research concepts than researchers who are diverse. Many people believe that clinical research to date has focused on the health status of white men because most investigators are themselves white men. One of the best ways to improve the quality and quantity of research and alter its focus is to increase the number of women and minority investigators. An additional advantage to cultural diversity among researchers is the enhanced effectiveness of recruiting the participation of women from minority communities.

Since 1989, NIH has encouraged the training of minority researchers through such programs as its Minority Research Supplement Program, which provides supplements to minority high school and college students, graduate research assistants, individuals in postdoctoral training, and investigators. In fiscal year 1990, NIH provided minority supplements to 376 members of ethnic groups: black (226), Hispanic (114), Native American (20), Pacific Islander (10), and unknown (6).[17]

Collaborative programs between majority and minority institutions can provide important training opportunities for the students at both institutions. A program established between Tulane University and Xavier University, a black university in New Orleans, provides a model for other institutions who want to increase the number of minority investigators. The two universities have established the Center for Bioenvironmental Research (CBR), which investigates the causes and effects of environmental problems and devises practical solutions for them.[18] One way in which the CBR fosters training for minority researchers is by offering fellowships to minority students of outstanding academic achievement and scholarly promise who have been formally admitted to a Ph.D. program and whose research topic is environmentally related. For the academic year 1996-1997, two minority women were among the six recipients of fellowships. Both women are graduate students in the molecular and cellular biology program. One will study the identification of phytosterols that have anti-estrogenic activity in breast and endometrial cancers. The second will investigate mechanisms of lung injury induced by environmental agents such as air pollutants and allergens.[19] The CBR also provides opportunities for investigators to work with minority communities. For example, CBR members provide an ongoing occupational health research and advisory function for the Southern Louisiana Industry Council, placing special emphasis on minority health. CBR's Coping with Community Stressors Program examines minority community responses to environmental risks, and the Environmental Justice Partnership Project addresses the environmental research, education, and outreach needs of community groups along the Mississippi River chemical corridor. Also, in cooperation with the U.S. Department of Housing and Urban Development, CBR members are working with residents of a public housing community in New Orleans to identify and act on environmental health issues.

Designing the Study To Include Minority Women

In planning clinical research, the NIH guidelines encourage investigators to first consider whether their scientific questions or hypotheses make the inclusion of minority women in the study appropriate. Investigators may limit the population to women from a single minority group if their scientific questions or hypotheses apply to majority women as well, and if the condition to be studied is more severe or prevalent among a particular group of minority women than among majority women, or if less is known about the disease or treatment in minority women than in majority women.

For an NIH-defined phase III clinical trial, the investigator should determine whether important minority differences are to be expected in the intervention effect. (NIH defines a phase III clinical trial as a broad-based clinical investigation to evaluate an experimental intervention in comparison with a standard or control intervention or to compare two or more existing treatments.) If so, the investigator should design the trial so that the intervention effect can be tested for minorities or their subpopulations.

Understanding the Study Population

To obtain valid data, researchers must clearly define the populations they are studying. Countries of origin, immigration status, level of acculturation, socioeconomic status, and cultural and linguistic characteristics vary widely. A cultural or racial label for a minority group may fail to reflect the heterogeneity of individuals or groups to which the label is applied. For example, the label “Southeast Asian” refers to Philippine, Hmong, Laotian, Vietnamese, and Cambodian peoples, and the term “Native Americans” is used to describe more than 500 federally recognized tribes. Similarly, “Hispanic/Latino” populations include Mexicans, Puerto Ricans, Cubans, and other Central and South Americans whose ethnic origins and racial characteristics are varied. Yet, health studies on “Hispanics” commonly include a larger number of Mexican Americans (who constitute almost 65 percent of the Hispanic population in the United States) than members of any other Hispanic subpopulation. Generalizations based on data from these participants may be valid for Mexican Americans, but invalid for Hispanics of other origins.

An understanding of cultural and linguistic differences is essential to ensuring that methods used in screening and interviewing are culturally sensitive. For example, the Hmong have views regarding blood that prohibit its sampling. Some groups take offense at questions about sexual issues. One recent recruitment effort among black women students at Howard University failed because the women thought that the questions about sexual behavior were inappropriate, and they simply refused to answer them. In addition, important linguistic differences often exist among speakers of the same language who come from different countries; an inoffensive word for an Puerto Rican, for example, may be an obscenity for a Mexican.

Collaboration with the Community

Successful research efforts in minority communities depend on collaboration with members of the community at every phase of the research. Community leaders and other residents, as well as the study participants themselves, should be involved in setting research goals, designing appropriate methods for informing the target population about the planned research, determining appropriate instruments for collecting data, and evaluating outcomes.

A major barrier to recruitment in many minority communities might be distrust of scientific researchers because of historical incidents of abuses of research by outside organizations and researchers, or because they may feel that the researchers have been insensitive to the health concerns of their community. Therefore, enlisting the support of community leaders may be essential to gaining access to a community. Researchers who meet with community leaders to define the health or disease problems they want to study and to explain the benefits and risks of the research are likely to find that the leaders are eager to provide a perspective on the cultural, behavioral, social, and economic factors that may contribute to or interfere with the research protocol. The community leaders can also help researchers form networks with other community organizations that will facilitate development and acceptance of the planned research.

Collaboration with religious leaders has been found to be especially useful for several reasons. First, churches are usually interested in participating in primary prevention efforts, operating health care and wellness programs of their own. Also, since churches serve as natural community centers, establishing the church as the place of contact between researchers and participants partially eliminates the transportation problems that constitute a barrier to participation in studies. Furthermore, churches tend to involve entire families. The importance of the family among many minority groups makes the inclusion of the individual's family desirable in dealing with the individual's health problems. For example, smoking cessation research shows that Latino men are more likely to stop smoking if they are encouraged to do so to benefit their wives and children. In the African-American community, too, a health care project is always a family project.

Ministers and other community leaders may also be able to help researchers gain access to those populations who can most benefit from the research effort, such as those minority women who never use the health care system or who use it only at times of crisis. Too often, researchers in minority communities have had to select their samples from the people who have access to health care, simply because they had no access to those who most needed health care.

Community leaders and other members can also help define the problem to be studied, ensuring that the priorities of the researchers pose no conflict with those of the participants. For example, a community concerned with alcoholism, drug abuse, and AIDS may have little interest in participating in a study on dietary cholesterol.

Recruitment and retention efforts are much more likely to be successful if the recruiters are local residents of the same race and ethnicity as the defined study population. At one west Philadelphia clinic, for example, nurse practitioners are collaborating with the principal investigators from the university in a highly successful weight loss program for black women. Also, a study on how to reduce prenatal transmission of AIDS in southeastern Pennsylvania is using HIV-positive women as part of the investigative team. The researchers trained the women in how to gather data through personal interviews and telephone conversations. As a result, the women have a sense of accomplishment, and the project has reported a tenfold improvement in access to information.

Local residents may also have better insight into the problems that are causing participants to drop out of a study. For example, researchers assume that low retention is the result of child care and transportation problems, only to find out that the real reasons are quite different. Community residents may be able to suggest ways to retain participants in the study, such as by setting up a network relationship among the participants so that they will remind each other to visit the clinic at the appointed time.

Giving Back to the Community

Researchers in minority communities have a moral obligation to give something back — whether that return be health care, education and training, or even employment. Several institutions have established programs that can serve as models for a reciprocal relationship between researchers and the communities in which they work:

- The Emory School of Nursing has opened clinics in what are called "undeveloped" poor neighborhoods.
- At the University of Wisconsin, professors from the School of Nursing and health professionals donate their time on evenings and weekends to a community center. They also do intensive community education. In return, they ask the community to participate in their research projects.
- In setting up the Navajo Research Program in early 1996, an institutional review board was first established to ensure that researchers would benefit the health of the Navajo people. The board asks researchers to (1) provide educational materials to help the people or the Navajo service providers, (2) train the Navajo staff in existing health care

facilities and programs, and (3) return to the reservation when the research is completed to explain the results of their studies in layman's terms and to explain the significance of those studies for the Navajo people.

Publication of Research Results and Experiences

Published research data should show results by gender and minority group status. In spite of the general recognition of the importance of including minority women as study participants, journals still frequently publish studies that give no information on the race or ethnicity of the populations studied. For example, a recent survey of all the articles published in the *New England Journal of Medicine* in 1995 revealed that 80 percent of the articles gave no information on the race/ethnicity of the populations studied.

Biomedical science would also benefit from increased reporting of research outcomes, successful and unsuccessful, involving minority groups. Although many research institutions have developed excellent relationships with minority communities, they have not published these experiences, which would be useful to other investigators.

Social, Cultural, and Psychological Issues

Clinical research is needed that takes into account the social, cultural, and psychological issues relevant to health, especially in the study of health problems of minority women. More studies are needed on the ways that the cultural and social environments of minority women, and their perceptions of these environments, influence their health and quality of life. Working member felt that progress in minority health research depends on developing and applying research models that integrate quantitative and qualitative methods to study the social, economic, and biomedical determinants of health. A holistic approach that overcomes the false dichotomy between body and mind is needed. In that vein, a study of black working class women and black professional men, conducted by epidemiologists at the Harvard School of Public Health and the Kaiser Foundation Research Institute, found a link between hypertension and race, gender, and socioeconomic class, and between hypertension and the way in which an individual reacts to the perceived discrimination.[20] More research of this type is needed to understand how the variables of race, class, and gender affect health.

RECOMMENDATIONS

The Working Group on Racial, Ethnic, and Cultural Diversity recommended the following ways in which NIH can more effectively involve and benefit diverse communities of women in research projects:

- Give peer review groups strict criteria to follow in reviewing grant applications and proposals, specifying requirements as to gender, race, and ethnicity of study participants.
- Diversify peer review groups, ensuring that they include women and minorities.
- Encourage collaborative research with minority institutions, states, and communities.
- Award more grants to minority women investigators.
- Examine the cultural and financial barriers to the participation of low-income populations in research.
- Increase the number of supplemental awards to minority students.
- Meet with journal editors to encourage them to require that clinical studies report data classified by race and ethnicity.
- Encourage researchers to publish their experiences, successful and unsuccessful, in working with minority populations.
- Establish a clearinghouse for the publication of research experiences with minority populations.
- Relax guidelines for inclusion in studies so that potential participants are not excluded from studies

because they have some disease or condition that makes them ineligible to participate.

- Encourage a more comprehensive approach to the study of health problems of minority women than the traditional medical model allows.
- Encourage the development of research models that study population assets and resiliencies that prevent disease and promote survival.

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

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

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RESEARCH DESIGNS: GENDER

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BACKGROUND

With the founding of the Office of Research on Women's Health and the enacting of the mandate that women and minorities be included in clinical studies, the National Institutes of Health (NIH) has responded to the issues raised about gender in medical research. The Food and Drug Administration (FDA) has echoed this concern about gender in medical research by changing its policy on the study and evaluation of drugs in women. These policy changes by NIH and FDA reflect the growing concern for women's health, and have also opened the door to other issues regarding clinical studies, gender differences, and new approaches to medical studies.

CLINICAL STUDIES

Designing Clinical Studies

NIH guidelines are still evolving; many in the medical community view them as a starting point in the discussion of gender and clinical studies. For example, the issues mentioned by the working group included the implications of the semantics of the NIH guidelines on "inclusion" of women and minorities in clinical studies. That women and minorities should be included suggests that it is appropriate to design a study with men as the major focus as long as women are included. This concept should be addressed more clearly to promote studies that are initially designed for women or minorities. The point is not to merely increase the number of women in clinical trials, or even how to determine if they are eligible for trials, but rather what is being studied, the nature of how the experimental groups are being determined, and how drugs and devices are being tested. The design of the research study must derive from the questions being asked. Designs will differ for the questions being asked, for example, whether there is a difference between men and women in response to a drug and whether the drug works in women. Even when women are included in clinical trials, the data may be aggregated in such a way that investigators analyze the data overall and not by sex.

Many researchers have noted that politics can prevent or hinder the study of sexual differences in clinical trials. For example, until recently, it was difficult to publish a paper with the words "sex differences." The paucity of studies on neuroendocrine aspects of female functions may be attributable to a belief that it was not politically correct to acknowledge different functioning at different times of the month or to a fear of discrimination based on the differences.

Socioeconomic factors applicable to women can complicate research design. Socioeconomic differences cannot be measured in the same way in men and women because there are no good gender neutral measures of socioeconomic status. Three basic measures of socioeconomic status are income, occupation, and education. These factors tend to correlate better in men than in women. Women can be highly educated and have a low household income, and be in a pink-collar job.

Finally, there is a lack of studies on healthy people, an area for which research designs must be unique to healthy women. For example, the effects of the menstrual cycle on drugs and other therapies should be analyzed in clinical trials.

Although incorporating women into the designs of clinical studies may create logistical issues, it may result in new areas of research, innovative research designs, and cost-effective options. A well-designed and well-conducted study involving women and minorities can provide information about treatment and care of direct benefit to men and women alike. In addition, results from such studies can enable policymakers to make decisions that will improve the overall health of the nation.

Balancing Research Cost While Asking Clinically Significant Questions

Adding gender issues to a biomedical study can considerably increase study costs, at a time when pharmaceutical companies and grant agencies are cutting costs. "All of our costs in industry have been cut, are being cut, and will be cut in the future. What this means is that any increase in cost in any area of drug development will be carefully considered."[1] Although the inclusion of women as research subjects may initially cost more, the savings will be realized in the longer term. Excluding women from trials would result in inadequate data, which could lead to inappropriate treatment, added risks for women, and increased costs to society.

How can costs in clinical trials be kept at a minimum and still have women participate? One possibility is for investigators to do multi-institutional, collaborative studies. Another possibility is for investigators to ask smaller questions and be willing to be patient to get meaningful answers. The focus of research should be on clinically significant questions, the answers to which will change how health care providers take care of their patients, whether women or men. The medical research community is currently examining the role of managed care organizations (MCOs) in women's health research. Because large numbers of people use the services of MCOs, there is an extensive pool of data potentially available to researchers. However, the role of MCOs in women's health research is more extensive than just as a data source — MCOs could significantly affect clinical research in general.[2] At the Society for the Advancement of Women's Health Research Annual Corporate Advisory Council Conference in 1996, attendees generally agreed that MCOs could have a negative effect on traditional clinical efficacy research because of financial, political, and operational concerns. These concerns require that knowledge be practical and that practicality be incorporated into research design, costs, measurement, and potential application.[3] MCOs that perceive research as increasing costs, rather than generating profits, have been reluctant to become involved in research.[4] The trend of MCOs and women's health research is "improved processes for providing care, but reduced technologies for implementing cures. The challenge for the research advocacy community will be to ensure the former without sacrificing the latter."[5]

Recruiting and Retaining Women in Clinical Trials

Unless the appropriate women, in sufficient numbers, participate in clinical trials, the base of biomedical knowledge about specific conditions and diseases will always have major gaps. For example, generally women do not use the health care system for menopause, unless they need a hysterectomy. This absence creates difficulties for capturing an accurate picture of women and menopause, and is one of numerous barriers to addressing the health issues of women: "Access to health care, mistrust of the medical system, language barriers, cultural beliefs, and even transportation and child care are all issues that must be addressed to ensure that women are able and willing to participate in clinical studies."[6]

Designing research models to include women in clinical studies presents new questions about how to recruit women. The recruitment techniques that are used for men may not be effective for women.

On some occasions, when pharmaceutical companies opened trials to women, they did not come forward to participate. In such cases, investigators may be inclined to assume that women do not wish to participate and may wish to proceed with the trial as before. Thus, there is a need to train investigators to use different strategies to increase women's participation. For example, typically the first step in recruiting potential participants is to advertise in newspapers. Whereas newspaper advertisements may be effective in recruiting men, studies indicate that women are more likely to respond to radio messages or television advertisements. In recruiting women for some AIDS trials, investigators found that they had to offer incentives, such as transportation and day care, to enable women to participate.

Informing the appropriate people is key to recruiting for clinical trials, and yet two major considerations are often overlooked. One, although physicians' referrals can be crucial to successful recruitment, many physicians are not informed about clinical trials. Two, if the potential population to be recruited includes women whose native language is not English, the recruitment plan should include disseminating information in languages other than English.[7]

Once informed about a study, whether or not women decide to participate may depend on their attitudes toward the medical profession, research team members, and clinical studies in general. Participants' confidence in those conducting the research, and even their opinions about the quality of study design, can be important determinants of enrollment and retention. The recruitment and implementation plans should take into consideration establishing one-on-one relationships between research staff and study participants, having as many women as possible be members of the clinical staff, encouraging joint decisionmaking and informed consent, and establishing educational and support networks of former and current study participants.[8]

The relation between the research institution and the community participating in the study should be considered when recruiting participants. Clinical studies may fail if the researchers and community do not have common goals or a shared recognition of the needs of the community. Trust should be established between the research institution and the community, along with a partnership approach. Partnerships can be established by having members of broad-based groups, such as religious groups, participate as early as possible in the recruitment process, preferably at the planning stage. Partnerships that create strong personal relationships between participants and clinical staff can lead to such benefits as higher participant retention and compliance with study protocols: "An attitude of caring and assistance on the part of investigators and staff may keep participants returning to the facility not only to participate in the study, but also for the personal and social contacts."[9]

When recruiting and retaining women in clinical trials, investigators need to consider all the above-mentioned concerns, but these concerns should not be viewed as absolute obstacles to having women participate in studies — the obstacles can be overcome with careful planning and persistent efforts.

Ethical and Liability Considerations

A major ethical and liability consideration is the inclusion of women of childbearing age in clinical trials. In particular, pharmaceutical manufacturers worry that including women of childbearing potential in clinical trials can make manufacturers vulnerable to lawsuits. NIH and FDA guidelines address this issue. In 1993, FDA reversed its recommendation that women of childbearing potential be restricted from participating in drug trials. FDA issued new guidelines about including both genders in drug development, analyzing clinical data by gender, assessing potential pharmacokinetic and pharmacodynamic differences between genders, and conducting specific studies in women. It should be noted that excluding women does not exempt manufacturers from liability risks; the manufacturers are still responsible for knowing how pharmaceutical agents affect women.

Scientists, pharmaceutical companies, and FDA emphasize the problems of testing pharmaceutical agents in pregnant women. They are concerned about protecting fetuses from potential toxic therapies as well as the possibility of liability and law suits.

During pregnancy, physiological changes occur in the cardiovascular, renal, gastrointestinal, pulmonary, and hepatic systems. These changes can affect how a drug is absorbed, distributed, metabolized, and eliminated. According to a white paper by the American College of Clinical Pharmacy, pregnancy significantly influences the pharmacokinetics, and possibly pharmacodynamics, of various compounds.[10] The fetus and placenta should be regarded as different compartments in the pharmacokinetic model in pregnant women.

Although pregnant women have been excluded from clinical trials in the past, they use drugs during pregnancy. Companies have marketed drugs used by pregnant women without having knowledge about the maternal and fetal effects of the drugs. An Institute of Medicine report states that 75 percent of pregnant women use prescription and over-the-counter medications.[11] In 1992, investigators discovered that pregnant women with hypertension who used angiotensin-converting-enzyme inhibitors during the second and third trimesters sometimes experienced fatal neonatal renal problems.[12]

FDA is examining the issues of having pregnant women participate in clinical trials of new drugs and biological agents. The agency has acknowledged the importance of including pregnant women in trials that use experimental therapies for life-threatening conditions, such as new therapies for AIDS. New models are needed, including animal models, and followup procedures, such as postmarket surveillance for drugs.

Animal Studies

Research on animals can lay the foundation of progress toward developing research designs for clinical trials, yet female animals are generally not used in research because of the rate and complexity of the estrous cycle. Few animal models mimic the menstrual cycle and when they are used it is almost exclusively for contraceptive research. Otherwise, if a study uses female animals, the animals are basically "castrated" before being studied. Investigators should investigate the use of female as well as male animals and differences in the hormonal milieus in these animals and consider looking at several animal models, not just a rodent model.

GENDER DIFFERENCES

Women and men are obviously different in regard to the presence of hormones, such as testosterone, estrogen, progesterone, and prolactin. Since these hormones affect gender-dependent physiological characteristics, they may also modify the pharmacokinetics and pharmacodynamics of selected drugs. Yet, the scientific knowledge base does not provide information about gender differences in responses to drugs. It is vital that investigators determine under what conditions gender differences happen and design clinical studies appropriately to examine these situations.

Women and men also differ biologically in body composition, size, and metabolism. These factors may influence the dosage, disposition, and metabolism of drugs. Therefore, when determining drug dosing it may be appropriate to consider these differences, especially body size and composition, instead of using standard fixed doses.

The way diagnostic technology and medical devices are designed poses concerns. Most medical diagnostic technology is built with a man in mind; and, because some medical devices are designed for men, women are often too small for the use of the devices.

Differences between women and men are more than just biological. There are also behavioral and psychosocial differences between the sexes. Differences in lifestyles, such as exercising, alcohol consumption, and cigarette smoking, affect health. Women and men perform different roles in society, which influence their health. Women are more often the victims of domestic violence and have higher rates of depression and eating disorders.

Another important gender issue is aging. On average, women live 7 years longer than men; they constitute the majority of the population over 65.[13] Therefore, research on the aging process should include women. Women and men are affected by different diseases and conditions. Rheumatoid arthritis and osteoporosis are more common among women than men; whereas, more men than women suffer from gout. In addition, older women tend to experience more adverse reactions to medications than men.[14]

In 1994, the Institute of Medicine Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies concluded that gender differences are relevant to how clinical drug trials are designed. They summarized that "differences in size, fat ratios, and metabolic rates are associated with differences in drug concentration, metabolism, and response. Psychosocial differences are associated with differences in risk factors and, more important, in adherence to experimental protocols. These differences can change over time, both in the short term (during menstrual cycle) and the long term (with pregnancy, lactation, and aging)."[15]

LONGITUDINAL AND LIFE PHASE RESEARCH

Because of the unique role that female hormones play in women's lives, women go through various stages based on hormone support. These stages influence the development of diseases such as myocardial infarction and osteoporosis. Thus, a study in which only premenopausal women participate may not reveal findings that are applicable to postmenopausal women. If women participate in pharmacokinetic and pharmacodynamic studies, it is vital to establish whether they are premenopausal or postmenopausal and whether they are receiving hormone replacement therapy or oral contraceptives.

It is essential to conduct studies that include and describe the different phases of a woman's life, and to classify women by the menopausal stage, instead of by age only. This was not done in breast cancer screening trials. In these trials, women were grouped by age, instead of by pre- or postmenopausal status.

Research designs and study instruments should be developed that describe the menstrual cycle longitudinally and assess hormone differences across menstrual cycles. Clinical trials that include premenopausal women should study changes not only month to month, but also week to week, plotting information over two or three menstrual cycles. A single blood level is not particularly helpful, because it represents a single point in time, instead of a view of dynamic change. New technologies may be needed to perform studies: instead of blood measurements, investigators should explore using less intrusive measures in population-based studies, such as saliva and urine samples.

INSTITUTIONAL REVIEW BOARD SHOPPING

Before conducting research, some pharmaceutical companies go "institutional review board (IRB) shopping," looking for the appropriate IRB for the investigation. IRBs may find equitable selection criteria confusing if the private and public sectors present conflicting policies. Sometimes IRBs get requests from pharmaceutical companies to do research that specifically excludes women. When an IRB questions a protocol or tells a pharmaceutical company to change the protocol to allow women in the studies, the company may threaten to take their studies elsewhere. Money for research is at such a premium that if a pharmaceutical company has any conflict with an IRB, the company can move the study elsewhere.

To deal with IRB shopping, IRB chairs have proposed establishing a network of IRBs so that IRBs can communicate with each other and be aware of pharmaceutical companies' studies and activities. Another way to avoid IRB shopping is to have pharmaceutical companies contribute to a pool of funds (perhaps managed by NIH), which would separate research money from pharmaceutical companies' perspectives. Such a pool could also be established with funding from MCOs.

Another concern with IRBs is that the boards do not learn about the population composition of the study until the annual or interim project review, which restricts an IRB's capability to secure a balanced population study. Involving IRBs in the early design phases of research would help to ensure that there is an equitable representation of study subjects.[16]

IN SEARCH OF A NEW PARADIGM

In 1995, Gerhard Levy wrote about patient-oriented pharmaceutical research that focuses on the individual. This research would extend beyond pharmacokinetics, pharmacodynamics, and medication adherence to include the behavioral sciences.[17] In a similar vein, the World Health Organization's Tropical Diseases Research Program uses a multidisciplinary approach that views women's health as a result of sociocultural interactions and economics.[18] A framework for health research is supported that would create a gender framework that incorporates research from such diverse fields as medicine, pharmacy, public health, epidemiology, anthropology, economics, entomology, agriculture, environmental engineering, ecology, and health education. In this approach, women and men are seen as principal agents of their own health, with personal needs, priorities, and preferences.

