

guide them as they deal with questions of including women and persons from minority groups in clinical research studies. Neither the burdens nor the benefits of research should be exaggerated. To overstate either burdens—as was done in the 1960s and

1970s—or to overstate expected benefits—as is frequently done at the present time—is to do research subjects an injustice.

It is hoped that our society will find a way to balance the burdens and benefits of research more accurately so

that subjects can be recruited in a manner that is fair to women as well as men, and to persons from minority groups as well as those from the majority group. In seeking these goals, let us learn well the lessons of the past.

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## The Role of the NIH's Office of Research on Women's Health

**Abstract**—The Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) was created in 1990 to carry out three major mandates: (1) to strengthen, develop, and increase 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 for women than for men; (2) to ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially clinical trials, that are supported by the NIH; and (3) to direct initiatives to increase the number of women in biomedical careers. One of the ORWH's first accomplishments was a 1992 report that serves as a basis for the ORWH's research agenda; its recommendations focus on scientific issues affecting women's health from birth to old age. To implement these recommendations, the ORWH does not fund studies directly but instead provides funds through NIH institutes and centers to augment new research initiatives, to expand ongoing studies to address high-priority areas concerning women's health (14 of which were identified for special consideration in FY 93), and to

increase the participation of women in clinical studies. In addition, the ORWH is playing a key advisory role in the NIH's Women's Health Initiative, a long-term study of over 100,000 women to examine the major causes of death, disability, and frailty—heart disease and stroke, breast and colorectal cancers, and osteoporosis—in older women of all races and from all socioeconomic strata. Also, as part of the NIH's overall effort to include more women and minorities in clinical research, the office formed a task force to address concerns about the recruitment and retention of women in clinical studies and is disseminating information to help investigators to recruit and retain more women as research subjects. The office is also involved in the development of NIH guidelines on the participation of women and minorities in clinical research, to be implemented in FY 95. A major goal of the ORWH and the NIH is to promote greater participation of women in biomedical research careers; the steps being taken to identify barriers and to increase opportunities are explained. *Acad. Med.* 69(1994): 698–702.

Traditionally, in both research and health care delivery, women's non-

reproductive health issues have been viewed with the implicit assumption that diseases behave the same in women and men. This pervasive scientific posture has been reflected in the widespread exclusion of women from clinical trials. And it has been reinforced by the so-called "glass ceiling" in the professional ranks of biomedical research institutions, so that women's voices were rarely heard in policy-setting bodies that might have prevented the lack of research directed toward women, and both men and women of color, in the past.

The National Institutes of Health's (NIH's) Office of Research on Women's

Health (ORWH) was founded in 1990 to address these inequities. The specific event that led to the creation of the ORWH was a report by the U.S. General Accounting Office in June 1990 that women were routinely excluded from medical research studies supported by the NIH, and that although NIH policies encouraged researchers to analyze study results by gender, the policy for the inclusion of women in clinical research was not well communicated or understood.<sup>1</sup> This report was greeted by a wave of public and Congressional anger and serious concern that many medical research findings might not be applicable to the female body.

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Three months later the NIH's acting director William Raub announced the creation of the Office of Research on Women's Health, naming Dr. Ruth Kirschstein as acting director of the new office. Dr. Kirschstein served in this position until the appointment of the full-time director in November 1991.

The Office has three major mandates. They are

1. to strengthen, develop, and increase 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 for women than men;

2. to ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially clinical trials, that are supported by the NIH; and

3. to take initiatives to increase the number of women in biomedical careers.

## ADDRESSING GAPS IN KNOWLEDGE ABOUT WOMEN'S HEALTH

The ORWH initiated a year-long process to help define an NIH research agenda for women's health for the coming decade. The culmination of this project was a 1992 report entitled *Opportunities for Research on Women's Health*<sup>2</sup> that serves as a basis for the ORWH's research agenda and assists in setting priorities for NIH-sponsored research in women's health.

The recommendations in this report focus on scientific issues affecting women's health from birth to old age. Emphasized is the need for basic information about what constitutes normal growth and development in girls and women. The report stresses the concept of the whole woman and recognizes the full range of influences that can affect women's health; these influences have implications for many areas of biomedical research and health care.