EDUCATION

The issues discussed above all require education. The general public needs to learn more about women's research issues and about participating in clinical trials; pharmaceutical companies about inclusion of women in trials; and investigators about how to design trials for women's participation and how to create new research models based on women. Moreover, society, the medical establishment, and investigators should be educated on the importance of having more women investigators.

CONCLUSION

Scientists will continue to struggle with the fact that they serve a diverse society — diverse in sex, size, age, culture, and income. The population is not only diverse, but dynamic. Given the nature of society, it is vital to recruit, retain, and observe diverse populations in an ethical manner. The public needs to be informed and educated about medical studies and their importance. Ultimately, scientists must search for the most significant findings, those that will affect the practice of medicine. Part of science's responsibility is to serve all; yet, science must also focus on the most meaningful issues, and not be diverted by simplistic academic issues.

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HEALTH IMPACT AND HEALTH OUTCOMES: ADVANCES IN BIOTECHNOLOGY

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How can advances in biotechnology be incorporated into clinical care and health professional education programs for women's health, including prevention, screening, and treatment? What is the role of gender in access to care, diagnostic and therapeutic interventions, and patient-provider communication? What are the ethical, legal, and social issues? How can the diverse community of women benefit from state-of-the-art research?

INTRODUCTION

A vaccine offering protection against serious illness, an effective drug treatment for HIV/AIDS patients, a diagnostic test capable of detecting a treatable disease at its earliest stage, and artificial joint replacement devices: these are examples of the biotechnological advances that offer immeasurable benefits for the health and quality of life of all Americans. But as these "miracles of modern science" are developed, important gender-related questions must be asked: Are the side effects of a vaccine the same for men and women? Do men and women react the same way to new HIV/AIDS drugs? Are the biotechnology applications that have become standard clinical care appropriate and advisable for women? Should artificial joint devices be designed differently for male and female patients? The answers to these questions are the essence of this discussion because, in fact, many biotechnological advances are put into common use without regard to gender-specific considerations.

Biotechnological advances are the result of a lengthy process that most often begins as a new idea or concept in the laboratory, continues through various clinical research stages, seeks approval for clinical care applications, and ultimately reaches the marketplace and the consumer. The extent to which this process takes into account gender-specific considerations has important ramifications for women's health. It is important not only to look at new advances but also to consider existing or older technologies that may not be considered in gender terms, that is, technologies that are gender-neutral, and possibly not advantageous to women. The recommendations presented in this report are intended to integrate and focus attention on women's health concerns so that biotechnological advances benefit all segments of the population.

BIOTECHNOLOGIES: CONCEPT TO MARKETPLACE

Technology transfer has been defined by the National Institutes of Health (NIH) as "the process by which the fundamental discoveries of laboratories are brought forth into practical knowledge and useful products for the benefit of humanity." The Federal Government, particularly the Public Health Service, including the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), and the National Institutes of Health and its grantee institutions, plays a major role in biotechnology transfer.

The Bayh-Dole Act of 1982 and the Federal Technology Transfer Act of 1986 encourage greater interactions between the Federal Government and universities, foundations, and industry through cooperative research and development agreements and through the licensing of patented inventions developed by public health agencies or by researchers at universities and not-for-profit institutions funded by NIH.

Mechanisms for technology assessment to determine safety and effectiveness are evolving. Traditional methods, based on peer review, are being transformed by information technology that makes dissemination of research findings more immediate and eliminates filters. The criteria for such assessments are open for debate. Although "safety and effectiveness" are important principles, many people — practitioners and consumers alike — hold different concepts of what these terms mean. Disagreements persist about what level of risk to the individual is acceptable, even in the face of substantial public health benefits to society as a whole. Is it appropriate to demand both the latest technology — whether adequately assessed or not — as well as the right to "sue" if there is a problem? Who should determine what level of safety and effectiveness is sufficient? An expanded public discourse on these matters is sorely needed.

There is also a need to recognize the practical business and economic implications of new product development. Traditionally, companies have looked at new technologies and asked how they could make a profit; some companies are now looking at unmet needs and considering how to respond in a profitable way.

BIOTECHNOLOGIES: OPPORTUNITIES AND RECOMMENDATIONS

The recommendations that follow are presented in four broad categories: (1) technology transfer and assessment, (2) patient care, (3) clinical trials and FDA approval, and (4) communication and outreach.

Technology Transfer and Technology Assessment

The process of moving biotechnological inventions and advancements from basic research to clinical testing to the marketplace inherently provides opportunities to consider and meet the unique needs of women. Any new drug, vaccine, device, or diagnostic tool must be methodically assessed as it moves from the laboratory to safe, efficacious clinical applications in women. The technology's commercial viability must also be appraised and confirmed before it is introduced as a new product.

The commercial introduction of a new product or procedure, however, is not the end of the process. Even after a technology has been introduced to the marketplace, there is a need for continual assessment to ensure that the product remains safe and efficacious and does not become obsolete. Prenatal ultrasound testing provides one example of the need for such assessment. The National Institute of Child Health and Human Development, along with the NIH Office of Medical Applications of Research, sponsored a workshop titled "Ultrasound Screening: Implications of RADIUS (Routine Antenatal Diagnostic Imaging Ultrasound Study)." RADIUS, a large, randomized clinical trial, assessed the effectiveness of routine ultrasound screening for pregnant women at low risk for poor pregnancy outcomes. Although the study results indicated no real medical value of ultrasound for this population, practitioners have continued to use the technology. This is an example of an adaption of a technology from an original application in high-risk situations to an entirely different application, the efficacy and cost effectiveness of which may be questionable.

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

- collaborate with technology transfer programs to identify and evaluate technologies that warrant further research based upon the ORWH agenda; and

- assess, in a systematic way, which technologies are obsolete and/or used inappropriately.

Clinical Trials and FDA Approval Process

Clinical trials are designed to establish a level of safety and efficacy prior to the development and marketing of a drug, device, or treatment. Usually undertaken as a three-phase activity, clinical trials may be sponsored and funded by the Federal Government and for private industry. Participation in clinical trials is voluntary and offers individuals who meet the specific medical criteria access to promising drugs, devices, and treatments long before they are approved for general use. Institutional Review Boards seek to protect participants' rights and safety by ensuring minimal risk through careful research design, appropriate recruitment strategies, and thorough informed consent procedures. Participants should also be provided medical care throughout the investigation.

As for all medical technologies, clinical trials are a key stage in the introduction of biotechnology products and raise many crucial overarching questions. For example, how can research designs be changed to encourage greater involvement by women (i.e., clinical trial participation)? Which populations of women are not now participating in trials? Can new kinds of trials be designed? Is it possible to design sound prospective studies? What ethical and social issues are involved? When is participation truly in the best interest of the individual?

Ensuring diversity and pluralism is part of the challenge. The involvement of communities in research design, implementation, and recruitment must be encouraged. The HIV/AIDS and breast cancer activist communities have been heavily involved in the clinical trials process in those disease areas, for example.

In addition to questions regarding research designs and recruitment, there are questions about what constitutes "safe and efficacious" drugs, devices, and treatments, and about what level of approval regulation is needed. FDA regulates medical devices based on their degree of risk to the public. Devices that are life supporting, life sustaining, or implanted must receive agency approval before they can be marketed. But what level of certainty should be required? What are appropriate end points? The approval process should take into account the range of societal values on these issues.

Another concern relates to the need for post-market assessments to identify standard practices that may no longer be medically desirable or advisable, and to identify low-level effects not initially evident. The FDA continues to collect and analyze reports on approved drugs and devices to monitor for any unexpected adverse reactions.

There is general agreement that there is a need for systematic dissemination of clinical trials results. Building on a congressional mandate to create a clinical trials registry for women's health, the NIH's Office of Medical Applications Research, the Office of Research on Women's Health, and the National Library of Medicine are working to assemble a database of trials that is relevant not only to women's health but also across the spectrum of research. Such a registry would contribute to a health care system in which evidence from clinical trials can be more rapidly incorporated into clinical practice. A systematic means of archiving and retrieving the experience of previous and ongoing research is central to the timely and ethical use of therapies and health resources. The Cochrane Collaboration is an example of such an effort on an international scale.

Research on biotechnology applications in the area of prevention also deserve greater attention. Traditionally, prevention has been underfunded relative to other categories of research. Two such areas that have and will continue to have a major impact on women's health are contraception and prevention of sexually transmitted diseases.

The clinical trial/approval process presents opportunities both for increasing the participation of women in study designs and for seeking a balance in research agendas. Recommendations to improve the process include the following:

- participate in efforts to improve the quality of study design, data collection, and analysis; and
- advocate for a better balance of research among preventive, diagnostic, and treatment initiatives.

Patient Care

The cost effectiveness of treatment, particularly in managed care environments, is becoming an essential part of choices in clinical care. But the question remains: When are technologies advanced enough to gain status for third-party reimbursement? Even in a climate of cost containment, physicians in managed care, specialists, and primary care physicians must be held to certain standards of care. Improvements in the education of health care practitioners and changes in clinical care practices are essential. In addition, the insurance industry should be included in the education process that addresses new and emerging applications of biotechnology.

Clinical practice guidelines, which recommend appropriate practices based on routinely available technologies and clinical experience, should incorporate gender as a variable. There is need to define quality and outcome measures that are broader and more sensitive to women's needs and better measures of quality of care. To illustrate, a manufacturer of a hip replacement device refused to make a device that would be compatible with the female anatomy despite problems that women were experiencing with the hip replacement device because of its large size. The issue is not just developing new technologies, but also refining technologies and practices from a gender perspective, particularly in managed care settings.

The NIH Consensus Development Program is a significant health technology assessment and transfer program. A consensus statement evaluates state-of-the-art scientific information on a given biomedical technology with the purpose of resolving a particular controversial issue in clinical practice. Statements answer a series of questions concerning efficacy, risk, and clinical applications and recommend future use. However, the effect of the Consensus Development Program on clinical practice is unclear, since there are various nonmedical factors involved. The program has, however, had measured success in influencing reimbursement policy and specialty organization policy, thereby indirectly affecting physician behavior. The Consensus Development Program offers one avenue for implementing the following recommendations:

- involve a broad constituency in developing professional practice guidelines that have sex- and gender-specific components;
- identify quality and outcome measures that are broader and more sensitive to women's diverse needs; and
- propose improvements to existing technologies based on new information on gender differences.

Communication and Outreach

On matters pertaining to new biotechnology developments, communication and outreach to health care providers, professionals, and the public remain an enormous challenge. What are the best ways to disseminate information on biotechnology advances both before and after they reach the marketplace? How can practitioners keep informed and current on the range and volume of developments in biotechnology? In addition, the translation of technical information into lay terms must accommodate the needs of different audiences. The role of the media in this process is also a factor. How do you create responsible media?

Identifying mechanisms by which new biotechnology advances may be integrated into the education process for practitioners is critical. For example, how can state-of-the-science information on such complex and dynamic topics as genetics be incorporated into medical school instruction? Epidemiologic and biostatistical training and education are also lacking despite the fact that these skills are fundamental to medical, nursing, and other disciplines.

Seeking input from diverse populations regarding their most pressing needs should be an ongoing process. How can we ensure that the interests of those outside the scientific and business worlds are served? For example, HIV/AIDS and breast cancer advocates represent a new level of involvement by nonscientific communities. How can meaningful forums be developed for the exchange of information between and among scientists and nonscientists?

Recommendations to improve these channels of communication are as follows:

- continue to sponsor dialogs among clinicians, scientists, advocacy groups, managed care providers, insurers, and other parties to improve overall communication on such topics as values, concepts of safety and efficacy, and consequences for both the individual and society;
- continue to seek input from diverse populations of women regarding their most pressing health needs and concerns to ensure their inclusion in the research agenda; and
- work with health professions educators to integrate gender-based science into the curriculum.

PREVENTIVE INTERVENTIONS: ADDRESSING GENDER DIFFERENCES

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INTRODUCTION

Preventive interventions for specific syndromes, diseases, or behaviors are typically developed through a series of steps. Each step builds on its predecessor and supports its successor. The sequence, as described in a report of the National Academy of Sciences, consists of seven steps: (1) recognizing and defining the syndrome, disease, or behavior to target; (2) delineating the risk factors involved; (3) conducting studies to identify relatively powerful and malleable risk factors and protective factors, individually and in combination; (4) developing and testing a variety of approaches to decrease risk and increase protection; (5) conducting field trials to assess the most efficacious and promising interventions; (6) implementing and evaluating the intervention in community settings, and assessing its effectiveness for the target population, sometimes at multiple sites; and (7) transferring knowledge gained by the intervention programs to the public domain as widely and rapidly as possible.[1]

Whereas the developmental sequence for preventive interventions may sometimes be the same for women and men, the nature of interventions designed for women, and the techniques for studying them, may require approaches that are different from those based on models of men's health and behavior (particularly in steps 1 through 4). Preventive interventions for women should take into account the special attitudes and values women tend to live by. Women feel social and financial pressures to care for others as much as, if not more than, they care for themselves.[2,3] Many women do not believe that self care is valid or is a highly prized facet of one's identity; their socialization too often promotes caring for others over caring for oneself in the physical, mental, and spiritual domains of life.[2,4] This issue varies in significance across ethnic minority groups. If women do not value self care, their attempts to adopt and continue preventive health measures are less likely to succeed. Basic self-caring behaviors, such as a healthy diet and adequate exercise, are critical not only for immediate health gains, but also to reduce the risk of disease in later life (e.g., heart disease and osteoporosis).[5]

PROGRESS AND GAPS IN KNOWLEDGE

Appropriateness to Life Transitions

One effective way of promoting good health practices among those at risk is to target preventive interventions at life transition points.[6] Examples of successful intervention programs aimed at particular life transitions include Early Intervention for Preterm Infants;[7] the Perry Preschool Program;[8] the Community Epidemiological Preventive Intervention: Mastery Learning and Good Behavior Game (first graders' adaptation to school);[9] the Family Bereavement Program (for children surviving the death of a parent);[10] the Positive

Youth Development (social competence for adolescents);[11] the Prevention and Relationship Enhancement Program (for couples in marital distress);[12] the Prenatal/Early Infancy Project (enhancing personal development of new mothers);[13] the JOBS Project for the Unemployed;[14] Comprehensive Support for Caregivers of Alzheimer's Disease Patients;[15] and the Widow-to-Widow Program: A Mutual Help Program for the Widowed.[16] Most of these programs are directed to men and women alike. However, a number of early intervention programs focus on women who are new mothers, or mothers of young children, both as targets of interventions and as "deliverers" of interventions to their children. Also, many available interventions focus on women who, during late adulthood, become widows or care givers for a dependent spouse.

Followup studies of a number of intervention programs for infants and toddlers have shown continuing positive benefits.[17] However, no one intervention, at any one time, is likely to accomplish the comprehensive goals of sustained disease prevention and health promotion for a lifetime. "Booster" interventions that take place at time-defined intervals or at transition-defined events (for example, the birth of a second child) may therefore be necessary. Interventions, including the promotion of certain values and norms, that support individual change through multiple levels of community structures may be more likely to effect desired behavioral changes than interventions focusing only on individuals.

There is an unfortunate lack of prevention research programs designed for the needs of many adults, such as middle-aged women or elderly men. Likewise, limited attention has been paid to risk factors that can occur across generations in the same family. The research design of prevention programs to reduce risks are beginning to evaluate outcomes and compare benefits and costs across generations within a household.[18] For example, interventions focused on helping an adult, child, or spouse care for a dependent parent within the household should consider the costs and benefits to both the care provider and the dependent parent.[19,20]

Cultural Relevance of Interventions

Advances in research on women's health will not be effectively available to women of all ages unless the inequities of access to health care that arise from poverty, racism, homophobia, and ageism are considered. These inequities are related to practical barriers, such as cost and distance, as well as to cultural factors.

A crosscutting issue in applications of research advances for health promotion is the double need to see that programs are designed to be culturally relevant to the targeted population and that researchers and practitioners be culturally competent with the specific population they are serving. "Cultural relevance" refers not only to ethnicity but also to the cultures of the inner-city poor, lesbians, older women, and of migrant, homeless, and rural women. "Cultural competence" refers to a person's ability to be sensitive to the attitudes, values, beliefs, practices, and desired outcomes of the cultural groups with whom one is working, as a matter of good science, therapeutic effectiveness, and professional ethics.[21–23] If beliefs and attitudes of certain cultures are maladaptive, developing programs to change them may be most efficacious if they begin with a good understanding of current beliefs or values. For example, a researcher working with an aging population must realize that many older women respect physicians deeply and will rarely question a doctor's recommendations or ask for information about alternative treatments. Certain cultures have evolved unique beliefs about the causes of specific diseases; for example, Dressler has described the differences between the beliefs of African-American women about the causes of hypertension and conventional models.[24] Different cultures also vary in the degree to which their members can comfortably discuss sexual behavior;[25] thus, programs designed to prevent sexually transmitted diseases must offer several levels of discussion to avoid insulting the intended audience and reducing participation.

Many effective preventive interventions include peer-provided counseling and peer supports, which promotes the community's values in health behaviors and lends credibility to the intervention.[26] Cultural competence is achieved through personal experience, typically by immersion in the field of treatment or research, which leads to the mastery of the skills necessary to develop or deliver preventive interventions.[27,28]

The degree to which prevention programs involve ethnic minorities varies as a function of the degree to which efforts are made to reach complete samples of those at risk. Samples drawn from county death records, unemployment records, or school registrations, for example, will be more representative of a population than samples drawn up in other ways. Programs whose participants are recruited through participants' self-identification or clinical referrals tend to have a nonrepresentative sample.[29]

Overall, the availability of prevention programs designed for women of ethnic or minority groups known to be at risk is not proportionate to their needs. Women known to be at high risk for certain health problems include Native American adolescents and adults for substance abuse, Hispanic and African-American women for diabetes, and African-American women for hypertension.[30] Few studies have included sufficient members of any ethnic or cultural minority to accommodate assessment of the variation within the ethnic or cultural group. Among lesbians, for example, random samples are difficult to obtain. White, middle-class lesbians tend to be overrepresented in study samples, and actual disease prevalence among lesbians as a whole is unknown.[31] Knowledge of within-group differences is as important as knowledge of cross-cultural differences as a basis for understanding health behaviors.[32]

Scope of Interventions: Comorbidity

Prevention efforts must increasingly recognize that physical health and mental health are not separate entities. Posttraumatic stress disorder, often associated with sexual abuse, is a common precursor of irritable bowel syndrome and other gastroenterological problems.[33] Rates of depression are highest among women[34] and among persons who experience acute or chronic physical disorders.[35] Rates of depression are also high among persons who have illnesses that predominately affect women, such as multiple sclerosis,[36] myasthenia gravis,[37] and chronic fatigue syndrome.[38] Women of ethnic minorities may be especially at risk for undetected (and untreated) depression, with negative physical and mental health consequences.[39] Homeless women have twice the prevalence of major depression than the general population.[40] Migrant and seasonal women farm workers are at risk for psychosocial distress because of their lifestyle.[41,42] Clinical depression often can be effectively treated,[43] and its successful and continued treatment can limit morbidity and mortality. This has been demonstrated, for example, among women with cancer [44,45] and among frail nursing home residents, the majority of whom are women.[46]

RECOMMENDATIONS

The working group made the following recommendations:

General Recommendations

- Encourage ORWH to promote further cross-agency prevention initiatives with relevance for women's health, such as the recent violence prevention efforts by the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and the Health Resources and Services Administration (HRSA); and
- Encourage ORWH to collaborate with the NIH Prevention Consortium to review portfolios and consider needed initiatives on understudied populations of women (e.g., women with disabilities, migrant women farm workers, and homeless women).

Specific Recommendations

- Encourage ORWH to sponsor requests for application on violence prevention, with cross-agency coordination by NIH, CDC, and HRSA;
- Expand the Women's Health Initiative to include more research questions on preventive interventions;
- Identify and replicate models that work: annual HRSA competition to find innovative, creative community-based models;
- Encourage the NIH Prevention Consortium to assess research portfolios on women's health;
- Document and enhance all research on women's health across all agencies (NIH, CDC, HRSA, the Indian Health Service, the Agency for Health Care Policy Research, and the Social and Mental Health Services Administration);
- Use technology to share strategies (i.e.,Websites);
- Utilize practice-based community research, physicians' networks (combined AHCPR/HRSA initiative) to test preventive intervention;
- Promote federal/state coordination; public-private partnerships in implementing effective preventing interventions;
- HRSA National Clinical Network — state and regional levels; and
- Collect data on the physical and mental health needs and health status of homeless, migrant, and seasonal women farm workers.

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WOMEN IN BIOMEDICAL CAREERS: ISSUES OF IMPORTANCE TO YOUNG INVESTIGATORS

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BACKGROUND

The Office of Research on Women's Health (ORWH) was established in September 1990 within the Office of the Director of the National Institutes of Health with three mandates, the third of which was "to develop opportunities and support for recruitment, retention, re-entry, and advancement of women in biomedical careers." In March 1992, ORWH sponsored a public hearing at which representatives of more than 70 organizations described the issues and barriers that women face when considering a biomedical career. A workshop that took place in Bethesda, Maryland, in June 1992, brought more than 400 women and men together to formulate recommendations for strategies to overcome these barriers. The summary report of that hearing and workshop, titled *Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century*, provided a starting point for a workshop on women in biomedical careers, which convened on September 27, 1996, in Philadelphia. That report presented nine areas of concern:

1. recruiting women for biomedical careers;
2. visibility: role models and mentors;
3. career paths and rewards;
4. re-entry into a biomedical career;
5. family responsibilities;
6. sex discrimination and sexual harassment;
7. research initiatives on women's health;
8. gender sensitivity; and
9. minority women in science.

Although women are entering medicine and biomedical research in increasing numbers, they are still not represented in the upper ranks in numbers comparable to their male counterparts. Figures nationwide attest to this trend. According to a report by the Association of American Medical Colleges, 41 percent of medical students are women, 32 percent of assistant professors in medical schools are women, 20 percent of associate professors are women, and 10 percent of full professors are women. The percentage of women at the highest professorial rank at Allegheny University of the Health Sciences, which boasts a higher than national average, is only 17 percent. Clearly, women in biomedical fields face unique challenges at *all* stages of a career, which is why the cochairs of this working group suggested eliminating the word "young" from the original working group title and focusing on issues for women investigators in general.

PROGRESS SINCE ESTABLISHMENT OF ORWH

The working group participants described new programs at their institutions designed to help women in biomedical careers. Among those programs discussed were educational efforts aimed at middle school girls, fellowships designed to buy protected time for junior faculty, and re-entry programs for biomedical researchers. Those programs are organized in this section under the following headings:

- Promoting career growth (buying protected time);
- Re-entry;
- Precollege programs;
- Sexual harassment and discrimination;
- Leadership development;
- NIH intramural initiatives; and
- Minority women efforts.

Promoting Career Growth (Buying Protected Time)

Dr. Eleanor Shore talked about Harvard Medical School's 50th Anniversary Program for Scholars in Medicine, created in 1995 to provide ten fellowships a year for junior faculty. The program is one of Harvard Medical School's efforts to increase representation of women in the higher faculty ranks. The women or men granted these fellowships must not only demonstrate academic promise but also be experiencing increased family or personal responsibilities that might be alleviated by a grant of $25,000. While not intended to provide total support, one of these fellowships might allow a physician to take time off from some clinical responsibilities in order to protect time to write a grant application, prepare a manuscript, complete a research project, or develop new curriculum. A scientist might use the fellowship support to pay for additional laboratory assistance at a time when there is not yet independent funding. The Office of Faculty Affairs at Harvard intends to continue these fellowships, with a new competition each year, for at least 5 years. The first year's fellowships were granted to nine women and one man out of 210 applicants.

Re-entry

Dr. Anne Sassaman talked about the ORWH Re-entry Program, which was developed in 1992 as a pilot program but is now a trans-NIH program supported by 17 institutes and centers. The program has helped women and men who have been out of the biomedical research arena because of family responsibilities but who have strong potential to resume active research careers. By providing administrative supplements of up to 3 years to existing NIH research grants, the Re-entry Program supports full- or part-time research by these individuals in a program designed to update their existing research skills and knowledge. At the completion of the supplement, most re-entry scientists are in a position to apply for the next step of funding — a career development award or a research award. An assessment of the program done in the fall of 1995 found the research supplements useful in re-establishing careers and that most of the initial 26 recipients were gainfully employed in research after 2 years. Most participants also felt that the mentoring component of the program was vital. The program is currently underutilized, and NIH wants to get the word out to more potential applicants.

Precollege Programs

Data have clearly established that most kids leave the fifth grade thinking that science is neat and is something they might want to do; however, these same students at the high school level, especially the girls, think that science is *not* something they would consider as a career. The focus of the NIH Office of Education (OE) is students — kindergarten age and up. Dr. Bruce Fuchs, acting director of that office, talked about efforts to reach girls and underserved populations in the precollege years. With funding from the ORWH, OE is working on a series of posters aimed at middle school girls that depict women in medical research. OE has also created a World Wide Web site aimed at middle and high school students. Some of the components of the site are "Research in the News," which talks about news and breakthroughs in science; "Cool Links," which points users to other science education resources; and "People Doing Science," which profiles a variety of NIH employees, for example, a genetic counselor, a speech pathologist, and a medical librarian.

Dr. Margaret Kemeny, Chief, Division of Surgical Oncology, Department of Surgery at North Shore University Hospital in Manhasset, New York, said that her department has also focused on encouraging girls in middle school to pursue biomedical careers. The department is developing a slide show for middle school students showing women of various ethnic origins performing a variety of jobs in surgery. When completed, this show will be presented to students by a woman surgeon.

Sexual Harassment and Discrimination

For information about the sensitive issues of sexual harassment and discrimination, the working group participants recommended several publications. The Council of Graduate Medical Education's *Fifth Report: Women and Medicine* found that the greatest obstacle for women in medicine is sexism. Men's sensitivity to women's issues in biomedical careers could be appreciably enhanced if they were to read this report. The Association of American Medical Colleges offers a variety of materials on the status of women in medicine — from statistics on women at all levels to a compendium entitled *Building a Stronger Women's Program.* Janet Bickel's book *Enhancing the Environment for Women in Academic Medicine* (1996) includes chapters on sexism in medicine and on salary-equity programs.

The Department of Surgery at North Shore University Hospital in Manhasset sends *The Pocket Mentor* to all new interns but particularly targets the women interns. A good resource for all institutions looking for women candidates is the reference manual that lists women with their subspecialty of medicine. The book by Harvard's Dr. Constance Buchanan, *Choosing To Lead*, addresses "Mommy-track" issues and suggests that if women are to take their rightful place in helping to lead the planet, they cannot assume the primary role in raising children; nurturing must be shared equally by women and men.

Leadership Development

Dr. Donna Murasko, Professor and Acting Chair of the Department of Microbiology and Immunology at Allegheny University of the Health Sciences, talked about the institution's program, Emerging Leaders in Academic Medicine, which was developed through the Office of Faculty Affairs. This program, open to many institutions, is designed for women at the associate professor level who want to progress to administrative levels, such as department chair. They must be referred by their deans to attend three groups of meetings. At these meetings they attend workshops on leadership skills, e-mail and the Internet, and mentoring. The Emerging Leaders program requires the active participation of the deans, who must attend at least 1 day to work on ongoing problems at their institutions.

NIH Intramural Initiatives

Catherine Didion, Executive Director of the Association for Women in Science, distributed materials about her organization's programs, including a leadership conference for midcareer women in science. Each participant must be sponsored by her institution, and she must attend workshops on how to negotiate, communicate, and so forth.

James Alexander of the NIH Office of Education described the Postdoctoral Fellows Committee, an intramural career development program. Although not gender-specific, women have been active in the program. In a series of workshops titled "Survival Skills," attendees learned about negotiating job offers, life as a professional, and making oral presentations. Job fairs, a Web site, and alternative career workshops also assist postdoctoral fellows. Another OE program that should help young women pursuing careers in science is the Predoctoral Internship Award for recent college graduates to spend a year in a laboratory while applying to graduate school. This program should have an advantage over some of NIH's summer internships because of the length of time.

Dr. Barbara Karp, Associate Clinical Director, National Institute of Neurological Disorders and Stroke (NINDS), discussed the purpose of the Women Scientist Advisory Committees, started 5 or 6 years ago at NIH. These committees have successfully helped women throughout NIH institutes on issues such as pay, promotion, and tenure equity. The discrepancy between women's and men's salaries seems to have arisen, in part, because women do not ask for pay raises at the same rate men do. NINDS has been using federal authority to grant single-time pay raises to women.

Minority Women Efforts

Dr. Bruce Fuchs talked about NIH plans to offer 15 to 20 annual undergraduate scholarships to students interested in science who are disadvantaged culturally, racially, financially, or even personally. The program would offer a stipend for the student to live at NIH every summer and do research, with a guaranteed position at the participating institute after completion of graduate or medical school.

Dr. Carol Brown of the Department of Surgery at Memorial Sloan-Kettering Cancer Center in New York City described a program that her department jointly sponsors with the Association of American Medical Colleges. The program offers a minority faculty development seminar each fall, at which minority women vastly outnumber minority men. She also described a program sponsored by the American Association of Cancer Researchers that sets up mentorships and offers funding for minorities to attend meetings. Although the program is not specifically for women, many participants are minority women.

GAPS IN ADVANCEMENT

The second part of the work session began with a discussion of the gaps and barriers that still hinder women in biomedical careers. The many points discussed can be summarized in four basic statements:

1. Mentoring, as it exists, is often inadequate for the needs of women and minorities.

2. The balancing of career and domestic roles lags behind in the biomedical arena.

3. The lack of institutional support for career development hinders women from advancing through the ranks.

4. Minority women are still not visible enough in biomedical careers.

Mentoring

Mentoring is a complicated issue, raising questions about how many mentors a woman should have to how a man effectively mentors a woman in an era of concerns about sexual harassment and sexual harassment charges. The complexity of the issue probably explains in part why there are still so many gaps and questions on the subject.

During the discussion, Dr. George Bryan suggested sexual harassment should not be a concern if one separates the personal from the business by keeping mentoring sessions in the office during business hours. The business of mentoring, he said, is listening carefully and offering suggestions.

Dr. Roxanne Rodney of Columbia University's Division of Cardiology suggested that because women do not have access to informal mentoring networks, they require a formal mentoring program. Dr. Shore said that it is important for a woman to establish herself as an independent academic, getting what she needs from a variety of mentors. Dependence on a single mentor may be hazardous because that mentor may leave, may become a competitor, or may have expertise in only one of several areas a woman needs. Dr. Leah Dickstein from the Department of Psychiatry and Behavioral Sciences in the School of Medicine at the University of Louisville expressed a similar view and said that a woman's number one advisor is herself, and that she needs an array of assistant advisors so that she will not be left helpless if her central mentor does not help her. Dr. Kemeny stated that in many disciplines mentors do not even exist and that in surgery, specifically, few people are interested in furthering a person's career.

Stephanie Bird of the Massachusetts Institute of Technology, a member and past president of the Association for Women in Science, suggested that, although mentoring is important for everyone, it may be especially vital for underrepresented groups. She specified areas of basic science and research in which many trainees are foreign born and need help in the basics of understanding how the system works, as well as in learning how to advance through the ranks. Sharon Jackson, a clinical researcher with the NIH's National Institute of Allergy and Infectious Diseases, said that there is a gap in the definition of mentoring that does not take into account someone like herself who may have a variety of mentoring requirements not only as a woman but also as a woman of African-American and Caribbean descent.

A Biomedical Career in Today's World

The roles and boundaries of modern women and men in their careers and domestic lives are no longer distinct by gender. There is no longer a clear divide between men as breadwinners, able to spend unlimited hours in their career roles, and women as housewives who raise the children. Therefore, an updated concept is needed of how to balance a biomedical career with home life and other responsibilities.

Dr. Brown said that only *one* way is still considered *the* way to succeed in a biomedical career and that involves giving up any outside life and family. That perception needs to change, and groups such as this working group should make recommendations and ask questions such as "Why not work on changing institutional perceptions?," "Why not day care centers at institutions?," and "Why are there meetings at 7:00 a.m.?" Dr. Shore mentioned that after 100 years, Johns Hopkins moved its medicine grand rounds from Saturday mornings to Friday mornings in order to be more accessible to women with young children. Nancy Teed, project manager and senior analyst at Houston Associates, Inc., mentioned that although women re-entering a field may have gained many skills outside that field, their newfound skills are not accepted in the workplace, and their reputations are tainted by judgments like "They don't care enough" or "They're not good enough."

Institutional Responsibility and Career Development

The working group expressed concern about the serious gap in institutional programs and support for women in career development. Each major institution should have programs to help its faculty members progress through the ranks, but they should also offer programs for professional development tailored to women's needs. Institutions lack a structure of rewards for women and fail to recognize that this support is in their own best interest.

Minority Women in Biomedical Careers

For women and men, minorities are underrepresented in biomedical careers. Too few minority women pursue scientific and biomedical careers, including African-American and Asian-American women, and too few African-American men are in scientific and biomedical careers.

RESEARCH RECOMMENDATIONS

Acknowledging that changing institutional attitudes and behavior is slow work, the working group presented seven recommendations for fostering the growth of women in biomedical careers. The group recognized that only a few women can be helped by any given program or fellowship, but it perceived these programs and women as models for ongoing change around the country.

Define, Facilitate, and Reward Mentoring

Progress can be made in helping women advance in their biomedical careers if they have the proper mentoring. To facilitate the mentoring process, the following steps should be taken:

- *Define mentoring as it applies to women and minorities.* Mentoring is not just one kind of activity or service; the concept should be made relevant to women in biomedical careers.

- *Train individuals to be mentors.* While some people may be natural mentors, others would be good mentors if provided effective training.

- *Reward mentoring institutionally.* For example, one of the ten Harvard fellowships awarded $5,000 to the mentor selected by the fellowship recipient as a person who had stepped forward to assist a more junior colleague.

- *Counteract institutional attitudes that penalize mentors for their efforts.* In academia and industry, individuals in the highest leadership roles should assume the responsibility of counteracting the negative influences on mentors.

Define What Work Is; Study the Different Ways Men and Women Spend Their Days

A new paradigm is needed for what a career path is. Instead of talking exclusively about "women's issues," we should also talk about *generational* issues. Balancing work and family is not just a woman's problem; today, women and men care about flex time, dual careers, and making institutions more responsive to all.

Participants recommended that institutions recognize the legitimacy of different work styles. A perception persists that women in biomedical fields work part-time or are not fully committed to their fields. For example, studies show that men physicians on average put in 57-hour workweeks, while women physicians average 55 hours per week. Men take time to go out to lunch and to exercise, and they consider those activities to be part of their workday. Women, on the other hand, want to get the job done and get home to children or families. Both may work the same number of hours, but it appears that women are not putting in as many hours as men.

Recruit More Women; Increase Their Visibility

Not only is it important to focus on recruiting more women to scientific and biomedical careers, but it is also important to increase their professional visibility by having more women serve on editorial boards of journals, on tenure committees, and on committees that admit students and promote faculty.

Encourage NIH To Assume a Strong Leadership Role

NIH should assume a strong leadership role in addressing the needs, issues, and barriers of women in biomedical careers. NIH should continue its leadership role in developing programs for teaching the "responsible conduct of science," and should address such issues as gender differences, sexual discrimination, and racial discrimination in such programs. NIH should consider sponsorship of national fellowships to help junior faculty buy protected time at the most vulnerable point in their academic careers, when expanding family responsibilities coincide with the need to teach, do research, compete for grants, publish, and practice (if a clinician).

ORWH should work with programs required of graduate students, postdoctoral students, and all those who do research to make sure that the issues relevant to women's careers are introduced. The National Institutes of Health, the National Science Foundation, and the National Research Council are already collaborating to develop guidelines to direct that kind of interaction.

Establish Partnerships Between Academia, Industry, and Professional Societies

Academia should look for ways to partner with industrial organizations. Cross-fertilization could help both sectors. It is important to bear in mind that industrial scientists constitute the majority of scientists in this country. The Catalyst Foundation provides an example of how these partnerships might be approached.

Academia should also look for ways to call upon the strong relationship between professional science societies and academic institutions to help develop programs at institutions. The impetus should come from within the institutions, but professional societies can serve as leverage to get institutions to spend their resources.

Encourage Each Institution To Have, as Part of Its Cultural Values, Assistance for Women and Minorities

The working group participants also recommended that each institution develop formal programs to address inequities; the advancement of women and minorities has to be an intramural commitment that should be promoted through a dedicated office at each institution. In addition, it is important to look beyond institutional mandates and influence the level where the real power is — with the department and division chairs of medical institutions. These “fiefdoms” typically have no sense of responsibility toward minorities. Financial reward to those departments that *do* recruit women and minorities would go a long way.

Gather Statistics on Gender Gap Issues Such as Salary, Tenure, and Percentages of Women at Senior Levels

Accurate, comprehensive information and statistics on women in biomedical careers should be collected and used as a tool. Unless actual figures are published, people give little credence to the inequities that exist in salary, promotion rates, and so forth. However, before publishing such data, it would be essential to seek legal consultation to ensure that no legal liabilities are incurred. The results of a survey, for example, could become grist for the lawsuit mill. In describing how institutions set aside money to correct inequities, the institution must set criteria for applicants to meet, for example, to encourage a department to advance women.

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

The Office of Research on Women's Health (ORWH) received public testimony concerning the National Institutes of Health's (NIH) women's health research agenda for the 21st century.

I am extremely pleased that so many came to express their interest in women's health and related research and career issues. The giving of their time and energies to be with us was a sign of hope and support for the improvement of women's health through biomedical and behavioral research, and we were very appreciative of their efforts and wisdom, from which we can benefit through their participation and testimony.

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 on women's health issues and to establish a science base that will permit reliable diagnoses and effective treatment and prevention strategies for women.

The major objectives of our office are:

- To develop an integrated strategy for increased research into diseases, disorders, and conditions that are unique to, more prevalent among, or more serious in women, or for which there are different risk factors of interventions for women than for men;
- To ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially clinical trials, that are supported by NIH; and
- To 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. We shall further build upon the testimony we received through the scientific workshop.

This public hearing was convened to provide guidance and assistance to us in re-examining our mandates as we move toward the 21st century. We specifically requested participants' perspectives concerning continuing or emerging gaps in knowledge about women's health and successful models for the recruitment, retention, re-entry, and advancement of women in biomedical careers.

Testimony was received and reviewed by our task force on revisiting Hunt Valley, which was the site of our first workshop, held in 1990, at which we began formulating our national agenda on women's health research. We are fortunate to have members of the NIH scientific community, as well as by women's health advocates, scientists, and health professionals from across the country who are serving as members of this important Task Force.

The members of the Task Force, and all of those who participated in our workshop, were asked to do the following:

- Identify scientific progress since the establishment of ORWH.

- Highlight successes in the advances of scientific knowledge about women's health and gender/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/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.).

We appreciated hearing their recommendations and benefiting from their expertise.

The cochairs of the Task Force, Dr. Donna Dean, who is one of the cochairs of our NIH Ad Hoc Subcommittee on Research, and Dr. Marianne Legato, who is a member of our Advisory Committee on Research on Women's Health, presided over the afternoon's proceedings.

PUBLIC TESTIMONY
PHILADELPHIA, PENNSYLVANIA
SEPTEMBER 25, 1996

Mary J. Berg, Pharm.D.
College of Pharmacy, University of Iowa

Mary G. Bonk, R.N.
Complications of Gynecologic Surgery (COGS)
Women's Support Group

Mary Ann Burg, M.S.W., Ph.D.
Florida Institute for Women: The Health Gatekeepers
University of Florida

Bente E. Cooney, M.S.W.
National Osteoporosis Foundation

Michael J. Gast, M.D., Ph.D.
Wyeth-Ayerst Research

Barbara S. Giesser, M.D.
Arizona Health Science Center

Phyllis Greenberger, M.S.W.
Society for the Advancement of Women's
Health Research

Mary Hammond, M.D.
American Society for Reproductive Medicine

Hazel J. Harper, D.D.S., M.P.H., F.A.C.D.
National Dental Association

Laura L. Hayman, Ph.D., R.N.
American Heart Association

Penelope J. Hitchcock, D.V.M.
Sexually Transmitted Diseases Branch
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Lisa Kaeser, J.D.
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American Autoimmune Related Diseases
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Sjögren's Syndrome Foundation, Inc.

Margaret K. McLaughlin, Ph.D.
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American Society of Clinical Pathologists

Marj Plumb, M.N.A.
National Center for Lesbian Rights

Linda Quander, Ph.D.
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James M. Roberts, M.D.
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Roxanne A. Rodney, M.D.
Association of Black Cardiologists

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Eleanor G. Shore, M.D., M.P.H.
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Martha Torres-Montoya, M.S.P.H.
Hispanic Women's Health Association

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

Jacqueline Lee Wolf, M.D.
Gastroenterology Women's Coalition

Elizabeth Yoffe, M.A.
Self

Mary J. Berg, Pharm.D. *University of Iowa*

The University of Iowa is a research-based university composed of ten colleges, with a student body of approximately 28,000.

Dr. Berg became the first woman president of the University of Iowa in December 1995. The presence of a female leader in this institution, founded in 1847, gives great hope to women in academia who are forwarding their credentials for promotion with the expectation that fairness will prevail.

The promotion and tenure list at the University of Iowa doubled from 1995 to 1996. This remarkable achievement was noted at the annual ceremony of the "Celebration of Excellence and Achievement Among Women" in May 1996.

Mary G. Bonk, R.N. *Complications of Gynecologic Surgery (COGS) Women's Support Group*

Current U.S. public health policy, statutes, and state health laws adversely affect women who have experienced complications of gynecologic surgery. Occult obstetrical injuries to the pelvic floor, and complications of gynecologic surgery not made known to women, may lead to progressive digestive and urinary dysfunction and disease. Diagnosis, information, and prognosis have been strictly suppressed by medical politics. Examples include permanent ostomies surgically accomplished in the absence of fully informed consent; cancer, autoimmune diseases, and other disorders that may result from surgically implanted foreign material/devices; critical complications of gynecologic surgery such as post-hysterectomy pulsion enterocele and vaginal/rectal prolapse; and secret surgical research. Patients with postoperative pain and persistent dysfunction are often relegated to psychiatry.

Information and health records of these conditions and injuries have been withheld from patients and family/representatives under Georgia health law §31-33-2(c). Because all research in Georgia is tightly protected from legal discovery by Georgia health laws, the family/representative is also excluded from documentive research information. Furthermore, we believe that health care data systems, comprising patient information with diagnostic codes, personal identifiers, and other categorical divisions, are coded with psychiatric diagnoses which blacklist surgically injured persons and/or subjects of secret surgical research from all information and diagnostic health care, except in a life-threatening event. Through mental health laws, interstate compacts, and committees, there is reinforcement beyond state boundaries by codes with personal identifiers which blacklist the patient throughout the United States and Canada.

Investigative and documented procedures have been obtained on a patient from world experts outside of the United States and their assessments have been sent to the patient's established physician in Georgia. Under Georgia health laws and regulations, this physician cannot provide the information to the patient or representative, and third-party release of records cannot be obtained by process of Georgia law. In January 1996, a formal written complaint, with request for investigation of this specific case, was submitted by COGS to the Office for Civil Rights, HHS Region IV, in Atlanta.

COGS requests the interest of this workshop's cochairs, leaders, and participants and asks for inquiries through the Freedom of Information Act to the Office for Civil Rights, HHS Region IV in Atlanta, Georgia.

Mary Ann Burg, M.S.W., Ph.D. *University of Florida*

Our country needs major support to establish a National Network of Centers of Excellence in Women's Health. Without it, women's health services will remain fragmented and insufficient.

Although some of the lessons from the women's health movement of the 1970s were absorbed by mainstream medicine, an oppressive climate still persists. Too many women have adverse experiences with the health care industry. Too many physicians disregard their symptoms and "talk down to them." It is clear that women's health care needs are different from men's, yet they are not given the same attention and respect. This deficiency is reflected in morbidity and mortality statistics.

I believe that coordinating women's health must be a top priority for those of us who provide health education, research, and services to women. A network of Centers of Excellence in Women's Health is the most efficient and effective remedy for today's disjointed service delivery system.

The Florida Institute for Women: The Health Gatekeepers at the University of Florida offers a model for establishing a Center for Excellence in Women's Health. We have built partnerships with other academic health centers and women's research institutes across the country to foster collaboration and linkage on the national level, which is essential to make a significant impact on women's health. In fact, we intend to construct a first-class National Center for Excellence in Women's Health to foster cooperative efforts to build upon existing efforts to improve the sharing of data, the mentoring of researchers in women's health, and the development of models for delivering women's health services.

A long-term strategy is critical to the success of a project like a national network of Centers for Excellence. It will require a concerted effort from foundations, philanthropies, and other private funding groups, as well as volunteer organizations. It also needs formal sanction by a host academic health center in order to have the influence necessary to survive in today's political environment. The Brain Institute of the University of Florida, which was founded 5 years ago by a coalition of educational and research interests, provides an exciting model for establishing a unique, dedicated facility.

One of the lessons learned from the self-help movement of the 1970s — the foundation for the very notion that women's health is a unique field deserving distinct services — is that in order for a cause to flourish, it must be firmly institutionalized. I applaud the recent RFP from the Department of Health and Human Services to develop a Model Center of Excellence in Women's Health. It is an exciting start to institutionalizing women's health. Now is the time to capture this strategic opportunity.

Bente E. Cooney, M.S.W. *National Osteoporosis Foundation*

A comprehensive national strategy to address osteoporosis, including a coordinated program of basic, clinical, and behavioral research, is urgently needed before the baby-boom generation reaches the age of osteoporotic fractures. Although progress has been made during the last 5 years towards preventing, diagnosing, and treating this disease, there are still unanswered questions that need to be addressed.

The National Osteoporosis Foundation is the only national nonprofit organization solely devoted to reducing the widespread incidence of osteoporosis. The major goals of our research are to uncover the molecular and cell biology of bone and the factors that regulate bone cell activity; to identify the genetic and environmental risk factors that contribute to bone loss; and to develop methods of prevention, diagnosis, and treatment. Because women are four times as likely to develop the disease, and based on data provided by the National Health and Nutrition Examination Survey, NOF estimates that by the year 2000, a total of 25.5 million women either will have osteoporosis or be at risk for osteoporosis due to low bone mass. Therefore, we encourage and appreciate the continued research efforts on osteoporosis, especially as it relates to women. It is our hope that research will address those unanswered questions women need to learn about osteoporosis.

In basic research, questions concerning restoring and reversing skeletal functions need to be addressed. Moreover, investigation surrounding predetermining factors such as menopause, hereditary factors, and the role of genes must be explored.

Relevant to clinical research, we need to know the most efficient and cost-effective way to diagnose and treat patients with osteoporosis. While progress has been made to isolate certain risk factors such as race, smoking, weight, family history of fractures, and previous fractures, further research is necessary to refine and clarify risk factors. In addition, more clinical studies on treatment measures, including exercise, must be conducted to better understand, prevent, diagnosis, and ultimately treat this complex disorder.

In behavior research, perhaps the most important progress we can make is in the behavior of children, adolescents, and young adults. We must learn to foster lifestyle behaviors that are conducive to healthy living, thereby reducing bone loss. Adequate calcium intake, exercise, and healthy, smoke-free lifestyles must be fostered. Also, as women approach menopause, they should discuss the potential benefits and risks of estrogen replacement with their health care providers.

The current biomedical and behavioral research for osteoporosis deserves much attention. If not provided, this disease will not only bankrupt our health care system, but the lives of million of women and men.

Michael J. Gast, M.D., Ph.D. *Wyeth-Ayerst Research*

Oral contraceptive and hormone replacement programs address a wide range of women's health care issues. With lower doses and changes in regimen, oral contraceptives have become safer over the years without a loss of efficacy. Noncontraceptive health benefits, including the prevention of sexually transmitted diseases, the lowering of the incidences of several of the reproductive cancers, and the prevention of a variety of medical conditions requiring hospitalization of women have been additional benefits. Hormone replacement therapies (HRT) are being recognized in recent medical literature as providing superb global benefits for women's health.

Unmet health needs of women include infertility, endometriosis, uterine fibroids, reproductive cancers, depression, and collagen vascular disease. Wyeth-Ayerst has elected to refocus it's own women's health care research and development activities with a capital investment of almost $35 million and the establishment of a Women's Health Research Institute devoted to the medical and social issues critical to female health. The Institute is devoted to the development of women's health care medications. By removing the boundaries and integrating women's health research with the company's other discovery efforts in areas such as heart disease, stroke, breast cancer, and Alzheimer's disease, the company is able to leverage all of its resources to find solutions that benefit women's health.

With a primary focus on the definition of steroids, nonsteroidal molecules, and nonhormonal targets for the treatment and prevention of women's health disorders, Wyeth-Ayerst also supports other biomedical and behavioral research issues in women. Improved screening techniques, important developments in chemical synthesis and molecular biology, and genetic techniques are helping to accelerate advances. Genomic technology, in particular, holds the potential for uncovering the mechanisms of disease that underlie many women's health disorders.

Wyeth-Ayerst recently funded a $16 million ancillary study to the Women's Health Initiative (WHI) to evaluate the role of HRT in the prevention and treatment of Alzheimer's disease, and is also providing Premarin and Prempro to the 6-year "WHI Memory Study," which involves 8,000 postmenopausal women age 65 and over. Wyeth-Ayerst is also sponsoring the Heart and Estrogen-Progestin Replacement Study, known as HERS, a 5-year, $40-million, multicenter, placebo-controlled, double-blinded trial of the impact of HRT on approximately 2,700 postmenopausal women with heart disease.