The report makes clear that much still needs to be learned about many aspects of women's physiology besides the reproductive system. For example,

national attention was only recently given to the fact that most women in the United States die of the same diseases as men: heart disease, cancer, and stroke. The report recommends that research must address those conditions and disorders that occur in both men and women but have been primarily studied only in men.

The report points out a number of other issues. For example, there are conditions that primarily affect only women that are not sufficiently understood; there is a need for more knowledge of whatever differences may exist between men and women in these conditions' natural histories and responses to therapy. Women's developmental and reproductive biology are still being defined, and more research must be done. Cardiovascular diseases must be more widely acknowledged as the leading causes of death in women, and research and health care measures must be taken to be sure that appropriate interventions are equally available to women and men. Cancers of the breast, lung, cervix, ovary, and colon are major contributors to women's deaths in the United States, in spite of the techniques available for diagnosis and treatment. Immunologic disorders, such as lupus erythematosus and rheumatoid arthritis, afflict more women than men. Acquired immuno-deficiency syndrome (AIDS) is rapidly becoming a major cause of death of women and is the leading cause of death of women aged 24–44 in nine cities located in five states.<sup>3</sup> Other sexually transmitted diseases are increasing in women to what some experts consider to be epidemic proportions.

Recommendations in the ORWH report were based on a multidisciplinary model to prompt studies that include social variables such as socioeconomic status, racial or ethnic background, family circumstances, biomedical factors, and biobehavioral considerations.

## IMPLEMENTATION OF THE RESEARCH AGENDA

The ORWH does not fund studies directly, but instead provides funds through NIH institutes and centers to

augment new research initiatives, to expand ongoing studies to address high-priority areas regarding women's health, and to increase participation of women in clinical studies. Such joint funding allows the ORWH to function as a catalyst and a facilitator, sharing responsibility for women's health research with the institutes, centers, and divisions of NIH. The ORWH supports research through administrative supplemental awards and by co-funding projects or special initiatives.

A significant portion of the ORWH budget supports new initiatives in high-priority areas for research on women's health; to expand the populations of selected studies to include special populations of underserved women (such as minority, low-income, inner city, and rural-area women); and to demonstrate the feasibility of innovative techniques for recruiting or retaining women in research studies.

In FY 1993, the ORWH provided administrative supplements to enable currently funded investigators to address some aspect of the diseases, disorders, or conditions specified in its 1992 report. However, the specific areas of interest that the ORWH identified for special consideration were

- Depression and its interaction with other health problems
- Alcohol use and responsiveness to interventions for women
- Problems of abuse and violence (including posttraumatic stress disorder)
- Behavioral factors for women and disease risk
- Lung cancer in women
- Improved recognition and treatment of coronary artery and thrombotic disease
- Congenital heart disease and genetic defects
- Immunologic factors and autoimmune diseases
- Inborn errors of metabolism
- Antiprogestins and reproductive health, cancer, or meningioma
- Gender differences related to disease manifestation and treatment
- Prevalence of risk factors for disease in women of different racial, ethnic, and economic groups

Occupation and disease and disability  
Sexual behavior and health

Special consideration was also given to enhancing the recruitment of women research subjects, particularly minority women, within an ongoing study, and/or demonstrating the feasibility of innovative techniques for recruiting or retaining women as subjects in research studies. In addition, it is important to realize that women's health research encompasses not only clinical studies but basic molecular and laboratory sciences as well.

### THE WOMEN'S HEALTH INITIATIVE

In addition to addressing the specific health concerns just outlined, the ORWH is playing a collaborative advisory role in the NIH's Women's Health Initiative (WHI), the largest disease-prevention study ever conducted in the United States. The WHI was created to examine the major causes of death, disability, and frailty—(heart disease and stroke, breast and colorectal cancers, and osteoporosis)—in older women of all races and from all socioeconomic strata.

The WHI has three major components:

1. A prospective surveillance study, which will include over 100,000 women, will examine specific risk factors and biomarkers for disease.

2. A randomized clinical trial, of 63,000 women 50 to 79 years of age in 45 centers across the United States, will examine the effects of diet modification, hormone replacement therapy, and dietary supplementation with calcium and vitamin D on the prevention of cardiovascular diseases, breast and colorectal cancers, and osteoporosis.