In addition to its research program, Wyeth-Ayerst's Women's Health Research Institute will also disseminate information about women's health and support a wide variety of education programs aimed at both patients and physicians. The benefits of HRT for protection against osteoporosis in women after menopause is one such area of education.

Barbara S. Giesser, M.D. *National Multiple Sclerosis Society*

Sexual Dimorphism in Neurologic Autoimmune Disease

Sexual dimorphism in immune function is well documented. The female immune function is more vigorous than that of men. Much of this distinction appears to be related to the most fundamental difference between the sexes: the ability to conceive and bear children. A connection between the reproductive and immune systems has been realized since the last century, although the complex network of interactions that are involved are only just now beginning to be understood. Neural control is well established; however, it is becoming apparent that nervous and immune function do not operate in an isolated fashion, but are interdependent as well.

One of the most important connections between the nervous and immune systems is via the hypothalamic-pituitary-adrenal (HPA) axis. Females of several species, including humans, have more HPA responsiveness than do males, and have higher cortisol levels in response to stress. Even at a basic level, there appear to be differences between the sexes. HPA axis also demonstrates communication between the neural, endocrine, and immune systems, for example by regulating the immune cell number, activity, and production of cytokines. Cytokines, in addition to their principle activities of immunoregulation, can act directly on the hypothalamus to influence release of hormone-stimulating factors. Estrogen, progesterone, prolactin, and testosterone also have been shown to affect immune function. A third way in which the immune and neural systems communicate is via neurally active substances that are produced by immune cells.

Effects of Pregnancy

Not only is immune function different in women in terms of responsiveness and activity, but there are marked fluctuations in immune status during a woman's lifetime. This is in marked contrast to relatively steady-state immune function in men. The most dramatic changes in female immunity happen during pregnancy. Teleologically, this must occur to ensure that the fetus, which is after all immunologically foreign to the mother, is not rejected. The immunosuppression that is seen in pregnancy also leaves the mother more susceptible to infection by certain viruses, such as rubella or herpes. There are also animal model correlates of pregnancy-associated changes in immune function. For example, it is more difficult to induce certain autoimmune diseases in pregnant rodents, compared to their nonpregnant controls. Two examples of this are the protective effect of pregnancy upon experimental allergic encephalomyelitis (EAE), and also experimental allergic neuritis (EAN), an animal model of an autoimmune peripheral nerve disease, Guillain-Barre syndrome. Additionally, skin grafts survive longer on pregnant than nonpregnant hosts. In humans, in vitro assays of immune cell function demonstrate decreased response in immune cells taken from pregnant women compared to nonpregnant controls.

A number of substances are believed to be responsible for this immunosuppression, including not only sex hormones, but several pregnancy-associated hormones and proteins, including cortisone, alpha fetoprotein, and human chorionic gonadotropin. Pregnancy is generally associated with suppression of cell-mediated immunity, and normal or increased activity of humoral (antibody) immune responses. It has also been demonstrated that the levels of cytokines that modulate the immune response are increased during pregnancy. One mechanism for mediating this may be increasing levels of estrogen and progesterone throughout pregnancy, in addition to other immunosuppressive substances such as cortisol.

However, after delivery, the immune system rebounds back to prepregnancy levels. Clinically, these changes are manifest symptomatically in women with autoimmune diseases. Often there is dramatic improvement seen during pregnancy, with relapses occurring postpartum. These clinical changes are likely to be mediated, at least in part, by the different concentrations of sex hormones that are seen postpartum, in distinction to their levels during pregnancy.

Effects of the Menstrual Cycle

In addition to the changes that may occur in women during pregnancy, premenopausal women undergo cyclic metabolic and hormonal fluctuations on a monthly basis. However, in contrast to the primarily immunosuppressed state that occurs during pregnancy, immune function may be suppressed or enhanced coincident with different phases of the menstrual cycle. There are well-documented reports of allergic reactions, including anaphylaxis, occur-ring during the luteal phase of the menstrual cycle. Changes in functions of different components of the immune system have also been reported to change with different phases of the menstrual cycle. Lastly, many autoimmune diseases, such as lupus erythematosus, idiopathic thrombocytopenic purpura, rheumatoid arthritis, and neurologic autoimmune and nonimmune diseases are recognized to have symptom fluctuation coincident with menstrual cycle phases. In addition to MS and MG, these include migraine and epilepsy.

Studies of immune function at different phases of the menstrual cycle have been somewhat contradictory. Some authors have reported that immune cell responsiveness is low during the midpoint of the cycle and increased during menses, while other experiments did not support this conclusion. In another study, immune responses to *Candida,* a common yeast, were shown to be reduced in women during the luteal phase. This would be consistent with the actions of progesterone as an immunosuppressant. However, synthesis of complement was found to be influenced by progesterone levels, and levels increased during the luteal phase of the cycle.

More recently, it was demonstrated that levels of interleukin-I are increased during the luteal phase of the cycle. The expression of prolactin receptors on immune cells has been shown to vary at different phases of the menstrual cycle in healthy women. It has been suggested that immune responsiveness is higher during the ovulatory phase of the cycle to ward off infection that might interfere with successful development and maturation of the oocyte, but that immune function is depressed following ovulation so that sperm will not be destroyed before successful fertilization can occur. Obviously, different levels of sex hormones during different phases of the menstrual cycle can and do influence immune responses in ways that have yet to be clearly defined.

Changes in clinical status of women with autoimmune rheumatologic and endocrine diseases during menses and pregnancy have been extensively documented. In contrast, less is known about autoimmune neurologic disease as a function of hormonal climate. The two most common autoimmune neurologic diseases in which there is a clear female preponderance are myasthenia gravis and multiple sclerosis (MS).

MS currently affects an estimated 350,000 people in this country; 73 percent of whom are women. A geographic gradient exists, with higher prevalence in temperate (as opposed to tropical) latitudes. The onset of disease is usually in the third or fourth decade of life. However, epidemiologic studies have shown that the risk of developing MS changes if one moves from a high-risk to a lower-risk geographic area before the age of 15. Obviously, there are factors associated with puberty that impact on genetically susceptible individuals to manifest disease. In both sexes, sex hormones become active at this time of life, with the female system becoming more "turned on," and testosterone exerting a more constant immunosuppressive effect. It is tempting to speculate that pubertal hormonal changes are, at least in part, responsible for the female predilection to MS, but this remains to be proven.

The pathophysiology of MS has been demonstrated to be autoimmune in nature, and primarily involves T-cell-mediated immunity, although abnormalities in humoral immune function exist as well. CNS myelin autoreactive T-cell clones are recruited into the brain and spinal cord to attack myelin and oligodendrocytes. Several cytokines have been identified as being key to this cascade of immune events that result in demyelination.

Cytokine Involvement in MS

IL-1. Monocytes from patients with MS have been shown to produce more IL-I than cells from healthy controls. IL-1-positive cells have been identified on chronic active plaques in the brains of MS patients.

IL-2. IL-2-positive cells have been demonstrated in chronic active plaques in the brains of patients with MS. Some authors have reported increased levels of IL-2 and sIL-2R (the soluble IL-2 receptor, a marker of immune activation) in MS patients compared to controls, although there was no correlation with clinical status. A study of patients with RA reported that levels of sIL-2R decreased in response to increased stress.

TNF alpha. TNF alpha has been demonstrated to mediate myelin damage and is cytotoxic to oligodenrocytes in vitro. Levels of TNF alpha are higher in MS patients than healthy controls, and they have been shown to increase just prior to exacerbations.

IL-6. One study has demonstrated increased levels of IL-6 in MS patients compared to healthy controls. To date, it has not been definitively demonstrated that MS has an affect on normal hormonal flux, fertility, or pregnancy outcome. There is one report of lower testosterone levels in 20 percent of a small sample of men with MS. There have been a few studies which have reported slightly different hormone levels in MS patients compared to non-affected controls, i.e., higher prolactin levels, and one report demonstrated an increased prolactin level in women with relapsing remitting MS just prior to exacerbation, with a drop in levels during clinical remission. These data need to be interpreted cautiously, as factors such as stress may be involved with these apparent hormonal changes. At least two studies in the animal model of MS, EAE have reported that the induction and severity of disease can be blocked by bromocriptine, a compound which inhibits secretion of prolactin at the neural level. Other observations in EAE have noted that administration of exogenous estrogen can suppress the disease in susceptible rodents. To date, there have been no systematic investigations of the use of hormone replacement or supplementation therapy as a treatment for MS.

There have been few studies on the effects of the menstrual cycle on MS. One anecdotal report in the 1950s commented upon a patient who had regular exacerbations, at the time of menses, which were controlled by the administration of oral contraceptives. More recent studies have investigated the effects of the menstrual cycle by means of self-report questionnaire. In our series of 150 premenopausal women who responded to a self-report symptom checklist, 70 percent reported that their symptoms changed at a consistent time during the month; 60 percent reporting worsening of neurologic symptoms within 1 week of onset of menses. A much smaller sample in Great Britain, which polled 11 premenopausal women, reported premenstrual worsening of neurologic symptoms in 82 percent of the respondents. These are very preliminary data, and more work needs to be done in this area to confirm and expand these results.

As stated, MS does not affect fertility, pregnancy outcome, or lead to an increased number of congenital defects. However, the effects of pregnancy on MS have been the subject of multiple studies. The data indicate that clinical exacerbations actually are decreased during the 9 months of pregnancy. Most patients do quite well during pregnancy although symptoms of MS, which are normally present in the nonpregnant state, such as fatigue, urinary symptoms, and difficulty in ambulating, can be made worse by the physiologic changes which accompany pregnancy.

The decrease in number of relapses during the pregnant period would seem to be congruent with the overall immunosuppression at this time, and therefore it is not surprising that there is an increase in the number of relapses seen in the several months immediately following delivery. Of interest is the fact that women who breast feed (and therefore have higher prolactin levels) do not have more relapses than women who bottle feed. It is important to note that, although the number of relapses are increased in women with MS who become pregnant compared to nonpregnant patients, the long-term disability in both groups is not significantly different.

Myasthenia gravis (MG) is another neurologic autoimmune disease, which currently affects an estimated 40,000 Americans. The autoimmunologic abnormality in MG is the presence of anti-acetylcholine receptor antibody. This interferes with neuromuscular transmission and causes weakness. Interestingly, in patients under age 50, the female to male ratio is approximately two to one, and the peak onset of symptoms occurs between age 20 to 30. After age 50, the sex ratios become more equal.

Reports of effects of the menstrual cycle on MG vary. Some authors state that up to 40 percent of women with myasthenia show worsening of symptoms just prior to menses, which do not respond to treatment with estrogen or oral contraceptives. There is at least one report of cyclic variation in the levels of acetylcholinesterase with patients showing worsening of symptoms perimenstrually, when the enzyme activity was high, and clinical improvement when enzyme levels were lower at different times in the cycle. It would be of interest to track levels of antibodies in women with MG at different times of the menstrual cycle and see if there are clinical correlations.

Estimates are that of those women with MG who do become pregnant, approximately two-thirds will stay the same or improve, with exacerbations being more likely during the first trimester. In a fashion similar to MS, the postpartum period seems to predispose to exacerbations, and it is thought that this may be due to the loss of some of the immunosuppressive factors that are produced during pregnancy. Approximately 10 to 20 percent of myasthenic mothers will transfer antibodies to their offspring and produce the syndrome of neonatal myasthenia, but otherwise, MG does not appear to affect fertility or other pregnancy outcomes.

Future Research Directions

While it is clear that autoimmune disease predominates in women as a result of a series of intricate interactions between the neural, endocrine, and immune systems, the precise mechanisms by which this happens remain to be elucidated. It is well known that autoimmunity to self components exists in all healthy persons, but it is not understood why in some individuals, this escalates into the manifestations of an autoimmune disease. There are large gaps in our understanding of autoimmunity not only at a cellular and molecular level, but also as related to clinical phenomena, both in healthy people as well as in patients with autoimmune disease. Several lines of investigation are immediately suggested by the information that is already known. For example, are levels of sex hormones in men and women with neurologic autoimmune disease different than healthy age-matched controls? Are there differences in levels of immunologically active substances such as cytokines during different phases of the menstrual cycle in healthy persons, and do cytokine levels correlate with hormone levels? Is there dysregulation of normal cytokine/hormonal relationships in patients with autoimmune disease? What other hormone receptors exist on immune cells in addition to the ones already described? At what other sites in the brain can substances such as cytokines affect function?

What is the natural history of autoimmune neurologic disease such as MS in women as a function of hormonal milieu? Do differences in neurologic status and clinical course exist between premenopausal and postmenopausal patients? What percentage of premenopausal women with MS in a large population-based sample have quantifiable changes in neurologic symptoms and function at a predictable time during the menstrual cycle? Do the abnormalities of the immune response that have been demonstrated in MS patients impact upon hormonal function? What part do lesions at a neural level play in dysregulation of normal endocrine/immune interactions? Finally, can manipulation of sex steroids be useful as therapeutic modalities for neurologic autoimmune disease? These and other questions provide fertile ground for future research endeavors.

Phyllis Greenberger, M.S.W. *Society for the Advancement of Women's Health Research*

Gender-based biology — the examination of basic biological and physiological differences between men and women — is the next frontier for women's health research. This protocol has implications for disease research, clinical practice, disease prevention, medical education, and public health policy.

It is a testament to those of us here that there is recognition of gender differences in disease manifestation. While we may continue to encounter skepticism on this, none of us doubt the reality and importance of gender differences.

There is increasing evidence to support the study of gender-based biology. Scientists have observed basic biological differences between the genders in areas of research as diverse as genetics, endocrinology and metabolism, cancer, and pharmacokinetics. These differences can significantly impact disease development and treatment. An organized and methodological approach to gender-based biology could promote better understanding of why gender differences exist and their implications.

Until recently, these discoveries were a by-product of other research. We need to create a system where such observations are recorded and disseminated along with findings from more specific gender-based research studies.

We believe that the potential implications of gender-based biology are dramatic — for research, clinical practice, disease prevention and manifestation, medical education, and public health policy. Issues associated with women's health represent the cutting edge of today's knowledge and have the potential to dramatically change the way clinical medicine is conducted.

Hazel J. Harper, D.D.S., M.P.H., F.A.C.D. *National Dental Association*

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Issues in Women's Oral Health: The Quest for Answers Continues

Dr. Pinn, and distinguished panelists, thank you for providing the National Dental Association with this opportunity to present testimony during this important hearing. We would first like to acknowledge and thank you for your tireless commitment to women's health. We extend our highest commendation to the NIH Office of Research on Women's Health for their steadfast pursuit of a research agenda that will provide answers to some of our most complex and compelling questions. The quest for answers continues.

From our perspective, there are many factors that affect a woman's oral health status. The special oral health needs of women, that set them apart from men, are greatly influenced by hormonal fluctuations, age, and stress. Socioeconomic status and its relationship to health status and access to care is also a very relevant issue. Since minority women are disproportionately represented in the low socioeconomic status, differential access has been a contributing factor to poor health among African Americans and other minority groups.

For the purpose of this presentation, however, we would like to focus on some factors that are age-related, gender linked, or specifically problematic for minority women: namely, menopause, osteoporosis, diabetes, and stress. A brief description of these conditions captures only a few of the common dilemmas. The role of vitamins, the benefit of hormone replacement therapy, and the effects of stress are questions that shout resoundingly for more research. In addition, because of their relevance to prevention as well as health outcome, issues related to “access to health care” should be included in any meaningful women’s health research agenda.

Menopause

Throughout a female’s lifetime, hormones and their “abundance of” or “lack of” greatly influence the physical and psychological health of women. In research conducted over the last four decades, we have learned much about the oral cavity’s response to phasic hormonal fluctuations including: puberty, pregnancy, menses, menopause, and postmenopause.[1–5] However, as millions of baby boomers stand at the threshold of menopause, we realize that there are still too many unanswered questions, too many problems, and not enough solutions.

Oral manifestations during menopause are profoundly different from those during other phases of a woman’s life. For example, studies have revealed that increased sex hormone levels (estrogen and progesterone) correlate with increased gingivitis, due to changes in the subgingival microflora,[2] and the synthesis of prostaglandin is a key to altered gingival inflammatory response.[6] On the other hand, however, with the cessation of menses and hormonal deprivation, although there are *some* associated changes in the gingiva, including gingival atrophy and menopausal gingivostomatitis,[7] there are *more* problems in *other* areas of the oral cavity. The most common complaints are pain, burning, and altered taste sensations. In some women, salivary gland changes cause a reduction of the salivary flow which results in xerostomia or dry mouth. One or more of these complaints have been reported in 20 to 90 percent of menopausal and postmenopausal women.[7–10] Another study revealed the vast majority of women (80 percent) with burning mouth syndrome experienced pain from 3 years prior to 12 years after the onset of menopause.[11]

The cytological composition of the oral mucosa is strikingly similar to that of the vaginal mucosa. However, what is still unclear is whether the oral epithelium is as good an indicator of hormone levels as the vaginal epithelium and whether oral epithelium exhibits the same characteristic changes.[7] Additional research in this area would be very beneficial.

Regarding decreased salivary flow as a consequence of age, it is now generally accepted that in an otherwise healthy individual salivary gland output does not diminish with age.[7] The findings of many studies investigating salivary functions and complaints of burning and/or dry mouth have, however, yielded conflicting results. It was reported as early as 1951,[8] that the symptoms of oral pain and discomfort were relieved by the administration of estrogen, either systemically or topically.[7] However, in some studies the administration of estrogen, either topically or as systemic supplementation, revealed no significant change in salivary flow.[7]

Since women comprise 60 percent of the population age 65 and older and 72 percent of the population age 85 and older, older adults are at risk for chronic dental conditions.[12] The special needs of the geriatric patient will most frequently be the needs of women;[12] with women of low socioeconomic status and/or African American and other minorities heading the list of high-risk patients. Continuing research on the appropriateness and effectiveness of estrogen in hormone replacement therapy will be extremely valuable in determining its role in the oral health of menopausal and perimenopausal women.

Osteoporosis

Changes that occur in the alveolar bone of the jaw, as a result of the aging process, are similar to those occurring in the remainder of the skeletal system. These include osteoporosis, decreased vascularity, reduced metabolic rate, and reduced healing capacity. There currently exists a very subtle distinction between oral bone loss and osteoporosis on one hand, and definite linkages, although still unclear, between the two, on the other hand.

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of the bone, which leads to increased bone fragility and risk of fracture.[13] Oral bone loss can result from several systemic diseases and has been linked mainly with periodontitis or residual ridge resorption.[13] A growing body of data suggests, however, that older women are at risk for both osteoporosis and oral bone loss;[13] and that generalized bone loss from systemic osteoporosis may render the jaws susceptible to accelerated alveolar bone resorption and subsequent tooth loss. Estrogen deprivation is an initiating factor for osteoporosis. By contrast, periodontitis is initiated by a bacterial infection, and alveolar ridge resorption is a consequence of tooth loss.

In edentulous women, the inevitability of age-advancing ridge resorption, coupled with the consequences of osteoporosis, is particularly troubling. It has been reported that the height of the alveolar ridge in edentulous women correlated with total body calcium, which may indicate that women with severe postmenopausal osteoporosis, retain less bone following tooth loss.[14] Rapid and continuing mandibular bone resorption contributes to ill-fitting dentures that require frequent replacement. In addition, in extreme cases, it becomes virtually impossible to fabricate a functional mandibular denture that has any retention or stability, because of loss of bone height. Decrease of mandibular bone mass has been positively correlated with tooth loss in female subjects.[15]

In many cases, deterioration of the bone mass also causes the mandibular nerve to be located in a position more juxtaposed to the surface of the gingiva. This position creates a condition where the proximity of the nerve to the denture's undersurface makes this interface extremely painful. The patient is unable to wear the denture, because any pressure contact at the denture/nerve interface is intolerable. This can give rise to serious nutritional deficiencies.

As a rehabilitative measure, osseointegrated dental implants, strategically placed in areas with adequate bone height, are proving to be very advantageous. The role of osseointegrated implants retarding further bone loss in osteoporotic patients is an area that warrants further study.

Preventive measures for osteoporosis include early identification of the risk factors, estrogen replacement therapy (ERT), calcium supplementation, and vitamin D.[16] In one longitudinal study which began in the late 1970s, researchers have evaluated the risks and benefits of ERT in one population of older women in the California retirement community of Leisure World. The ongoing results of this study indicate that ERT is the most effective method for preventing osteoporotic bone loss and fractures in postmenopausal women. In this population, ERT reduced the risk of hip fractures by 50 percent. In addition, estrogen users have retained more natural teeth than nonusers.[17]

Early detection of osteoporosis can be accomplished by new and improved diagnostic tests. The current method of diagnosing osteoporosis is the bone mineral density test (BMD test). The most commonly used BMD test is DXA dual-energy x-ray absorptiometry. There is evidence to suggest that DXA measurements at the time of menopause many accurately predict future fracture risk.[7] It is hoped that in the near future, serum and urine tests that assess biochemical markers will be available to determine resorption and bone formation, as well as identify possible causes of bone loss.[7]

Current FDA-approved therapeutic options for the treatment of osteoporosis include: ERT, calcitonin,[18] and alendronate.[7] The possible beneficial effects of fluoride on osteoporosis are also under investigation.[19] Ongoing research on the long-term effects of the therapeutic options of fluoride, and the trace elements such as zinc, copper, and manganese,[20] will be enormously helpful for the treatment and prevention of osteoporosis.

Diabetes

Diabetes is the third-leading cause of death of among black Americans. The disease is especially common among older black women. Over the age of 55, one out of four has diabetes.[21] However, the National Center for Health Statistics reports that in the United States, other minorities have even higher rates of diabetes than African Americans.[21]

Ten percent of the 11 million diabetics in this country have Type I Diabetes, also known as juvenile-onset or insulin-dependent diabetes (IDD).[21] At present, there is no way to prevent Type I Diabetes, but there are ways to control the condition: daily insulin, a special diet, and exercise help keep the blood-glucose levels balanced. Type II Diabetes, however, accounts for more than 90 percent of all cases among blacks, mostly women. This condition can be controlled through diet for weight control, exercise, and possibly oral medication.[21] When diabetes is out of control, oral health can be severely compromised.

Changes that can take place in the oral cavity include: cheilosis, burning sensation, decrease in salivary flow, and alterations in the flora of the oral cavity. The most striking changes in uncontrolled diabetes are the reduction in defense mechanisms and the increased susceptibility to infection leading to destructive periodontal disease.[22]

In addition to proper diet and exercise, stress reduction has also been found to control the disease. Stress can make diabetes spin wildly out of control. When this occurs, the periodontal tissues become very vulnerable to disease and the lowered resistance of gingival tissues gives rise to inflammation and infection. Diabetics are very prone to disease and have impaired wound-healing capabilities. One of the early warning signs of out of control diabetes is unmanageable periodontal disease accompanied by recurring abscesses, tooth mobility, and tooth loss.

Immaculate oral hygiene and regular visits to the dentist for removal of plaque and infection-causing bacteria will keep periodontal disease under control. An increasing number of dentists and physicians are routinely recommending vitamin supplements for the control of periodontal disease predisposed by diabetes. Additional research on the effects of specific combinations of vitamins, used in conjunction with pharmacotherapeutics, would enhance the management of this disease.

Stress

Tension, anxiety, worry, or fear — all are conditions of stress that can have dangerous, sometimes fatal consequences. Stress can be physical or emotional, and can also exhibit many oral manifestations. Although stress is experienced by everyone, everyone does not respond the same way. In fact, it is not the stress itself that does the damage, but rather the way we handle it. For far too long, the consequences of stress on women and minorities has been minimized or disregarded. However, current research has shed some new light on an old subject.

Although stress is an integral part of all our lives, recent research suggests that stress poses profound difficulty for blacks and other minorities.[21] The everyday struggle of dealing with prejudice and racism produces a steady suppressed anger that many scientists believe is the reason for the explosive rate of hypertension among blacks.[21] Low socioeconomic status (SES) is directly proportional to poor health status and decreased access to care. There is a vicious cycle of poverty and stress that compromises health status and complicates health care.

Oral manifestations of stress include a myriad of conditions: painful and recurring aphthous ulcers, gingivitis and bleeding gums, bruxism (grinding and clenching teeth resulting in the abrasion and erosion of enamel, myofacial pain, and soreness), and temporomandibular disorders (TMD). TMDs alone, represent a cluster of related ailments with overlapping signs and symptoms. It is believed to be one of the most common outward manifestations of stress. However, recent research suggest that the risk factors, causative factors, and perpetuating factors, are multifactorial and may involve not only stress, but physical factors of dental malocclusion and the musculoskeletal relationship of jaw function to the head, neck, and face.[23,26]

Clinical findings in TMD include jaw aches, earaches, headaches, facial pain, muscle tenderness, joint soreness, limited movement of the mandible, joint sounds, and even chronic pain behavior. It is estimated that while 28.96 percent of the adult population has mild or self-limiting TMD, only about 5 percent require treatment. Of those presenting for treatment, females are estimated to outnumber males from a 9:1 to 3:1 ratio.[24,25] TMDs today are enmeshed in a raging scientific debate. Future research is needed to diagnose and classify TMDs. Unfortunately, clinicians and researchers have reached a frustrating impasse and are unable to arrive at a consensus on the appropriate standards of clinical care for these patients. The clinical management of these patients is often very difficult and perplexing with clinical failures estimated at 10 to 20 percent. Future research must not only bridge the diagnostic and treatment gaps but also focus on improving the education of the dental professional.[26]

Stress has been implicated in the etiology of periodontal disease, but the mechanism by which it acts as a pathogenic agent has not been fully delineated.[27] Although much of the research conducted has focused on the relationship between emotional stress and acute necrotizing ulcerative gingivitis (ANUG), other studies suggest that stress may even result in vertical and horizontal bone loss with associated pocket formation. This disease entity has been called "periodontal emotional stress syndrome (PESS)."[28]

The occurrence of ANUG, associated with negative life events and stress arising from life events and life situations, has linked psychosocial factors to this disease with abundant evidence.[29] Involuntary physiologic mechanisms that may induce stress-related periodontal disease include four major factors: impaired gingival circulation, lowered host resistance, decreased salivary flow, and endocrine imbalance.[27] In addition to the physiologic components, *psychological distress* and its relationship to myofacial face pain among women is an area currently being examined.[30] The correlation of emotional stress and myofacial face pain is one that merits further investigation.

To combat stress, in addition to stress release mechanisms — like exercise — most nutritionists recommend vitamin supplements in addition to a quality diet. Vitamin supplements are especially important for people whose health is compromised by specific illness, stress, smoking, alcohol, or poor diet. Specific vitamins and minerals have been found to be essential for healthy teeth and gums including: vitamin C, beta carotene (vitamin A), vitamin D, calcium, fluoride, magnesium, zinc, and copper.[21]

As far as we are concerned, health professional schools should assume more responsibility to provide adequate training in the area of nutrition. Most health care providers currently take continuing education courses to acquire knowledge in this discipline. Many have been motivated by the knowledge and interest of their patients to pursue nutrition as a critical course of study, and to incorporate nutrition counseling into their practices.

The effects of stress and the role of vitamins, minerals (and herbs), and other nutritional variables on a woman's health cannot be overemphasized and must not be overlooked. Oral health, as an integral part of overall health, can benefit from continued research, with accompanying curriculum changes in this area.

Closing Statement

When it comes to women's health, although we have come "a long way," we still have a long way to go. There are still too many unanswered questions swirling in a sea of controversy. As we forge into the 21st century, we contemplate a new era in women's research, with the mysteries surrounding women's oral health issues looming near the surface of discovery. In order to witness this imminent breakthrough, there must be continued and relentless commitment to the women's health research initiative. As caretakers of this nation and the world, women deserve better.

The gender gap in health research must be closed. There must be more emphasis placed on prevention, education, health promotion, and access. The physiologic, as well as the psychologic components, of health must receive more attention, with greater emphasis being placed on gender specificity and gender sensitivity in research, methodology, and design.

In order to adequately address the issues that surround the oral health status of women and minorities, this country must establish, maintain, and expand the pipelines that will produce black women dental researchers for the turn of the century and beyond.[31]

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Biomedical and Behavior Research Agenda

It is my pleasure to present the American Heart Association's (AHA's) comments focusing on the biomedical and behavioral research agenda for women's health in the area of cardiovascular diseases. AHA commends the National Institutes of Health Office of Research on Women's Health for holding this regional meeting to update the "Report of the NIH: Opportunities for Research on Women's Health."

The American Heart Association is the nation's largest voluntary health organization dedicated to the reduction of disability and death from heart attack, stroke, and other cardiovascular diseases. Annually, AHA's 52 affiliates nationwide coordinate the activities of about 4.3 million volunteers in carrying out this mission.

Cardiovascular diseases remain a major cause of disability and the number one killer in the United States; killing more than 954,000 Americans each year. About 13.5 million Americans, including 6.6 million under age 60, now live with the effects of heart attack. Approximately 3.8 million Americans, more than 900,000 of whom are under age 60, suffer from the consequences of stroke, the main cause of permanent disability in the United States.

In the United States, someone dies from cardiovascular diseases every 33 seconds. In 1992, cardiovascular diseases accounted for 4.7 million years of potential life lost before age 75, followed by cancer and accidents. Recent estimates by the National Center for Health Statistics show that the number of deaths from cardiovascular diseases began to rise in 1993 after years of decline.

More than one in four Americans suffer from some form of cardiovascular diseases at an estimated cost of $151 billion in 1996. Costs for patients with cardiovascular diseases are growing because we are treating disease with expensive technology, not preventing it. Moreover, there will be even more cardiovascular disability in the future because many people who have had effective treatment for coronary artery disease and prevention of atherosclerosis at age 40 to 60 will develop further cardiovascular diseases later in life unless effective prevention methods are discovered.

Cardiovascular diseases remain the number one killer of females. About 45 percent of female deaths in the United States are from cardiovascular diseases. Cardiovascular diseases kill almost twice as many American females as all cancers. Heart attack, Americans' single largest cause of death, kills more than *five times* as many females as breast cancer. Of the more than 489,700 deaths from heart attack each year, more than 48 percent occur in females.

Importantly, the heart attack death rate for African-American women age 35 to 74 is about twice that of white women and three times that of women of other races. Stroke, America's number three killer, kills *twice* as many females as breast cancer. However, until recently, heart attack, stroke, and other cardiovascular diseases in women had not been recognized as serious health problems, particularly by women themselves.

Women develop heart disease later in life than men. But, at any age, heart attack in women is a more deadly disease. Older women who have suffered heart attacks are twice as likely as men to die from them within a few weeks. About 44 percent of women who have heart attacks die within a year, compared to 27 percent of men. In 63 percent of women who died suddenly of coronary heart disease, there were no previous symptoms, compared to 48 percent of men.

About one in five females suffers from heart attack, stroke, or other cardiovascular diseases. Women experience unrecognized heart attacks more often than men. After suffering a heart attack, 18 percent of women will suffer a stroke, compared to 9 percent of men. More than 60 percent of men and women who suffer a stroke die within 8 years, but long-term survivorship is higher in women than in men.

Other cardiovascular diseases are prevalent in women. More than 87,000 of fatal stroke victims are female. This comprises 60.6 percent of fatalities from stroke. Much less prevalent are cases of rheumatic heart disease, an inflammatory disease that permanently damages the heart and its valves. Even in this disease, the number of deaths is higher in females (69.9 percent) than in males.

Despite the increasing attention being focused on health issues directly relevant to women, there remain continuing and emerging gaps in knowledge about women and cardiovascular diseases that need to be addressed. Throughout this testimony, examples of research studies needed to answer some of the most perplexing questions relevant to women and cardiovascular diseases are cited.

The major cardiovascular disease risk factors apply to women in the same manner as they do to men. There are, however, differences in the evolution of atherosclerosis between men and women and the risk of disease. These are probably related to the interaction of sex hormones and specific risk factors. Interventions should be tailored to sexual differences in factors such as body fat, behavior, or estrogen.

Research Needs

- What is the basic mechanism of action of both endogenous and exogenous reproductive hormones in the development of atherosclerosis?
- Will estrogen and estrogen-progestin combination alter the risk of coronary heart disease?
- What is the relation of estrogen to other risk factors, on vasoregulation, and other atherosclerotic processes?
- What are the metabolic effects of estrogen replacement therapy or hormone replacement therapy (HRT) on patients presenting with other metabolic abnormalities?
- How efficacious is HRT on cardiovascular disease in postmenopausal women?

The major risk factors for coronary heart disease (CHD) and stroke are similar for men and women: particularly high levels of low-density-lipoprotein cholesterol (LDLC), low levels of high-density-lipoprotein cholesterol (HDLC), smoking, high blood pressure, diabetes, obesity, and physical inactivity. The gender differences appear to be in the distribution of risk factors, levels of risk, and risk of disease at similar risk-factor levels. Estrogens have direct effects on the arterial wall and appear to enhance the activity of LDL receptors, resulting in lower levels of LDLC among premenopausal women compared with men. As the estrogen level and ovarian function declines, almost all postmenopausal women have higher LDLC levels. This increase of LDLC in older women probably accounts for much of the increase in atherosclerosis and CHD. The prevalence of thyroid disease is higher in women than in men; however, the relationship between clinical and subclinical thyroid disease and change in cardiovascular disease (CVD) risk factors, during and after menopause, is unknown.

Research Needs

- Can the rise in LDLC level and development of atherosclerosis in women be prevented?
- What changes occur in risk factors during the peri- and postmenopausal periods in nonwhite populations?
- Do differences in hormonal measures, dietary factors, and genetic characteristics influence the changes in risk factors and the progression of atherosclerosis?
- Why are HDLC levels higher in women after puberty compared with men? Are they determined solely by sex-steroid metabolism?

Weight gain occurs between 30 to 50 years of age in women; in men it usually occurs between 20 to 40 years of age. The distribution of body fat is different in women than in men. For example, more central obesity exists in black women than in white women, but body mass index and waist:hip ratio predicted cardiovascular death only in white women. Gender or racial differences in HDLC levels among women is partially a result of individual differences in obesity, distribution of body fat, insulin, glucose, metabolism, obesity-related effects on Lp(a) and hepatic lipase, insulin resistance, and fatty acid metabolism.

Research Needs

- How do the patterns of obesity and fat deposition relate to cardiovascular disease in women?
- What are the determinants of weight gain in women?
- What are the most effective approaches to preventing obesity among minorities?
- Is there an association between number of pregnancies and weight gain?

Mortality rates for heart disease are higher among women with less than 8 years of schooling. In 1960, the mortality rate for these women was 80 percent higher than among women who had some college education. These differentials exist 20 to 30 years later. In 1988, 40 percent of families were dual-worker families in which both husband and wife worked; compared with 9 percent in 1940. There has been a dramatic increase in divorce and one parent families. Social environment and income, as well as access to and quality of medical care, play a direct role in risk factor levels.

Research Needs

- What are the roles of poverty, work environment, and family responsibilities in the etiology of CVD risk factors or events in women?
- What are the psychosocial factors related to CVD in women?
- What are specific CVD risk factors in women?
- Do hormonal or psychosocial factors explain why childless women have a higher risk of sudden death?
- What is the relationship of pregnancy history to CHD risk factors?
- What are the associations between social factors and risk of CHD in women?

Recommendations for research from the National Heart, Lung, and Blood Institute Task Force on Sociocultural Factors in Cardiovascular Disease in Women should be reaffirmed. The task force emphasized the importance of developing valid and reliable measures of work and family exposures for women, rather than using measures from studies of men. Measures are also needed to record women's situations in terms of socioeconomic positions, occupation, family life, psychosocial demands, social support, and discrimination. Certain characteristics among premenopausal women provide natural experiments for studying the interrelationship of lifestyles, obesity, hormones, and coronary artery disease. Women who have polycystic ovary syndrome have obesity, more androgenic sex-steroid hormones profiles, insulin resistance, amenorrhea, and high blood estrone levels primarily from the adrenal gland. Women who have this syndrome generally have low HDLC levels, but it is not clear whether they are at increased risk of atherosclerosis, whether treatment of obesity modifies clinical aspects of the syndrome and risk factors, and what changes in risk factors and CHD risk factors occur with aging. The relationship of premenopausal hormone patterns and CHD has not been studied adequately.

About 50 percent of African-American women have a hysterectomy prior to the time of natural menopause. A leading cause of hysterectomy in these women is uterine fibroids. Fibroids may be part of a syndrome of obesity, elevated estrogens, hypertension, diabetes, and subsequent risk of vascular disease, especially among African-American women.

The use of luteinizing hormone-releasing hormone (LDRH) agonists and antagonists in the treatment of uterine fibroids effectively cause oophorectomy. Their use provides a natural experiment for evaluating the acute effects of chemical oophorectomy on HDLC, LDLC, and clotting factors in subgroups of women.

Women are more likely than men to die of stroke. Twice as many black women die of stroke in all age groups. Multiple pregnancies may increase risk of cerebrovascular disease through the mechanism of insulin resistance. Diabetes triples the risk of stroke in women. The increased risk of subarachnoid hemorrhagic and ischemic stroke in women who smoke may be reversed in 2 to 4 years after smoking ceases.

Research Needs

- Are there other potentially reversible stroke risk factors in addition to smoking?
- Why is there a later onset of stroke, other cardiovascular diseases, and coronary heart disease in women versus men?
- What is the extent of various venous disorders seen predominantly in women? Can they be prevented?
- What is the effect of estrogen therapy on the reversal and progression of stroke and peripheral vascular disease?

Other cardiovascular disorders that particularly affect women cause inflammatory microvascular and macrovascular diseases. The most important of these is systemic lupus erythematous (SLE). Coronary heart disease is higher in these patients. While part of the excess death is probably related to treatment, corticosteroid drugs, and renal disease, it is possible that the autoimmune inflammatory process of SLE affects the coronary and cerebral arteries, thus increasing risk of CHD and stroke. SLE should be considered as providing a natural experiment for measuring the effect of autoimmune disease and inflammatory cytokinins on the development of CHD and atherosclerosis, as well as dysfunction of the heart muscle which can cause serious arrhythmia. The relationships of physical activity and cardiorespiratory fitness with hemodynamics, risk-factor levels, and behavioral studies need to be assessed in pre- and postmenopausal women and minority populations.

Insulin-dependent diabetes mellitus is an important cause of premature CVD among young men and women less than 45 years of age. CVD is especially high among premenopausal women with insulin-dependent diabetes mellitus who smoke cigarettes. Studies are needed to ascertain why diabetes is one of the few conditions that greatly reduces the favorable CVD status of premenopausal women. Data are needed on efficacy of medical and revascularization therapy, and on exercise rehabilitation for CHD failure and stroke.

The apparent differences in presentation of CVD and response to intervention, which may be complicated by menopausal status in women compared with men, should be studied.

Additional Research Needs

- What are the qualitative aspects of angina in women versus men?
- Do women have subtle asymptomatic limitations in coronary reserve?
- Are there gender-related differences in silent ischemia in coronary artery disease?
- How is response to diet modification affected by age, status, hormone replacement therapy, and baseline lipid lipoprotein levels?
- What are the outcomes of antihypertensive therapy by gender?

Unique scientific and logistical issues must be addressed in any randomized trial of CVD in women. These relate primarily to hormonal differences, psychosocial variables, and possibly anatomical factors peculiar to women.

Our ability to combat cardiovascular diseases correlates directly with the level and quality of overall support for basic and clinical research and prevention efforts.

Since 1949, the American Heart Association has invested almost $1.4 billion in research to increase knowledge about cardiovascular diseases. The size of this financial commitment makes AHA second only to the federally sponsored National Institutes of Health in the amount devoted to cardiovascular research. Although AHA will continue to commit increased resources toward research, larger efforts by the Federal Government are essential to win the battle against cardiovascular diseases. A significant increase in funding for federal biomedical research is critical.

In constant dollar from FY 1985 to FY 1995, the budget for the National Institutes of Health increased by 31 percent compared to a 4.8 percent decrease for the National Heart, Lung, and Blood Institute's Heart Program. Since FY 1992, funding for National Institute of Neurological Disorders and Stroke-supported stroke research increased by less than 1 percent in constant FY 1985 dollars. Yet, an overwhelming number of respondents in a

1996 nationwide American Heart Association-commissioned survey support increased funding for heart research (79 percent) and stroke research (77 percent).

Chronic underfunding of heart and stroke research has discouraged young people from entering the field. This is dramatically reflected by statistics showing that in 1994 there were 63 percent fewer research grants awarded by the National Heart, Lung, and Blood Institute's Division of Heart and Vascular Disease, to individuals under the age of 40, than there were in 1994. In absolute numbers, this is only 123 research grants currently to doctors and scientists under the age of 40, approximately 1 per medical school, in the whole area of heart and vascular disease. As a result, this nation has lost, or is losing, a whole generation of cardiovascular disease researchers.

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Adolescents and Sexually Transmitted Diseases

This paper presents a brief overview of sexually transmitted diseases (STDs), including acquired immunodeficiency syndrome (AIDS), in adolescent populations. Using the framework of a mathematical model (which considers how, why, and whether an infection spreads within a population), the epidemic of STDs among adolescent populations is considered. The unique aspects of adolescent behavior, adolescent biology, and the social context of adolescents' lives are highlighted.

Magnitude of the Problem

The majority of young people have sexual intercourse for the first time in their teens.[1] A recent report indicates that more than half of women and almost three-quarters of men have had sexual intercourse by their 18th birthday.[2] Two recent studies have provided data indicating that sexual activity among teenagers is increasing.[3,4] Other studies have also documented that adolescents and young adults are inconsistent users of male condoms.[5]

Given these behavioral factors, the implications for risk of sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infection, are undeniable and are supported by the data trends for STDs in teen populations. Recently the Centers for Disease Control summarized reported AIDS cases in teenagers for the first 6 months of 1995. The cases increased 524 percent compared to 1994. Furthermore, if one assumes an incubation time of 8 years from the time of HIV infection to the onset of AIDS, 20 percent of all persons with AIDS were infected as teenagers.[6] A closer look at the demographics of the new AIDS cases reveals that gay teens account for most of these. Arguably this trend represents cases among new susceptibles in a larger population that has been at high risk for HIV infection since the beginning of the AIDS epidemic.

If other STDs are considered, however, a larger picture of high-risk adolescent populations emerges. In the United States, it is estimated that 12 million incident cases of STDs occurred in 1994; the majority of these cases are in young adults, with an estimated 3 million occurring in teenagers. Age- and gender-specific rates are depicted for two bacterial STDs, gonorrhea and chlamydial infection. Cases of gonorrhea are found among populations of low socioeconomic status (SES) in urban and rural areas of the United States. The highest rates are seen in young men 20 to 24 years of age and in teenage girls 15 to 19 years of age.[7] There is enormous heterogeneity, however, depending on the geographic area, with the highest U.S. rates reported from the District of Columbia, where one in ten 10- to 14-year-old boys was infected.[8]

The national picture of chlamydial infection is harder to bring into focus for several reasons: (1) not all regions are reporting data yet; (2) not all regions have the resources to implement chlamydial control programs now recommended by the CDC; and (3) new diagnostic methods have increased our ability to identify patients. Two trends are clear, however. First, rates are highest in 15- to 19-year olds regardless of SES. Second, where screening and treatment programs are implemented, rates among teens have dropped.

For the other viral STDs, the situation is similar to that for gonorrhea and chlamydial infection, although the trends have more serious implications for transmission. Because these viral infections are incurable, each incident case becomes a prevalent case. Furthermore, any STD, whether it is theoretically curable with treatment or not, can accumulate in the population *if* the patient is not effectively treated.

The Reproductive Rate of Infection — How It Applies to Adolescent Populations and Sexually Transmitted Diseases

Early on in the AIDS epidemic, May and Anderson took a mathematical view of the potential for HIV infection to spread through a population.[9,10] Although the mathematical proofs are complicated, the basic principles of the formula that they derived are not. They tried to identify how fast an infection can "reproduce itself" or the speed and extent to which an infection can move through a population. They recognized that there are three essential components of any epidemic: (1) the infectious organism or the "bug;" (2) the biologically susceptible host; and (3) the behaviors of both. They then determined the mathematical relationship among the essential components. The simplified version of the formula is $R_{o=cd.}$ R_o is the reproductive rate of infection; o is the infectivity rate: in other words, how easily the infection is transmitted from one host to the next; c is the rate at which new partners are chosen, as well as the characteristics of the partner; and d is the duration of the infection: in other words, once established, the infected person may be "infectious" for a long or short time. The duration would reflect whether the infection is self-limiting, or curable with treatment, or incurable. Subsequently, this approach has been used to look at other sexually transmitted diseases and the behavioral risk factors associated with transmission and development of long-term consequences or sequelae.[11,12]

Within each factor of the equation there are biological and behavioral risk factors that have been causally associated with increased risk of transmission/acquisition. In addition, a number of associations, or markers of risk, have been identified. With risk markers, however, a direct causal link to STDs/HIV infection has not been demonstrated. The interested reader is referred to the paper by Padian and co-workers for a more complete discussion of risk factors versus markers.[13] Among the biological and behavioral risk factors/markers that alter the risk of STDs, those that are of particular concern in adolescent populations are highlighted.

Infectivity Rate

Within the risk factors/markers, 9 of 13 represent particular risks for adolescent populations. Several merit particular comment. Genetic susceptibility: the hormonal changes of puberty and arguably those induced by some hormonal contraceptives are manifested by changes in the epithelial surface of the cervix. The surface of the epithelium is covered with a mucous coat; the tissue surrounding the opening to the uterus, the cervical os, is covered with stratified squamous epithelium. Close to the cervical os, the tissue changes into columnar epithelium; the small zone of transition is dark pink. When we look again at a healthy cervix, the zone of transition is much larger because of hormonal influences. This enlarged transition zone, known as the zone of ectopy, is the site of attachment and establishment of infection in gonorrhea and chlamydial infection. The larger the zone of ectopy in the cervix of the adolescent, the larger the target for these infections.[14,15] Sexual practices: in some adolescent populations anal intercourse is practiced in order to “preserve virginity” and as a method of birth control. Rectal transmission of HIV infection is facilitated by trauma and direct contact with blood and by receptor-mediated uptake of the virus owing to CD4-like receptors on rectal epithelial surfaces.[16] Contraceptive method: as mentioned above, hormonal methods of contraception may alter susceptibility to infection because of alteration of tissue architecture, or changes in the character and amount of mucus, or changes in pH.[17]

Rate of Partner Change and Partner Characteristics

Within the risk factors/markers, four to five have special implications for adolescents. Number and types of partners: given that adolescents begin having sexual intercourse at an early age, the likelihood is that for many the lifetime number of partners will be large. When looking at the sexual behavior of 20 year olds, it is estimated that one-third have had two to five lifetime partners by this age.[3,18]

The significance of lifetime partners can be best appreciated with a simple arithmetic problem. Keeping in mind the concept of incurable viral STDs accumulating in the population and two assumptions: (1) that adolescents practice serial monogamy (i.e., one partner at a time in series); and (2) that all adolescents in a given population have the same partner acquisition rate, how many exposures, real and phantom (partners of partners), are represented in an adolescent’s life between the ages of 15 and 24 if:

- the adolescent has sexual intercourse for the first time at 14;
- each relationship/partner lasts 1 year; and
- they have a new partner each year?

In the 9 years, they will have *nine real partners.* In terms of incurable viral STDs, where both the real and the phantom partners are relevant, they have been exposed to *more than 500 partners.* The significance of exposure to phantom partners is reflected in recent studies of human papillomavirus infection; high infection rates were observed in college-aged women during their first year of sexual activity. An attack rate of 25 percent was seen among women in Seattle; interestingly the average number of partners for the first year of sexual activity was fewer than two.[19]

Duration of Infection

Aside from the characteristics of the infectious agent, all of these risk factors/markers represent particular problems for adolescent populations. Of the seven infections that are solely or primary sexually transmitted, four are treatable/curable bacterial infections (chlamydial infection, gonorrhea, syphilis, and chancroid); one is a treatable/curable parasitic disease (trichomoniasis); and three are incurable viral infections (human papillomavirus infection, genital herpes, and HIV infection). For the most part, all of these infections can and do manifest without symptoms.[15] As a result, people without symptoms, with unrecognized symptoms, or with symptoms so indolent as to preclude health care-seeking behavior represent a continued source of infection for their partners.

In addition to the absence of symptoms, the lack of access to health care, the policies of parental and partner notification, the expense of health care, and the failure to accept and comply with treatments are some of the factors that increase the duration of infection.

Distribution of STDs, Including HIV Infections, in the Population

For some infections, virtually all cases are found within populations that are at high risk. As discussed earlier, the demographics of those populations include low SES, rural or inner-city residency, and partner number. In the case of chlamydial infection, genital herpes, and human papillomavirus infection, the diseases are “clustered” to a lesser extent and are more evenly distributed in the population.

Although AIDS cases in the United States are currently clustered in high-risk populations, there is no reason, based on the models that have been used to analyze the epidemic, why they will remain clustered. HIV infection has a number of characteristics that contribute to sustained presence within a population:

- HIV is transmitted sexually, a behavior that is required to reproduce our species;
- HIV infection is an asymptomatic disease; the host is infectious for many years;
- the viral genome becomes a part of the host’s genome and can remain “invisible” for a long time; and
- HIV lives within the body’s disease-fighting system, making vaccine development efforts extremely difficult.

Because we neither screen for nor report HIV infection in a systematic way, we are forced to extrapolate HIV-infection trends from AIDS cases. Unfortunately, the development of AIDS is the terminal phase of the infection, and AIDS cases do not reflect trends in HIV-infection rates *today.* Some argue that the epidemic has leveled off and that we are experiencing the saturation of susceptibles in high-risk populations. This could be the explanation for the data; the other possibility is that we are experiencing the end of the first phase of the epidemic, during which high-risk populations became infected at very high rates. During the plateau that separates phase 1 and phase 2, the infection moves clandestinely into the general population, and then the AIDS case rates would begin to climb again. This time, however, the slope would be less steep, since the cases would be occurring in lower-risk populations.[20,21] The possibility that adolescent populations and STDs (chlamydial infection and genital herpes) could provide the messenger and the opportunity for HIV infection to become more broadly distributed in the population is raised in studies of adolescent populations that are geographically and socially juxtaposed to high-risk populations.[22–25]

Whether we will be able to aggressively and effectively address the implicit research and program needs and opportunities that must be met in order to prevent the spread of HIV infection into adolescent populations remains to be seen.[26] The risk factors/markers represent a very formidable research agenda: basic biomedical and behavioral research, applied research, and clinical and operations research. Furthermore, more support for clinical services for adolescents in a variety of settings is implicit in an effective approach to prevention and control.

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Lisa Kaeser, J.D. *The Alan Guttmacher Institute*

The Alan Guttmacher Institute is a not-for-profit public education and public policy organization that focuses on reproductive health. This testimony addresses the needs in one area of reproductive health, that of further research into successful use of contraceptive methods to prevent unintended pregnancy.

An increasingly greater portion of women's lives is spent attempting to control their fertility. During the last century, both puberty and sexual initiation have moved to earlier ages. The interval for women between puberty and marriage has risen and most married women choose to delay or limit the number of children they have. Women today spend three-quarters of their reproductive lives, from menarche to menopause, trying to avoid becoming pregnant.

Unintended pregnancies, and their outcomes, carry significant health and social consequences for both the woman and, if she carries to term, the child. However, in 1988, more than 3 million unintended pregnancies occurred in the United States. If contraceptives were always used perfectly by everyone who wanted to avoid becoming pregnant, the rates of unintended pregnancy in the United States would be a fraction of where they now stand. Current wisdom, which provides a major rationale for continued research on new contraceptives, points to difficulties women and men have integrating correct and consistent use of current methods into their daily lives. Clearly, a better understanding of the needs of women and their partners who wish to use contraception is needed, both to increase the use of currently available methods and for the development of new ones.

Specifically, a better understanding is needed of what causes people (1) to delay initiating use of a contraceptive method once they become sexually active, (2) to permit gaps between periods of contraception use, or (3) not to use their chosen method as well as possible.

Obstacles that may prevent couples from using contraceptives when they are at risk for unplanned pregnancy include: (1) women not initiating the use of, or stopping the use of, contraceptives due to a lack of accurate information or fear of side effects, and (2) access to and payment for family planning services. Research is needed on what may contribute to using contraceptives. Such research may focus on: a woman's ambivalence about childbearing, common mistakes in the use of contraceptives, concerns about disease that prevent women from using the most effective contraceptive method(s), and the impact of education and counseling on the successful use of contraception.

Although contraceptives have been used for decades, many questions remain unanswered. While answers to these questions will not necessarily "solve" the dilemma of unintended pregnancy in the United States, if the answers can assist in reducing the rates of unintended pregnancy, a substantive contribution to women's health can be made.

Virginia T. Ladd *American Autoimmune Related Diseases Association*

Autoimmunity is a debilitating condition in which the immune system attacks the body's own tissues or cells. The condition is the root cause of more than 80 serious and chronic diseases, including connective tissue diseases (lupus); diseases involving the joints (rheumatoid arthritis); skin diseases (scleroderma); neuromuscular diseases (multiple sclerosis); and endocrine diseases (Graves disease). The American Autoimmune Related Diseases Association (AARDA) is the nation's only organization dedicated to raising the awareness of early warning signs of autoimmune diseases and promoting collaborative research efforts to cure autoimmunity.

During its recent Health Women 2000 conference in Washington, the Office on Women's Health recognized that autoimmunity is largely a women's health problem, representing approximately 75 percent of all autoimmune patients. ORWH has a great opportunity to increase the visibility and focus on autoimmunity as a common cause of diseases that disproportionately affect women.

For many women, getting a proper diagnosis for an autoimmune disorder is as difficult as the disease itself. Misdiagnosis and late diagnosis, and their associated problems, are major concerns of AARDA. Several factors contribute to improper diagnosis, which delays appropriate treatment. For instance, symptoms of autoimmunity vary and they may come and go. Also, symptoms are often difficult for a woman to describe precisely to her physician. The multiplicity of symptoms and affected body systems may cause the patient to undergo a series of unsuccessful tests as specialists attempt to establish a diagnosis. The difficulty in identifying symptoms may result in a physician not taking the patient's complaints seriously. A survey AARDA conducted found that over 65 percent of patients with autoimmune diseases are labeled hypochondriacs in the earliest stages of their illness. The psychological impact of late diagnosis can be devastating.

The problems of timely recognition and diagnosis results from the fragmented way in which the medical community approaches autoimmunity. Unlike cancer, autoimmunity has yet to be embraced by the medical community as a category of disease. Discovering the root cause for all autoimmune diseases depends on basic research. ORWH is well positioned to take a leading role in organizing a concerted education and research campaign to improve recognition of, and early testing for, autoimmune diseases and in promoting basic research into autoimmunity. Basic research will yield information that benefits the treatment and diagnosis of all autoimmune diseases and represents the most promising approach to finding a cure.

AARDA desperately seeks to bring a national focus to autoimmunity. We feel that ORWH, perhaps more than any other office or institution, can substantially improve our country's approach to this critical women's health issue. We strongly urge ORWH to push for collaborative efforts to conduct basic research that would bear fruit for all autoimmune diseases, rather than continuing to focus more narrowly on individual diseases. It is through combined research that we will be able to diagnosis, treat, and ultimately cure this debilitating disorder.

Dorothy Mann *Family Planning Council*

The Family Planning Council is a private, nonprofit organization which receives all Title X federal family planning funds for Philadelphia and its four surrounding counties. With these and other public funds, the Council subcontracts with 24 local health care organizations. The typical Title X family planning patient seen in any one of our programs is an African-American women between the ages of 20 and 29. She is poor, and the family planning clinic offers the basic health care she needs to stay in school, keep a job, or pursue vocational training.

Gaps in knowledge about women's health involves reproductive issues. Specifically, the need for knowledge is greatest in the areas of pregnancy and disease prevention. According to the Institute of Medicine, the rate of unintended pregnancy among American women is disgracefully high, with almost 60 percent of all pregnancies unintended. Regardless of a woman's economic level, unintended pregnancy affects every sphere of a woman's life, threatening her physical well being, her emotional stability, and her ability to obtain or keep gainful employment. The high rate of unintended pregnancy among American women should be a clarion call to the health care and medical research establishments and the pharmaceutical companies to devote the resources necessary to significantly reduce this statistic. Contraceptive research is needed to find methods that offer the full range of protection against unplanned, unwanted pregnancy as well as debilitating, highly contagious diseases.

A number of other questions also have important implications for women's health. These questions relate to HIV/AIDS; the reproductive health care needs of premenopausal, perimenopausal, and postmenopausal women; risks for unintended pregnancy, sexually transmitted diseases; cancer; education about the use of hormone replacement therapy; and infant mortality among African Americans.

Unlike with research and medical service delivery for cardiovascular disorders, breast cancer, endocrine disorders, and Alzheimer's disease, Congress dictates the methodology, scope of research, and medical procedures in the area of reproductive medicine. Currently, Congress is considering legislation that will require the written consent of parents for any research that involves adolescents. Although strict consent requirements and protection of human subject regulations exist, Congress wants to curtail research that examines any research related to adolescent sexual health. In this way a political agenda takes precedence over the quest for knowledge and understanding. It is easier to allocate public and private resources to politically palatable research in such areas as breast cancer and osteoporosis than it is to devote the necessary resources to other equally important areas of women's health that are related to sexuality. While adding women to clinical trials and other research efforts is necessary and important, it will not matter if political agendas dictate subject, method, and outcome. In women's health research, it is important to invest in and examine controversial issues of sexuality and reproduction. It will take courage to expose and stand up to powerful political forces that would otherwise impede this research.

Rita M. May *Sjögren's Syndrome Foundation, Inc.*

Autoimmune and rheumatoid diseases are the stepchildren of the women's health initiative. Despite the fact that diseases such as multiple sclerosis, scleroderma, and Sjögren's syndrome profoundly affect women, they are not considered topics of high priority on any of the women's health agendas.

Medicine and science favor the so-called "interesting questions." They attract the greatest scientific intellects, are well funded, and reflect social priorities. For example, AIDS, a comparatively rare disorder, was successfully transformed from an interesting scientific problem into a well-funded institution. During the 14-year period from

1981 to 1995, about a half-million Americans were diagnosed with AIDS compared to more than 37 million Americans who suffered from other autoimmune diseases. The drive to find a cure for AIDS has made NIAID the third most heavily funded NIH institute, while funding for more widespread autoimmune diseases has declined.

Probable reasons for the lack of interest and minimal funding include the following:

- the sheer number of autoimmune diseases and the dearth of clear diagnostic guidelines;
- the association of autoimmune diseases with aging but not death, and the subsequent lack of urgency to discover treatments and cures; and
- the higher prevalence of autoimmune disease among women than men.

Sjögren's syndrome presents an excellent example of the ignorance, invisibility, and unpopular nature of autoimmune and rheumatoid diseases in general, and within the scientific and women's health communities in particular. Although it affects 2 to 4 million Americans — 90 percent of whom are women — it is one of the least diagnosed. Moreover, none of the most likely NIH institutes — NIAMS, NIAID, NEI, nor NIDR — has sponsored epidemiological studies directed at Sjögren's syndrome. Indeed, the chances for even highly sophisticated audiences to have heard of Sjögren's (much less be able to spell it!) are low, sadly demonstrating the lack of interest in these diseases and in the women who suffer from them.

I ask that NIH dedicate research monies to autoimmune disease research and conditions affecting the aging as well as diseases affecting reproductive issues and youth.

Margaret K. McLaughlin, Ph.D. *Magee-Women's Research Institute*

At the Magee-Women's Research Institute, we believe that increasing the number of women scientists and facilitating their careers will result in more women's health researchers.

This task requires a concentrated effort to increase public awareness about the significance of scientific research. We believe that our outreach work will result in greater awareness of, and interest in, science and research on women's health. Our efforts target high school and college students — both boys and girls, men and women. We host tours of the Institute, provide hands-on demonstrations of our work, sponsor a summer research volunteer program, and provide stipends for college students studying the sciences. Some programs we target directly at young women. For example, we have a special relationship with a local girls' high school and pay special attention to women's colleges in our geographic area.

At a more advanced level, we recognize that nursing is a severely underutilized source of women in science. The Institute pays part of the salary for the director of nursing research at Magee-Women's Hospital, where she educates nursing staff about research opportunities and recruits participants for Institute projects.

Retention, as well as recruitment, is critical to ensuring there are women in science. We feel that it is important to not lose sight of the problems that face men and women embarking on careers in scientific research. It is critical that they understand the gender issues in research and are supported in their efforts to advance in the areas in which they choose to specialize. Our proactive mentoring program is a crucial tool for assisting new researchers in overcoming these challenges and encouraging them to remain in the field.

We are proud of these efforts and hope others can learn from them in their quest to demonstrate and increase public awareness about the joys and excitement of careers in science.

Powers Peterson, M.D.

Allegheny University Hospitals
American Society of Clinical Pathologists

New developments in the area of women's disease research and diagnosis, as well as the increased participation of women in biomedical careers, have been encouraging. However, more needs to be done if progress in the field of women's health is to continue successfully into the 21st century.

Women currently comprise a large sector of the health care community. In 1994, women represented 18 percent of all physicians in the United States. In the field of pathology, women comprised 24 percent of all pathologists in the country and 83 percent of the medical technologists certified by the American Society of Clinical Pathologists (ASCP) in 1995.

ASCP has been indirectly involved in efforts to recruit, retain and advance women in biomedical careers on a project-to-project basis. ASCP volunteers have been involved with educational projects, funded through the Title VII Allied Health Project Grant Program, designed to enhance recruitment and retention of minority and disadvantaged populations. One model program utilizes the mentor concept and promotes the recruitment and retention of medical technologists through a four phase design that begins with career awareness activities for elementary and middle school students. Similar projects could be established for the recruitment and retention of women in biomedical careers.

Offices of Women in Health Professions on some medical school campuses provide another successful model. These offices serve as excellent resource centers and bring together a variety of health care providers, both physician and nonphysician, to address issues related to women in biomedical careers. In addition, ASCP offers print and video materials describing careers in laboratory medicine; maintains a scholarship fund for individuals wishing to pursue such careers; and has a Career Recruitment Network, which provides mentors for those seeking to enter the field of laboratory medicine.

Although progress in addressing women's health issues is being made, a stronger infrastructure needs to be established to identify and respond to new challenges for women's health. Adequate funding is imperative to explore further and better understand the implications for women regarding new advances in disease research in the areas of cancer, heart disease, and HIV and other infectious diseases. In particular, more must be done to research further and investigate various aspects of women's health and coronary heart disease. In addition, women's health care could be better served as a comprehensive discipline that uses a combination of medical perspectives in patient care. The future of women's health research also needs to include a focus on emerging infectious diseases including chlamydia, sexually transmitted human papillomavirus, and Group B Streptococcus. Despite the continued threat of emerging infections, support for applied research and control efforts has declined during the past decade. For this reason, it is critical that women's health research, and the resources to conduct such research, focus on addressing emerging infectious diseases.

Marj Plumb, M.N.A. *National Center for Lesbian Rights*

The National Center for Lesbian Rights (NCLR) was founded in 1977 as a lesbian, feminist, multi-cultural legal and public policy resource center. In the past 4 years, NCLR launched several pioneering programs in order to better serve all members of the lesbian community. One project was our Lesbian Health Project, which supports grassroots organizing and advocates for equitable public policies regarding health care for lesbians. Since this project's inception in 1993, NCLR has become a leader in helping build what is now a vital and growing national lesbian health movement. Through this project, NCLR publishes a *Lesbian Health Issues Newsletter,* a *Lesbian Health Bibliography,* and other publications of interest on the issue of lesbian health and parenting.

The purpose of my testimony is to begin to articulate a common understanding of what lesbian health issues are, to share the successes of the modem lesbian health movement in order to provide encouragement for continued inclusion of lesbian health issues, and to present a universal list of recommendations that can be enacted by public health departments, health agencies, research institutions, and medical schools.

Introduction

Few would disagree that the lesbian health movement is at a unique moment in time. We have a community more interested in health issues than ever before, more knowledgeable about the health system and health terminology, and we have greater access to the federal health department than under any other administration. This convergence of experience, access, and visibility creates the possibility for us to make significant advances in the development of a health care system truly responsive to lesbian and bisexual women's needs.

Throughout the country, we have seen that our individual organizing efforts to provide services — often by lesbians for lesbians — is effective and powerful. Local grassroots groups have developed and implemented lesbian and bisexual women's health needs assessments and begun strategic planning for program development in many communities. Some of these efforts have resulted in new organizations specifically formed to address lesbian health. Some efforts have resulted in forming lesbian health projects within gay and lesbian organizations or even mainstream health organizations. But we can't and shouldn't do it alone. There needs to be lesbian and bisexual women's voices in the debates over changes in Medicaid and Medicare, in the movements to create national health reform, in the development of research agendas, in advocating for changes in medical school curriculum, and in setting priorities within public health departments.

Lesbian Health Overview

Women's health issues are defined by the Public Health Service (in the 1991 Action Plan for Women's Health) as "diseases or conditions which are unique, more prevalent, more serious, and for which risk factors and interventions are different for women or *some subgroups of women*." It is within this framework that I discuss lesbian health issues: the diseases, conditions, risk factors, and interventions that impact lesbians, as a subgroup of all women; there are distinguishable factors attributable to this population.

A lesbian is a woman whose sexual and affectional orientations are directed towards other women. Her behavior may range from exclusively homosexual, to bisexual, to situationally heterosexual prompted by economic status, cultural factors, or sexual desire. Not all women who partner with women consider themselves lesbians. The process of choosing to identify with the term is highly individualized and may be fluid over time. The decision may be influenced by issues of race/ethnicity, socioeconomic class, culture, age, gender presentation, or personal history. Women who identify themselves as lesbians may do so in their teens, in young adulthood, in middle age, or in later life. Lesbians are as diverse as the population at large, crossing all geographic, economic, racial, religious, ethnic, age, occupational, and other boundaries.

Lesbians and other women who partner with women have unique health concerns which often go unaddressed in a medical setting which generally assumes heterosexuality. These specific issues may include cancer screening, sexually transmitted diseases, human immunodeficiency virus (HIV), depression, substance abuse, relationship issues, aging, pregnancy, and parenting. Among the most significant health issues for lesbian and bisexual women is lack of access to sensitive medical services. Barriers to care may include lack of financial resources or insurance coverage, past negative experiences with homophobic providers, fear of compromised care related to lesbian identity or behavior, lack of accurate information among both lesbians and clinicians as to the health risks and standards of care appropriate to the population, and exclusion (or perceived exclusion) from health promotion campaigns. In addition, barriers affecting all women such as lack of transportation or child care, language, literacy or cultural accessibility, fear of painful or embarrassing procedures, fear of test results, and discrimination based on race, socioeconomic class, age, or disability impact lesbians as well. For all of these reasons, lesbians may avoid presenting for care until forced to by the severity of their symptoms. This delay in diagnosis and treatment may result in poorer health outcomes for the population.

Often articles written about lesbian health issues point to a paucity of research on the population of lesbian women. Yet in 1994, the National Center for Lesbian Rights published a bibliography of lesbian health research and articles that included over 800 citations. Many of the articles in that report had been published in peer-reviewed scientific journals, such as the *New England Journal of Medicine*, the *American Journal of Public Health*, the *Journal of General and Internal Medicine,* and the *Journal of Nursing Scholarship*. Additionally, significant research has been conducted that has been either published in non-peer reviewed "trade" journals or has not been published at all, leaving distribution of the analysis of local and regional research projects to informal networks. All of this constitutes a growing body of knowledge about lesbian health.

The difficulties researchers face in studying the lesbian population are numerous and complicate our ability to present health status information about this population. Random sampling is complicated when studying a marginalized, stigmatized, and fragmented population. Thus, many researchers rely on convenience sampling, raising concerns as to the systematic bias in sampling as well as the generalizability of results. Because researchers face particular difficulty in accessing the most severely marginalized of the lesbian population, study samples tend to be comprised of predominately white, middle-class "out" lesbians. Women of color, poor and working class women, and women who have sex with women but do not self-identify with the term "lesbian" or participate in mainstream gay culture remain severely undersampled.

Sampling may be further complicated by the fact that many women, even in anonymous research, do not feel safe in disclosing their sexual orientation or the gender of their (current or past) sexual partners. A study of self-reported sexual behavior in a sample of women in prison, compared different assessment techniques and found that same-sex behavior was reported by nearly twice as many women through qualitative assessment with a social worker as disclosed via structured questionnaire.

There are extensive data on women in the general population, yet researchers, until very recently, have failed to collect or report data on women who have sex with women. These general population surveys include women of all sexual orientations but are not analyzed or stratified by the variables of sexual behavior or identity.

Despite these limitations, the available analysis on lesbian and bisexual women's health issues is extremely provocative, indicating critical areas for future research. Points for consideration include:

- The incidence of breast cancer among lesbian women is unknown. There is evidence to suggest some lesbians may have a higher incidence of nulliparity (bearing no children), oligoparity (bearing few children), and heavy consumption of alcohol compared with heterosexual women, and may therefore be at increased risk. Existent research has represented primarily younger, white, well-educated, "out of the closet," lesbian-identified women, and is not generalizable to the full diversity of the population. The current data is useful, however, in demonstrating the underutilization of breast self examination (BSE), clinical breast examination (CBE), and screening mammography among the women surveyed.

- Lesbians appear to be less likely to receive regular Papanicolaou (Pap) smears than heterosexual women. This is true even among lesbians with a past or current history of heterosexual intercourse, multiple sexual partners, or sexually transmitted diseases. Often clinicians will consider their lesbian clients to be low risk based on incorrect assumptions about sexual behavior. In addition, lesbians may be misinformed about their own risk and the importance of screening.

- Clinical experience suggests that many STDs can be passed between female sexual partners. These include, but are not limited to, bacterial vaginosis, trichomoniasis, chlamydia, vaginal candida, herpes simplex (HSV), human papillomavirus (BPV), the hepatitides, and HIV. Again, insufficient research into woman-to-woman sexual transmission leaves us without clear standards of care for treatment of the female partners of women with the above listed infections. Prevention guidelines are likewise limited. In addition, the stigma and misperception surrounding lesbian sexuality leaves many women without access to accurate information or a safe venue to discuss sexual concerns with health care providers.

- Lesbians are at risk for contracting HIV through sharing needles for injection of drugs or other substances, and through unprotected sexual activity with infected male or female partners. Recent research indicates that among drug-using women, those who reported having any same-sex activity were more likely to engage in multiple high-risk behaviors including unprotected anal and vaginal intercourse with bisexual or drug-using male partners, sex for money or drugs, sex while high, and sharing injection materials. They were also significantly more likely to test positive for HIV than drug-using women who reported sex with men only.

- Many lesbian families include children from previous heterosexual relationships of one or both partners, through adoption, foster parenting, donor insemination, or heterosexual intercourse for the purpose of conception. Same-sex relationships have no legal protection and, without documents conferring power of attorney, lesbians may be denied the authority to make decisions regarding the care of their partners or children, or left without access to or information regarding hospitalized or incapacitated loved ones.

- Although mental illness appears to be no more common among lesbians than among heterosexuals, women who partner with women do have unique concerns related to their stigmatized status in a homophobic society. Lesbians are often the victims of hate crimes, including verbal or physical abuse or attack, damage to property, sexual assault or murder. They may be rejected by family, friends, religious community, co-workers or schoolmates; and they may be denied housing, custody, employment, health care, or legal representation. Equally devastating are the effects of internalized homophobia, which can lead to low self esteem, isolation, depression, or self-damaging behaviors. Lesbians affected by domestic violence may not have access to support services sensitive to their needs.

- As with other highly stressed or marginalized populations, lesbians may be at increased risk for the use or abuse of cigarettes, food, alcohol, and other drugs. While the percentage of lesbians engaging in addictive patterns of usage has been posited to be greater than that of heterosexual women, research samples may not have been representative of the population as a whole. It is more likely that prevalence varies among sub-populations of lesbians, as it does for other communities.

As discussed earlier, the determination of disease prevalence for this population is complicated due to the difficulties with research sampling. It is very important, then, to not rely on prevalence alone to determine the importance of an issue to the lesbian and bisexual women's community. Diseases or conditions which do not appear to be at a higher prevalence for this community, or for which reliable data is not available, can be considered lesbian health issues based on the need for targeted interventions such as lesbian-specific health educational materials and outreach campaigns. Women who are multiply marginalized as ethnic minorities, as transgendered or transsexual, as old or young, or as women without financial access face compounded risks. Culturally competent services, sensitive to the unique needs of lesbians and other women who partner with women, must be made available to all members of this diverse and underserved population.

Two Decades of Community-based Organizing

Like other communities with poor access to the health care system, the lesbian community has had to build elements of it's own health system in order to survive. Throughout the country there are individual service programs for the lesbian, gay, and bisexual communities: youth programs, elder programs, substance abuse and mental health programs, cancer care and prevention projects, HIV prevention and treatment services, smoking cessation classes, hotlines, primary care clinics, and community centers. Two cities (San Francisco and New York) have offices of gay and lesbian health in their local public health departments. Local grassroots projects addressing the specific health care needs and concerns of lesbian and bisexual women have been springing up across the country for the last several decades, and are potential sources for researchers to gain technical assistance and access to lesbian research subjects, a few examples include:

- Lesbian Resource Project, Phoenix, AZ
- Women's Cancer Resource Center, Berkeley, CA
- Audre Lorde Lesbian Health Clinic, Los Angeles, CA
- Lesbian Health Project at The Center, San Diego, CA
- Lyon-Martin Women's Health Services, San Francisco, CA
- Lesbian Health Project, West Hollywood, CA
- Lavender Project, Denver, CO
- Lesbian Health Services at Hartford Gay and Lesbian Health Collective, Hartford, CT
- Lesbian Services Program at Whitman-Walker Clinic, Washington, D.C.
- Mautner Project for Lesbians with Cancer, Washington, D.C.
- GYNA, Miami, FL

- Lesbian Outreach Services at AIDS Atlanta, Atlanta, GA
- Women's Health Program at Howard Brown Memorial Clinic, Chicago, IL
- Lesbian Community Cancer Project, Chicago, IL
- Emma Goldman Clinic for Women, Iowa City, IA
- Lesbian Services at Chase-Brexton Clinic, Baltimore, MD
- Lesbian Services at Fenway Community Health Center, Boston, MA
- Helping Our Women, Provincetown, MA
- Women's Community Cancer Project, Somerville, MA
- Women's Cancer Resource Center, Minneapolis, MN
- New Jersey Women and AIDS Network, New Brunswick, NJ
- Fennimore Initiative for Lesbian Health Care, Pennington, NJ
- Bronx HIV Lesbian Task Force, Bronx, NY
- Shades of Lavender, Brooklyn, NY
- Lesbian Services at Community Health Project, New York, NY
- Lesbian AIDS Project, New York, NY
- Lesbian and Gay Health Project, Durham, NC
- Women's Services at Nelson-Tebedo Community Clinic, Dallas, TX
- Lesbian Health Initiative, Houston, TX
- Seattle Lesbian Cancer Project, Seattle, WA

National Advocacy Organizing in the 90s

Besides the local and grassroots service agencies, and the national AIDS organizations throughout the country, other national organizing efforts are taking root to advocate on behalf of the full spectrum of lesbian, gay, bisexual, and transgender health issues. There are national organizations of lesbian and gay doctors, nurses, social workers, physicians assistants, addiction professionals, researchers, and gerontologists. Since the early 1990s, there has been an explosion of national projects addressing the specific health care needs and concerns of lesbian and bisexual women. These organizations are potential sources for researchers to gain technical assistance and access to lesbian research subjects. They include:

- The National Coalition of Feminist and Lesbian Cancer Projects, was formed in 1991, by grassroots projects from across the country, to provide national leadership and support the founding and development of other cancer projects.

- The Lesbian Health Fund, a project of the Gay and Lesbian Medical Association, was founded in 1992 at an annual conference of lesbian physicians and has distributed over $125,000 to fund research and education of special interest to lesbians.

- Lesbian health advocates in Washington, D.C. formally established the Lesbian Health Advocacy Network in 1993 to share information regarding lesbian health and coordinate activities among individuals and organizations interested in the advancement of lesbian health.

- The National Advocacy Coalition on Youth and Sexual Orientation was founded by the Hetrick-Martin Institute in 1993 to address public policy issues related to lesbian, gay, bisexual and/or transgender youth through the collaboration of a broad spectrum of national and community-based organizations.

- The National Center for Lesbian Rights began working on lesbian health issues in 1993 with the opening of their Policy Project in New York City. NCLR publishes a quarterly *Lesbian Health Issues Newsletter* which provides grassroots advocates around the country with resources and information important to their work, a *Lesbian Health Bibliography* with over 800 citations, and other health and legal publications of interest to lesbians and bisexual women.

- *Lesbian Health News,* a bimonthly national newsletter, was launched out of Columbus, Ohio, in November 1993. The newsletter works to bring awareness to the lesbian community about women's well being by publishing information about health issues, medical conditions, and related problems of interest to lesbians.

- The National Gay and Lesbian Task Force, the National Center for Lesbian Rights, the Human Rights Campaign, and the National Gay and Lesbian Health Association were the lead agencies who organized the first Lesbian Health Roundtable held in February, 1994. Over 60 lesbian and bisexual women's health activists were brought to Washington, D.C. to establish a lesbian health agenda and to attend meetings with representatives of the Department of Health and Human Services and members of Congress.

- National Lesbian and Bisexual Women's HIV Network was formed in 1994, by the Lyon-Martin Women's Health Services in San Francisco, to enhance the development of HIV-prevention programs for women who have sex with women throughout the United States.

- The National Lesbian and Gay Health Association was formed by a merger between the Association of Lesbian and Gay Community Clinics and the National Lesbian and Gay Health Foundation in 1994. This merger created the only national lesbian and gay organization focused on health headquartered in our nation's capital.

- The American Association of Physicians for Human Rights, a 15-year-old membership organization of U.S. and Canadian gay, lesbian, bisexual, and transgender physicians, officially changed it's name in 1994 to the Gay and Lesbian Medical Association in order to be more public about gay and lesbian health issues.

- An international Lesbian Research Network was formed in 1996 to assist lesbian researchers from all disciplines in gaining access to information, mentoring, technical assistance, and specialized expertise on research methodology, funding, and publication.

Inclusion in the Federal Public Health System: 1993-1996

The following list reflects efforts by the U.S. Department of Health and Human Services to include lesbian and bisexual women's health issues in programs, conferences, and written materials since January 1993. This is not a complete list of all the ways that lesbians or lesbian health issues have been included but represent those areas where significant advancements in lesbian access to the federal public health department have occurred. One of the most significant advances has been in the open inclusion of lesbian and bisexual women presenting at conferences, attending meetings, and participating on advisory committees, thus ensuring the infusion of lesbian and bisexual women's health concerns throughout the department.

- An historic meeting was held between representatives of national and local lesbian and gay health organizations and Secretary Donna Shalala, prior to the 1993 March on Washington, to begin addressing ways the Department of Health and Human Services can better meet the needs of lesbians, gay men, bisexuals, and transgender individuals.

- The National Institute of Mental Health (NIMH) and the Centers for Disease Control and Prevention (CDC) cosponsored a workshop in 1993 on suicide and sexual orientation to identify the gaps in scientific knowledge on lesbian, gay, and bisexual youth suicide and make recommendations to researchers.

- The National Institutes of Health (NIH) expanded research on lesbians and bisexual women in 1994 by providing supplemental funding for NIH-funded researchers to include lesbians and bisexual women in current studies. In 1994, sexual behavior questions were included in the NIH Women's Health Initiative and sexual identity questions were included in the Harvard Nurses Study after extensive advocacy efforts.

- The Center for Substance Abuse Prevention (CSAP) published the first ever, federally funded "Lesbian, Gay and Bisexual Resource Guide" in 1994. This free substance abuse prevention resource guide describes articles and reports on the topic, lists prevention materials available for this community, and gives resources for more information.

- In 1994, the U.S. Public Health Service Office on Women's Health (OWH) included a paragraph about lesbian health concerns in a new 4-page publication called *Women's Health Issues.*

- All major agencies in the federal Public Health Service met with representatives of the first Lesbian Health Roundtable in February 1994 to learn more about lesbian and bisexual women's health issues and to receive a series of recommendations for their departments.
- The Centers for Disease Control and Prevention (CDC) Breast and Cervical Cancer Early Detection Program funded a four-city pilot project, beginning in 1995, to develop effective outreach strategies to reach lesbian and bisexual women for low-cost Pap smears and mammograms.
- An historic meeting of the federal Public Health Service Coordinating Committee on Women's Health was held in January 1995 to address lesbian health issues and concerns.
- The CDC held the first federally sponsored meeting on lesbians and HIV in April 1995 to review the available research and knowledge on this topic and to develop recommendations for action.
- The Office of Minority Health (OMH), charged with improving the health status of ethnic minority populations, held an historic meeting with lesbian health advocates in 1996 to learn more about the health issues affecting lesbian and bisexual women of color.

Health System Recommendations

The D.C.-based Lesbian Health Advocacy Network recommends the following efforts be undertaken within the public health system (federal, state, and local) as well as in the private health care field, including hospitals, medical schools, research institutions, health clinics, and social service organizations to ensure the widest access to information, services, and research for lesbians, bisexual women, and all women who partner with other women.

Conducting Research

- Include sexual orientation (lesbian, bisexual, heterosexual) and sexual behavior (sex with men, women, or both) questions in all research and public health surveillance. Analyze data by the demographic characteristics of sexual orientation and sexual behavior, as well as by age, gender, race, ethnic origin, and income level.
- Undertake research to better understand those cultural conditions and socialization processes that affect lesbian and bisexual women's health and access to care differently than those of heterosexual women.
- Include lesbian and bisexual women on funding review panels and Internal Review Boards (IRBs). Provide sensitivity training for review panels and IRBs to reduce homophobia and increase understanding of lesbian and bisexual women's health issues.
- Fund researchers, especially lesbian and bisexual women researchers, to include lesbians and bisexual women as research subjects and to collect and analyze data stratified by sexual orientation and sexual behavior.

- Undertake research to evaluate the unique conditions that exist for lesbians and bisexual women in the causes, prevention, diagnosis, and treatment of cancer, HIV/AIDS, substance abuse, mental health disorders, and other chronic diseases.

- Publish recommendations on the methodology of researching lesbians and bisexual women.

Providing Services for the Prevention and Treatment of Disease

- Initiate and augment efforts to increase and expand access to health care for lesbians and bisexual women, especially those who are uninsured and underinsured, poor, from rural communities, or isolated by virtue of age, disability, or ethnic minority status.

- Include lesbians and bisexual women (as a specific subgroup of women) as a target population in all prevention and treatment initiatives for women and adolescent girls.

- Include lesbian health issues and concerns in all women and/or adolescent girls' health initiatives, educational materials, and programs.

- Include lesbian and bisexual health care consumers whenever consumer input is planned.

- Provide sensitivity training for all staff and members of committees or boards to reduce homophobia and increase understanding of lesbian and bisexual women's health issues.

- Include all culturally appropriate methods of treatment in services (including alternative care).

- Fund new and existing lesbian-specific service programs.

Educating and Informing the Public

- Initiate anti-homophobia public health campaigns to reduce the homophobia present in society.

- Develop and fund public health education campaigns targeted to lesbian, bisexual women, and all women who partner with other women.

- Include lesbian and bisexual women's health information and presentations at all conferences and meetings where women's health research, programs, and policy are discussed.

- Publish and distribute lesbian and bisexual women's health research, educational materials, and resource guides.

- Support local and grassroots organizing with an emphasis on developing consumer-based movements.

- Educate members of the media (including lesbian and gay media) to understand lesbian and bisexual women's health issues.

Recruiting and Training of Health Care Personnel

- Health care provider and care giver education programs (including continuing education) should promote sensitive, culturally competent, language-appropriate patient care for lesbian and bisexual women.
- Medical, nursing, and other health professional schools should incorporate training regarding lesbian and bisexual women's health and the provision of sensitive and culturally competent care as essential portions of the curricula.
- Ensure freedom of choice of medical providers in any health insurance plan (including managed care plans) or health system.
- Recruit and support lesbians, bisexual women, and lesbian-sensitive individuals as applicants to medical, nursing, and other health professional schools.

Designing Guidance on Lesbian and Bisexual Women's Health Initiatives

- Encourage health institutions to appoint a lesbian/bisexual health liaison to assist in the development of services to improve the health condition of lesbians and bisexual women.
- Encourage the formation of lesbian, gay, and bisexual employee groups to assist in the planning of services and research for the lesbian and bisexual women's communities.
- Encourage the development of consumer-based lesbian and bisexual women's health advisory committees.
- Develop a lesbian and bisexual women's health agenda to provide guidance for future health initiatives.

The Lesbian Health Overview section has been adapted with permission from: "Women's Health Issues: Planning for Diversity" by E.J. Rankow, 1995.

Linda Quander, Ph.D. *Clark Atlanta University*

Strategic management is a process which requires planners and decisionmakers to accomplish key tasks:

- Clarify purpose;
- Select goals and objectives;
- Identify present strengths and weaknesses;
- Analyze future opportunities and threats;

- Compare strengths and weaknesses to opportunities and threats;
- Decide on long-term strategy;
- Implement the strategy; and
- Evaluate the strategy.

Women's health researchers must learn to anticipate rapid changes that affect their projects, working groups, organizations, and even their careers. Conferences — such as this one — can facilitate this by basing training, education, and development on projected future needs.

Needs assessment is critical for identifying learning gaps and discovering weaknesses. It is part of the process in which we ascertain future needs relative to overall performance in women's health care. Therefore, effective communication about needs assessment is paramount in designing, implementing, and interpreting research programs. Researchers must be aware of how communication can ultimately enhance or adversely affect women's health.

NIH and the National Institute of Environmental Health Sciences are to be commended for recognizing that scientific knowledge, combined with effective communications, can empower women to better control their personal environments and thus improve their overall health. I am particularly enthusiastic about NIH's Women's Health Initiative, an important study of strategies that can enhance adoption of healthy behaviors by using a multidisciplinary approach in cooperation with various community-based prevention centers.

Researchers need to analyze various types of traditional and nontraditional channels. For example, studies of African-American women have found that churches are a particularly useful route. We now know that it is important to understand how and why community-based prevention centers appear to be effective in reaching minority populations.

Communication channels to women must be future oriented and proactive. Strategies need to see women as active, adaptive team members, not as passive obstacles to progress. Cooperative partnerships are effective tools for addressing inequality in health care for women and reaching women throughout the community.

James M. Roberts, M.D. *Society for Gynecological Investigation*

One of the refreshing aspects of the increased emphasis on women's health research attributable to the Women's Health Initiative is the heightened awareness that women's health is not limited to reproductive health. Research has shown that there are gender differences in many aspects of health and medicine, and recognition of this phenomenon has led to changes in how women are treated for illnesses not directly related to their gender.

Indeed, we are now seeing improvements in female morbidity and mortality statistics that reflect this revision in medical approaches and attitudes toward female patients.

It is now generally recognized that many diseases manifest themselves differently in women than in men. Women face different cardiovascular risks than men, which has certain implications for diagnosis. Similarly, women appear to be more susceptible than men to illnesses such as autoimmune disease, and we now know that women metabolize drugs differently than men.

Of course, we should not abandon research on reproduction health. Reproductive health statistics such as premature births remain alarmingly high, particularly in disadvantaged populations. Likewise, death from preeclampsia — a condition recognized for more than 1,000 years — is the highest cause of maternal death in developed countries. Death rates also remain high for infants of preeclamptic women.

Research in these areas has led to many exciting discoveries with important treatment possibilities for genetic ailments. New findings in molecular biology, and our ability to handle data more effectively, provide us with opportunities to solve major problems that have affected women and infants.

We must also ensure that researchers interested in women's health are nurtured and supported throughout their academic and professional careers. Money for training — both federal and private — is extremely important. Still, our most valuable resource is the cadre of talented individuals embarking on scientific careers, including the generation of future scientists now in grade school.

In this time of restricted resources and academic upheaval, we must resist the urge to complain that things are worse than ever. We must "hang tough" and remember the importance of our goal. We must convey to our young successors the rewards, excitement, and vital importance of research relevant to women's health.

Association of Black Cardiologists
Roxanne A. Rodney, M.D. *Committee on Cardiovascular Diseases in African-American Women*

(Testimony prepared by the Association's Committee on Cardiovascular Diseases in African-American Women: Sheila A. Robinson, M.D.; Roxanne A. Rodney, M.D.; Hannah A. Valantine. M.D.; and Jan D. Webber, M.D.)

Cardiovascular Diseases in African-American Women

The Association of Black Cardiologists is committed to the prevention, diagnosis, and treatment of cardiovascular diseases in African-American women.

Cardiovascular diseases are diseases of the heart and blood vessels which include: coronary heart disease (heart attack), stroke, and hypertension (high blood pressure). Cardiovascular disease affects 1 in 5 women, and is the major cause of death in women. In fact, more than 479,000 women die annually of cardiovascular disease, surpassing the 444,000 men annually who succumb to cardiovascular death. In women, cardiovascular deaths are almost double the 246,000 deaths attributed to all cancers. Indeed, five times as many females die from heart attack than from breast cancer.

African-American women are at greater risk; they have a higher prevalence of and a higher mortality rate due to cardiovascular disease compared with Caucasian women. The cardiovascular death rate in 1992 in African-American women was 69.2 percent higher than that in Caucasian women.[1,2]

Coronary Heart Disease, Hypertension, and Stroke

Coronary heart disease is the number one killer of American women. Approximately one half of all deaths, or one-quarter million deaths due to heart attack, occur in women. African-American women are disproportionately affected. In 1992, the death rate from coronary heart disease was 32.6 percent higher in African-American women than in Caucasian women. Between ages 35 to 74, the death rate from heart attack in black women is twice that in white women and three times that in women of other races.

It has been reported that black women had the highest mortality rate after heart attack at 48 percent compared with white women (32 percent), black men (23 percent), and white men (21 percent). The survival rate in African-American women is 69 percent lower than that in Caucasian women after an out-of-hospital cardiac arrest.

Approximately one-half million Americans per year sustain a new or recurrent stroke, according to Framingham Heart Study data. African-American women have the highest estimated crude prevalence of stroke at 2.5 percent (compared with 1.9 percent in white women, 2.2 percent in white men, 1.8 percent in black men, and 0.8 and 1.1 percent in Mexican-American women and men, respectively).[3] Women have a higher stroke death rate at 61 percent compared with men at 39 percent. In addition, the mortality rate in black women is 77 percent higher than that in white women.

Hypertension afflicts an estimated 43 million American adults. African Americans have a 40 percent higher age-adjusted prevalence of hypertension than that in Caucasians and Mexican Americans. The onset of hypertension is earlier, and it is more severe in blacks, resulting in a 1.8-fold greater rate of fatal stroke, a 1.5-fold greater rate of heart disease deaths, and a fivefold greater rate of end-stage kidney disease compared with whites.

Between the ages of 30 to 69, the prevalence of hypertension is greater, and the mean systolic and diastolic blood pressures are higher in African-American women than that in Caucasians and Mexican-American women. In the 60 to 69 age group, 80 percent of African-American women versus 55 percent of Caucasians and 60 percent of Mexican-American women have hypertension. The mortality rate due to hypertension is higher in women compared with men, 58 percent versus 42 percent, respectively.

Risk Factors

Hypercholesterolemia. Fifty-one percent of African-American women aged 20 and above have undesirably high serum cholesterol levels of greater than 200 mg/dl; 19 percent have levels above 240 mg/dl. In black females age 19 and under, hypercholesterolemia, defined as $\geq$ 170 mg/dl in this age group, is present in an estimated 46 percent of this group, compared with 32 percent in white females.

Lp(a) lipoprotein levels, which correlate directly with an increased, independent risk for coronary heart disease, are twofold higher in black than in white women.[4–7]

Diabetes. Eight percent of black women have diabetes, compared with and average of 3 percent for all other women. The risk of an initial heart attack is more than doubled in women with diabetes, and in contradistinction to men, diabetes contributes significant increased risk for subsequent heart attack in women.

Smoking. Twenty percent of African-American women over age 18 are smokers. Smoking and the concurrent use of oral contraceptives significantly increase the risk of stroke.

Physical Inactivity/Overweight. Lower socioeconomic and educational levels tend to correlate with a higher likelihood of a sedentary lifestyle. Physical inactivity is associated with an increased relative risk of coronary heart disease, which ranges form 1.5 to 2.4. This increased risk is comparable to that attributed to hypertension, hypercholesterolemia, and smoking. Physical inactivity contributes a 30 to 50 percent increased risk of hypertension. Approximately 68 percent of African-American and 56 percent of Caucasian women do not engage in regular physical activity.

Fifty percent of African-American and 32 percent of Caucasian women are 20 percent or more above desirable weight. More than 30 percent overweight is an independent risk factor for cardiovascular diseases.

Recommendations

Cardiovascular disease is the major cause of mortality in women. The number of deaths sustained by women due to cardiovascular diseases exceeds that in men. African-American women have a higher prevalence of, and a higher mortality rate due to, cardiovascular disease compared with Caucasian women.

The Association of Black Cardiologists unequivocally supports increased funding of clinical and basic science research in cardiovascular diseases in African-American women. Women in general, and African-American women in particular, have been underrepresented populations in research studies. Historically, the assumption has been that data collected in men would be applicable to women. Time has revealed this fallacy. Nor can it be assumed that data generated in studies of white women are translatable to black women, given the differences in risk factor prevalence and severity. In order to obtain accurate data on at risk populations, these groups must be included in research studies. It is cost effective to increase the fund of medical knowledge regarding disease processes in at-risk groups through targeted research, for this engenders appropriate interventional strategies in the modification of etiologic factors and in the treatment of disease processes.

The second critical component of this strategy to reduce cardiovascular morbidity and mortality in African-American women involves educational programs for at-risk populations specifically targeting primary disease prevention through risk factor modification, and emphasizing the importance of seeking early appropriate care if symptoms are present in order to reduce the incidence of secondary complications. Coupled with this, health care providers must also continue to be educated in the prevention, timely diagnosis, and appropriate treatment of cardiovascular diseases in African-American women.

In addition to the immeasurable impact of cardiovascular morbidity and mortality on the lives of African-American women and their families, the societal impact, in terms of lost productivity and health care expenditure, can not be understated. Health care dollars are more effectively utilized by the generation of accurate research data, which can then be appropriately implemented via the education of at-risk groups and health care providers. This strategy is medically appropriate and cost effective.

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Research Agendas Focusing on Diverse Pathways to Health

I will suggest that we need to refocus our national research agenda to address: (1) the prerequisites to women's health that are ignored in a narrow biomedical paradigm; (2) pressing issues in social and behavioral paradigms; and (3) ignored or suppressed research questions grounded in mind/body, alternative, and folk healing traditions.[1]

Why We Must Move Beyond Narrow Biomedical Models

My testimony today reflects disquietude with the definition of women's health that is widely used in government and medicine.[2]

> Women's health is devoted to the preservation of wellness and prevention of illness in women, and includes *screening, diagnosis, and management of conditions* which are unique to women, are more common in women, are more serious in women, [and] have manifestations, risk factors, or interventions which are different in women (1991:149 emphasis added).

This definition obscures critical dimensions of women's health and must be revised. Emphasizing the preservation of wellness implies that women have wellness to preserve, leaves where health comes from undefined, and glosses over the fact that some women do not have access to the basic life conditions that produce health. Retaining such a narrowly biomedical definition that focuses on diseases or "conditions" in women, institutionalizes individual expectations and collective demands for biomedical interventions at a time when access to medical care is particularly problematic. We need to more carefully weigh what research is needed to make the greatest improvements in the health status of women who are particularly disadvantaged in terms of health status. We need to question the wisdom of adopting a research agenda that may break new scientific ground, but widen the gap between the health of different groups of women.

Embracing the WHO Vision of Health

As we move toward global thinking, we may do well to adopt research priorities that reflect the vision of health that the World Health Organization (WHO) promotes as "a state of complete physical, mental, and social well being and not merely the absence of disease or infirmity." This often cited definition is very different from the Public Health Service definition in the attention given to medical services relative to well being. The WHO includes in its definition of health a number of "prerequisites for health:" freedom from the fear of war; equal opportunity for all; satisfaction of basic needs for food, basic education, water and sanitation; decent housing; secure work and a useful role in society; and political will and public support.[3]

The WHO prerequisites for health have important gender dimensions and raise critical issues about social class and culture in the production of health. For example, the threat of war reduces women's health not only directly through the threat of death, rape, or destruction of working and living conditions, but indirectly through emotional stress related to the survival and safety of communities and family members and the disruption of education. Does the "war on drugs" in inner cities have such an impact on women's health? Can we address how our social policies provide equal opportunity for women of all races, social classes, and with other particular social characteristics, to attain health? Should our research agenda on women's health include research on how the quality of housing, education, food, heating, water, and other necessities of life affect women's physical, mental, and spiritual well being?

In communities, women not only need to be free from the fear of war, but from all forms of violence. American society must come to terms with this prerequisite to health or all of the breast cancers "caught early," the chronic diseases avoided through positive health practices, and the benefits of new technologies will be undermined and overshadowed. The specter of women being screened annually for a multitude of diseases but remaining fearful of leaving their homes — or perhaps worse yet, fearing remaining in them — raises uncomfortable questions about how narrowly women's health is often defined. I hope that ORWH will take a leadership role in defining "what's important" for producing health by crafting a national research agenda that will address how to promote and preserve the health needs of women who are malnourished, homeless, or living under stressful social, psychological, and economic conditions. The complexities and differences in women's health by race, by social class, and by culture raise critical questions about how to assign priorities for research that will promote equity, not widen the gap between women in different social groups. May we be mindful of this larger social need as we develop our national research priorities.

Finding a Proxy Measure for Social Class

Since we resist measuring social class, a women's health research agenda might profitably build on National Center for Health Statistics (1995:108) reports of a clear gradient in mortality both for white women and women of all races by educational attainment. In 1992, the death rate was twice as high as for white women and women of all races aged 25 to 64 who had less than 12, compared to 13 or more years of education. If research on women's health included educational attainment, the importance of education for women's health would be more widely recognized. Including education as a variable in research would also help interpret findings that are reported by race or ethic group. Many socioeconomic factors are obscured when research is reported only by race, promulgating distorted views of relationships between race, per se, and health. More attention needs to be paid to health status differences among women within racial/ethnic groups. Such research provides clues to differences between sociocultural and socioeconomic factors that affect health status and thereby suggest different strategies for improving women's health. For example, some immigrants have better health and birth outcomes than native-born members of the same racial/ethnic group despite similar poverty levels (see, e.g., Kumanyika and Golden, 1991; Scribner and Dwyer, 1989). Such findings should spur research on the contributions of culture and acculturation as determinants of women's health.

Recognizing Alternative Models of Health

Emerging mind/body models that emphasize psychological and spiritual dimensions of health seem particularly invisible in federal agendas for women's health. These models start with the assumption that the mind and body interact in complex ways and challenge separating mental/emotional states from physical symptoms. We clearly need more research on how women's health needs are addressed in traditional non-western healing systems that posit spiritual as well as psychological dimensions of health. Christiane Northrup, former President of the American Holistic Medical Association (1994), cogently argues that surgery, drugs, and even good nutrition and health practices are not enough to promote healing. The emotional matters that brought about the physical symptoms must be resolved for real healing to occur. Surely these increasingly popular ideas are worthy of research attention.

When women's health problems are simply portrayed as "all in the head," physicians view them as unworthy of either scientific investigation or clinical attention. The stigma associated with psychogenic disorders contributes substantially to women's dissatisfaction with conventional medical treatment. If new research in psychoneuroimmunology and other areas scientifically demonstrate how what happens psychologically and emotionally "gets into the physical body," mind-body concepts may truly benefit women.

Important relational concepts, such as caring, deserve more recognition. Few research resources are available for studying how caring facilitates health and healing. The subjective, experiential dimensions of health and healing, addressed in the qualitative social sciences and in some areas in nursing, as well as in mind-body paradigms, deserve greater attention. So do alternative healing practices and the contributions of a much wider array of healers and helpers than are generally acknowledged under the rubric of "health care workers."

Looking for Integrative Concepts and Theories

Theoretical and conceptual work is needed to link empirical research areas to one another. Integrated models are needed to understand how working and living conditions, individual health behaviors, psychological and emotional processes, and effective biomedical interventions together contribute to health and well being. We can ill-afford to promote a research agenda that locates women's health only in the domain of biomedicine, ignoring the social forces that create — and undermine — health. New integrative concepts are sorely needed.

Women's health research must also explicitly take into account the health of men, children, parents, and life partners. Extending the analysis of health to include significant others in women's lives underscores the critical importance of gender in the production and maintenance of women's health. Women from all walks of life emphasize the need to be free from the fear of violence, in all its many sociocultural forms — including violence among and between men who are women's kin. Addressing violence against women outside the context of male as well as female gender expectations and opportunities is unimaginable. For women, a stable economic base of jobs is essential for maintaining the prerequisites for health as well as gaining access to medical services. Theories and concepts that lay out how to create and maintain social relationships and institutions that actually produce health are sorely needed.

Some Specific Research Questions for the 21st Century

In a broader framework for understanding women's health, there are many questions that deserve attention; I shall only sketch out a few here.

- *Culturally appropriate services.* Will more culturally relevant and effective care emerge from ethnically distinct service providers than "mainstream" institutions or dominant group providers, and if so, what provisions can be made to foster the continued existence of community-based services that are targeted to specific racial/ethnic groups? Do some forms of ethnically/culturally targeted services offer advantages that benefit women? What are the opportunities for fostering culturally appropriate services for other groups? Can such models of care, developed by and for specific populations, be "mainstreamed" successfully?

- *Health statistics within and between specific racial/ethnic groups and socioeconomic groups reveal widely divergent patterns of health and ill health.* These descriptive data should raise new research questions about links between race/ethnicity, socioeconomic status, the cultural context of health practices, and the availability of health services (Krieger, et al. 1993). The very favorable health status of most groups of Asian-American women should raise questions about how some groups generate such good health.

- *Qualitative research issues.* Women's experiences of health and illness needs greater attention to understand how women in different life situations view and make decisions about health, disease, and health-related issues on their own terms, drawing out culturally and psychologically relevant concepts. Related to this is investigation of women's own definitions of their health care needs and goals — that may differ from those that "experts" perceive as priorities. Research must also address what women perceive as poor, bad, demeaning, or coercive health actions. Narrative accounts and case studies provide distinctive insights into the actual conditions of women's lives that may offer clues for more effective preventive or treatment efforts. Other research questions address how women perceive that they are actually treated when medical technicians process them through mammography screening, draw blood for laboratory tests, or carry out diagnostic procedures. How is the experience different for women with disabilities? for women who do not speak the language of providers? for women whose cultural background differs? What is the actual experience of being an experimental subject to test a new drug or treatment? How does social class (approximated by education) shape this and other health care experiences?

- *Alternative health.* More research on alternative practitioners used by women in all ethnic groups, in both rural and urban settings, would alter dominant views of what constitutes "the" American health care system. Serious study of utilization of traditional healers, as well as other less conventional therapies, would tell us how women protect and improve their health. Given the documented use of alternative therapies and the anecdotal evidence about its popularity, research might profitably compare how patients are treated in such settings compared to mainstream medical institutions (Moore and Milligan 1994; O'Connor 1995). There is considerable anecdotal evidence suggesting that alternative practitioners often interact with patients in ways that are experienced as supportive and healing — and rarely found in impersonal conventional medical institutions. Is some of the appeal of midwives their interpersonal skills and their ability to respect the diversity of women's desires for positive birthing experiences?

  In mental health, where the cultural fit between patients and practitioners may be especially important, case studies of traditional healers may reveal conceptualizations of mental health and illness that are much more congruent with peoples' lived experience than the diagnostic categories currently used. For women of color and ethnic women, the constructs of psychotherapy need to be enlarged and revised to address ethnic and cultural issues that bridge the gap between the usually white middle-class world of professional therapists and their clients.

- *Epidemiologists must study social and environmental, as well as biological and behavioral, risk factors in diverse groups.* Socioeconomic status and race simply can not be treated as "control" variables but must be reconstructed as important independent causes of poor health status. Patricia O'Campo and her colleagues (1995) have proposed a promising contextual analytic approach that represents one promising direction to pursue. In short, a broader range of conditions than the "leading causes of death" also need to be studied in an epidemiological framework to counterbalance the dominant view that the so-called "killer diseases," such as cancer and heart disease, are more "important" to control than the living and working conditions that reduce well being over the entire life cycle.

- *Determining what is "important" to study.* A specific example is research on violence which includes the social and psychological effects of violence and perceptions of risk of violence, not just homicide rates. While it is often argued that homicide is the "tip of the iceberg," women should ask why the whole iceberg is not being mapped given the resources being spent on mapping the human genome. While genetic information may lead to improved health, changing social, psychological, and environmental conditions would surely have large pay-offs in terms of women's health and well being. And, as O'Campo and her colleagues (1995) point out, a clearer understanding of which elements of social environments are most predictive of violence against women could lead to better targeting of resources.

Summation

In sum, health is multifaceted and our national research agendas must include what women want and need to realize the vision of health set forth by WHO. Our research agendas must broaden to incorporate psychological and spiritual dimensions of health and healing that have particular significance to women who see these as contributing to their ability to resist and recover from ill health. Attention to the broader base of what actually produces health (as contrasted to managing or screening for disease) suggests that investments in a variety of areas are necessary to promote women's health. Women from diverse backgrounds must be involved in setting national research priorities to ensure that we address the prerequisites to health and disease states.

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

The representation of women at Harvard Medical School (HMS) and Harvard School of Dental Medicine (HSDM) in 1996 range from a high of 49 percent for students to a low of 7 percent for the rank of Professor. At the student, trainee (clinical or research fellow), and instructor levels, representation is consistent with or better than the availability pool; however, at the voting faculty ranks (Assistant Professor and higher), the percentages reflect a critical problem. Even among those women already appointed as Instructors or Assistant Professors, a smaller percentage are promoted over a 10-year period than their male colleagues.

The Office for Faculty Affairs has launched a number of interventions to try to correct this gender gap including the establishment of appointment procedures designed to assure that new faculty positions are accessible to all qualified candidates; the requirement for formal annual career conferences for women and underrepresented minorities to assist in career planning and direction; and career assistance by conferences, workshops, and ad hoc individual counseling for trainees and junior faculty through the Office for Academic Careers, Minority Faculty Development Program, Women in Academic Medicine Program, and the Office for Faculty Affairs.

The most serious problem faced by women in their academic careers is demonstrating independent academic productivity (research, teaching, grant application, and paper writing) because of a lack of sufficient protected time for these activities. Without substantial tangible evidence of academic creativity, promotion comes more slowly, if at all. The 50th Anniversary Program for Scholars in Medicine provides for ten fellowships a year for women or men who can demonstrate both great academic promise and complicating personal responsibilities which might be remedied by a grant of $25,000. In the first competition, more than 210 women and men applied for the ten fellowships.

A similar set of national fellowships could make a large difference in diminishing the gender gap. Given the challenges in the biomedical field for the 21st century, and the fact that more than half of the students in science and medicine at HMS are women, there is every incentive to support these women through the hardest time in their professional lives. Men qualify for the great majority of sabbaticals at HMS since they occupy 93 percent of the senior positions that are covered by the University's sabbatical policy. It seems only fair that institutional resources be directed at an earlier point in women's careers when the need is greatest, rather than saving the support for a sabbatical that few women will ever reach without this additional help earlier in their careers.

Martha Torres-Montoya, M.S.P.H. *Hispanic Women's Health Association*

Research into the health needs of Hispanic/Latina women is very limited at present. Notably meager are epidemiological data, program evaluation models, effective interventions, and clinical trials. Where such research exists, it generally focuses on issues of access — health insurance, geographic, language, and cultural barriers.

As a result, little is known about Hispanic/Latina women's health issues and status. The inability to describe the problems or document the needs has put these communities in a poor position to obtain government funding. This lack of original research has seriously impeded health service agencies and community-based organizations from addressing gaps in health care for Hispanic/Latina women. Until and unless community-based agencies are able to document health and social problems affecting Hispanic/Latina women, federal funds are unlikely to be forthcoming. The result is poor, ineffective health care policies that, in turn, impact the availability, distribution, and utilization of scarce health care dollars.

The Hispanic Women's Health Association (HWHA) has a strong commitment to developing and implementing successful research projects in the Hispanic community. We recommend that ORWH conduct research into the following areas of importance to Hispanic/Latina women:

- Differences in health perceptions, physical and mental health, and social support systems;
- Impact of welfare reform;
- Impact of acculturation on health status;
- Health beliefs and practices;
- Preconceptional health issues for use in a national campaign;
- Infertility;
- Depression, cultural perceptions, and coping strategies;
- Interventions to reduce teen pregnancy;
- Interventions that encourage men to become involved in family planning;
- Alcohol use/non-use; and
- Patterns of family formation.

HWHA also urges ORWH to revisit the recommendations made for Hispanic/Latina women in 1991. It requests that ORWH prepare a report that describes how those recommendations were implemented in the past 5 years and/or how they could be integrated into the 1996 agenda.

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

Women are far more prone than men to hip fractures and bone-related diseases such as osteoporosis, and their susceptibility increases with age. The associated loss of life and suffering involved in fracture and disease is enormous, as are the medical bills, which approach $10 billion each year.

As a mender of broken bones, the American Academy of Orthopaedic Surgeons (AAOS) is deeply concerned that nearly 300,000 individuals will suffer hip fractures this year and that women's fractures will outnumber men's by almost three to one. In addition, women over age 65 have a one in five chance of suffering a hip fracture during their lifetimes.

These statistics demonstrate the importance of early intervention in reducing the prevalence of osteoporosis. Since many orthopaedic injuries are preventable, early intervention provides the greatest potential for reducing the numbers. As such, education and intervention must begin in childhood. Although evidence shows that increasing calcium intake during adolescence is critical in the development of peak bone mass and growth, there is a desperate need for longer, prospective trials. We need data confirming the current actual intake of calcium in our young people. We also need to determine how we can encourage young people to alter their dietary lifestyles.

While the Academy is concerned with osteoporosis and resultant injuries, we are also interested in the incidence of sports injuries in young female athletes. Athletes and their coaches need to be instructed more effectively about the orthopaedic risks associated with playing sports. Investigation into the increased risk of knee injury in young female athletes, as opposed to young male athletes, in also essential. Strengthening strategies and training techniques must be explored at every level so that injuries can be prevented.

For many years, AAOS has devoted tremendous energy to osteoporosis research and injury prevention; a campaign called LIVE IT SAFE, which we sponsored with the American Association of Retired Persons, is one example. Although we believe these programs are effective, our own goals are to expand these efforts so that we can better understand the needs of young women and design effective educational strategies to improve their health habits.

The Academy commends the Office of Research on Women's Health (ORWH) for its extensive work in encouraging research on solutions to women's health problems, such as osteoporosis. We believe ORWH can and should play a leadership role in identifying the key cause-and-effect relationships of osteoporosis. The cost of education, intervention, prevention, and rehabilitation amounts to several billion dollars a year. Nevertheless, the improved quality of life is incalculable.

Gastroenterology Women's Coalition
(Representing the American Gastroenterological Association,
American Society for Gastrointestinal Endoscopy,
American Association for the Study of Liver Diseases,
and American College of Gastroenterology)

Jacqueline Lee Wolf, M.D.

Colorectal cancer is the second deadliest cancer in the United States and the third leading cause of cancer-related death in women. Women with hereditary colon cancer are at increased risk of ovarian and endometrial cancers. Further study of colon cancer in women may provide important information on the etiology of these associated cancers. Also, further research is needed on how gender and knowledge of genetic status affect screening participation.

Basic and clinical research is needed on the pathogenesis, immunology, and therapeutic approach to primary biliary cirrhosis, a disease nine times more common in women than in men. Among the additional aspects of liver disease in women that merit expanded study are: the impact of sex hormones on elements of the immune system and on the proliferation of liver cells; the factors responsible for differences between men and women in alcohol absorption and metabolism; and the effects of estrogen and progesterone on the development of alcoholic liver disease.

The Helicobacter pylori bacterium is a relatively new discovery that has revolutionized and advanced treatment for peptic ulcer disease. Studies show that H. pylori-infected women are 15 to 18 times more likely to develop gastric cancer than infected men. Further research is needed on the role of acid secretion in protecting against the development of gastric cancer and on clinical approaches to preventing gastric cancer. Research on the prevention of peptic ulcer disease induced by non-steroidal anti-inflammatory drugs (e.g., aspirin and ibuprofen) is needed.

Gallbladder and biliary tract disease are twice as common in women as men. The role of estrogens and progesterones in the formation of gallstones, particularly during and immediately following pregnancy; the basic biology of gallstone formation; and potential preventive measures merit further study.

Irritable bowel syndrome and functional bowel disorders are twice as common in women as men. Additional research is needed on the effect of the menstrual cycle on functional bowel disorders; and the relative impact of genetics, the environment, and social factors on the etiology and perpetuation of symptoms.

Aside from research priority objectives, the Coalition recommends the following mechanisms for enhancing biomedical research career opportunities for women: NIH should expand small grant support for mentoring programs for women; NIH should provide seed money for the initiation of special academic tracks for women interested in research careers; academic institutions should be encouraged to adopt "stop the clock" policies with regard to tenure and promotion of women faculty; NIH should allow institutions to include in their indirect cost calculations, programs to prepare women faculty members for senior administrative positions (departmental chairs or deans) through which they can continue to foster research and influence the research activities of their institutions.

Elizabeth Yoffe, M.A. *Self*

Conventional medicine is a wonderful, lifesaving, and life-enhancing tool. However, its long monopoly in the overall health care picture is beginning to loosen as lay people, insurance companies, and even parts of the medical establishment recognize that alternative therapies can complement conventional medicine.

My interest in the health care system was sparked after I suffered a crippling stroke at the age of 30. Conventional medicine and rehabilitative therapy literally got me back on my feet, but their value in the recovery process was limited. To improve my physical functioning, I turned to alternative healing methods: meditation, relaxation techniques, and visualization. I became more intrigued by what was then called “unconventional medicine” and set out to learn more about alternative modalities.

Today, more people — especially women like me — are questioning the existing medical system, taking control and responsibility for their health, and exploring alternative treatments for chronic or degenerative illnesses. However, resistance to alternative healing persists, particularly from conventional practitioners.

There are interesting links between the emerging fields of women’s health and alternative medicine. Both are regarded as outside the medical norm. The same can be said about medical practices that originate in China and India, which are far older and more refined than Western medicine. There seems to be an assumption that only medicine developed from a Western cultural perspective is “real.” Other medical traditions are regarded as backward or primitive. Alternative medicine may receive more acceptance from women patients and health practitioners because, historically, women have a deep bond with natural or folk remedies.

It is ridiculous to deny people education about, and access to, alternative therapies that might help them recover or better manage illness. I recommend the following steps:

- Increase cooperation between the Office of Research on Women’s Health and the new Office of Alternative Medicine (OAM);
- Integrate findings from OAM into public health education programs;
- Integrate alternative medical modalities in medical schools; and
- Increase communication between conventional and alternative medical professionals.

Neither conventional (i.e., Western) medicine nor alternative medicine can cure all our ills. However, now that we have access to therapeutic modalities from different cultures and philosophies, it is the responsibility of all medical practitioners to work together to improve on what we have today.

WORKSHOP AGENDA AND PARTICIPANT ROSTER

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

DoubleTree Hotel Philadelphia
Philadelphia, Pennsylvania

September 25-27, 1996

AGENDA

WEDNESDAY, SEPTEMBER 25, 1996

PREMEETING ACTIVITIES: A PUBLIC HEARING

1:00-6:00 p.m. *Public Testimony: The Women's Health Research Agenda for the 21st Century*
Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, NIH, and Director, ORWH

1. *Continuing or Emerging Gaps in Knowledge About Women's Health*
Task Force

2. *Successful Models for the Recruitment, Retention, Re-entry, and/or Advancement of Women in Biomedical Careers*
Task Force

6:00-7:30 p.m. *Meeting with Task Force/Ad Hoc Working Group and Workshop Cochairs*
Dr. Pinn

THURSDAY, SEPTEMBER 26, 1996

WORKSHOP DAY 1
Continuing and Emerging Scientific Issues for Women's Health Research: Influence of Sex and Gender on Health

8:30 a.m. *Workshop Welcoming Remarks and Overall Charge for the Conference*
Dr. Pinn

Introduction of Conference Cochairs

Donna Dean, Ph.D.
Acting Chief, Referral and Review Branch, Division of Research Grants, NIH

Marianne Legato, M.D.
Associate Professor of Clinical Medicine, Columbia University
College of Physicians and Surgeons

Introduction of Host Institution Cochairs

Jeane Ann Grisso, M.D., M.Sc.
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Bonita Falkner, M.D.
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Allegheny University of the Health Sciences

Overview: Beyond Hunt Valley: Research on Women's Health for the 21st Century
Charge to Working Groups

Dr. Pinn
Task Force Cochairs

Logistical Instructions

Local Cochairs
Dr. Grisso
Dr. Falkner

9:45 a.m. ***Break***

10:00 a.m. ***Concurrent Breakout Working Groups***

Consider overarching health issues of aging, chronic disease, the molecular bases for male and female differences in disease, behavioral and prevention strategies, risk factors for major health issues, gender, diversity, and the environmental impact on women's health.

GROUP 1. CARDIOVASCULAR DISEASE AND VASCULAR BIOLOGY

The role of gender in angiogenesis, vascular remodeling, cell structure and function, and thrombosis. Linkage with sex hormones and cardiovascular disease, diabetes, stroke, obesity, and role of nutrition.

GROUP 2. NEUROSCIENCE AND BEHAVIOR

The role of sex and gender in neurodevelopment, CNS structure and function. Linkage with sex hormones and cognitive function, perimenopausal cognition, aging cognition, eating disorders, and the impact of environmental exposures in women.

GROUP 3. IMMUNOLOGY, GROWTH, AND DEVELOPMENT

The role of sex and gender in inflammation and immune response. Linkage with sex hormones, aging, arthritis, and lupus. Role of sex, gender, signaling, and growth factors.

GROUP 4. INFECTIOUS DISEASES AND EMERGING INFECTIONS
Role of sex and gender in the etiology, transmission, course, and outcomes of infectious diseases, including HIV, STDs, and others involving emerging pathogens, with a focus on improved prevention, diagnosis, and treatment for women.

GROUP 5. MENTAL AND ADDICTIVE DISORDERS
The role of sex and gender in the etiology, course, comorbidity, and outcomes of mental and addictive disorders, including sex hormones, genes, gene-environment interactions, gender-related risk behaviors, depression, and eating disorders.

GROUP 6. REPRODUCTIVE HEALTH
Research to address life span issues including research on contraception (development, use, and post marketing evaluation), (IOM report), as well as the influence of contraceptive choice on infertility, STDs, (IOM report), acute and chronic conditions, and lifestyle. Consider particularly implantation, maternal issues, prevention, diagnosis, treatment of pregnancy complications and embryo or fetal loss and reducing morbidity from myoma, endometriosis, abnormal uterine bleeding, uterine prolapse, and other benign gynecologic diseases. Address hormone replacement therapy, menarche, menopause, postmenopausal issues, and cultural, ethnic, socioeconomic, and behavioral issues.

GROUP 7. CANCER
Address basic science, genetics, gender differences, and environmental factors contributing to mortality in breast, lung, colon, and gynecological cancers to understand the malignant processes and to lead to improved prevention, diagnosis, and treatment. Consider female populations that bear a disproportionate burden of cancer incidence and mortality. Ethical, legal, and social implications of new technologies including screening and genetic testing.

Noon	***Lunch Remarks*** Jo Ivey Boufford, M.D. Principal Deputy Assistant Secretary for Health U.S. Department of Health and Human Services
1:30 p.m.	***Working Groups (continued)***
3:30 p.m.	***Break***
3:45 p.m.	***Plenary Keynote Speaker*** Nancy Wexler, Ph.D. Higgins Professor of Neuropsychology, Columbia University
4:15 p.m.	***Working Group Summary Reports***
5:30 p.m.	***Adjourn***
6:00 p.m.	***Reception***

FRIDAY, SEPTEMBER 27, 1996

WORKSHOP DAY 2

Continuing and Emerging Scientific Issues for Women's Health Research: Research Strategies

8:30 a.m. ***Kickoff Speaker***

Ruth L. Kirschstein, M.D.
Deputy Director, NIH

9:00 a.m. ***Plenary Session***

Models for the Conduct of Research on Women's Health: Research Strategies and Methods

9:30 a.m. ***Charge to the Working Groups: The Future for Women's Health Research***

9:45 a.m. ***Break***

10:00 a.m. ***Concurrent Breakout Working Groups***

Consider overarching issues of life span, aging, prevention, diversity, and collaborative and multidisciplinary approaches. The impact of managed care, informatics, and what is ready for testing and commercial application should be considered as well as socioeconomic, cultural, and sex and gender factors in the identification of unique barriers for:

A. RESEARCH DESIGNS

1. *Multidisciplinary Perspectives:* How can synergy between scientific disciplines be achieved through a multidisciplinary perspective that incorporates biomedical, psychosocial, and socioeconomic approaches to women's health research?

2. *Cultural Diversity:* How can diverse communities of women participate actively in helping set research priorities, participate in clinical studies, and, most importantly, benefit from the implementation of the outcomes. Communities refer to different levels of social organization, from families to neighborhoods, and to other forms of community. How can cultural and socioeconomic factors be differentiated from race and incorporated into the study of health and disease of women? Culture refers to shared values and beliefs about the world. Epidemiologic analyses of health outcomes in diverse populations should also be addressed.

3. *Gender:* What are the best ways of conceptualizing and studying similarities and differences between males and females? As examples, effects might be due to genetics, sex-related hormones, gender role socialization, and disparities in power and status in society between women and men.

B. HEALTH IMPACT AND HEALTH OUTCOMES

1. *Biotechnical Advances:* How can advances in biotechnology be incorporated into clinical care and health professional education programs for women's health, including prevention, screening, and treatment? The role of gender in access to care, diagnostic and therapeutic interventions, and patient-provider communication should be considered. What are the ethical, legal, and social issues? How can the diverse community of women benefit from state-of-the-art research?

2. *Gender Differences:* How can knowledge of gender differences across the life span be applied to preventative interventions? Consideration should be given to what constitutes successful life course transitions (entrance to school, adolescence, entrance to parenthood, widowhood).

C. WOMEN IN BIOMEDICAL CAREERS: ISSUES OF IMPORTANCE FOR YOUNG INVESTIGATORS

Positive ways to advance women's careers through training, leadership opportunities, and mentorship. What are successful examples of recruitment, retention, re-entry, and advancement?

12:15 p.m. ***Break***

12:30 p.m. ***Lunch***
Keynote Speaker
Karen Davis, Ph.D.
President, The Commonwealth Fund

1:45 p.m. ***Plenary (Working Group Reports)***

3:30 p.m. ***Closing Remarks and Adjournment***
Dr. Pinn

PHILADELPHIA, PENNSYLVANIA
SEPTEMBER 25-27, 1996

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