3. A multi-community prevention study will examine risk factor modification among women.

It is estimated that the WHI will cost, over a period of 10 to 15 years, more than \$625 million. This study will be supported by approximately

55 contracts awarded in FY 92 and FY 93. Within a decade, the WHI should contribute substantially to understanding and reducing morbidity in postmenopausal women and to enhancing their quality of life.

### ENSURING PARTICIPATION OF WOMEN IN RESEARCH

Ensuring the appropriate inclusion and participation of women in biomedical and behavioral research, especially clinical trials, was a focal issue in the establishment of the ORWH. The General Accounting Office Report of 1989 demonstrated that while women were not being systematically excluded from studies, they were not systematically included and were, in fact, excluded from several landmark studies that affected public health practice.

The ORWH was charged with monitoring the inclusion of women in research that addresses the normal and abnormal psychological and physiological processes that affect a woman across her life span. The ORWH collaborates in these responsibilities with the ORMH, which monitors the inclusion of minorities in such studies.

Guidelines on the inclusion of women had been in place at the NIH since 1986. With the release of the findings from the General Accounting Office Report, the NIH revised and strengthened the guidelines on the inclusion of women and minorities in clinical studies.<sup>4</sup> In 1993 the guidelines were revised yet again in response to the congressionally legislated inclusion of women and minorities as specified in the NIH Revitalization Act of 1993, Public Law 103-43 (FT NT). What had been NIH policy for inclusion had now become law.

In a section entitled "Women and Minorities as Subjects in Clinical Research," the Act requires that the director of the NIH shall ensure that women and members of minority groups are included as subjects in each project of such research. The director of the NIH must ensure that clinical trials are designed and carried

out in a manner sufficient to provide for a valid analysis of whether the variables being studied affect women or members of minority groups differently from other subjects in the trial. Further, the Act specifies that the term *minority group* includes subpopulations of minority groups. The Act directs that the NIH must conduct research programs for the recruitment of women and minorities to meet these requirements.

Another important provision of this law is that costs of such inclusion in the trial is not a permissible consideration in determining whether such inclusion is inappropriate. However, exclusion from research projects is allowed if there are substantial scientific data demonstrating that there is no significant difference in variables between women and/or minority groups and men.

The legislated policy and subsequent 1993 guidelines are intended to elicit information about individuals of both genders and diverse racial and ethnic groups such that biomedical and behavioral research can better provide scientific evidence to determine whether the interventions or therapies being studied affect women or men or members of minority groups and their subpopulations differently.

The 1993 guidelines<sup>5</sup> continue the 1990 guidelines with four major additions in response to the Act: (1) that subpopulations of minorities are included in human subject research; (2) for Phase III clinical trials, that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished; (3) that cost is not allowed as an acceptable reason for excluding these groups; and, (4) that programs and support for outreach efforts to recruit these groups into clinical studies must be developed. Inclusion must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of gender and racial/ethnic group, and provide a rationale for selection of such subjects.

This process stretches across the biomedical and behavioral research spectrum and affords investigators the opportunity to gather information on women and minorities early in the research process when hypotheses are being formulated, baseline data are being collected, and various measurement instruments and intervention strategies are being developed. Broad inclusion at these early stages of research provides valuable information for informed decisions in designing subsequent broadly based Phase III clinical trials that test intervention effects.

In order to meet the requirements for outreach (recruitment and retention) required in the law, investigators and their staffs are urged to develop appropriate and culturally sensitive outreach programs and activities for recruitment and retention of the most diverse study population consistent with the purposes of each research project.

While meeting the requirements of the law is important, scientists and their staffs, institutional review boards, NIH internal review groups, and advisory groups must assure that study participants are protected from undue coercion and from harm. An important effort is to ensure that the relationship is mutually beneficial between the investigators and staffs and the populations and communities of interest.

Several efforts have been initiated to facilitate and assist investigators, their staffs, and potential study participants in appropriate inclusion efforts. The ORWH convened the Task Force on the Recruitment and Retention of Women in Clinical Research. The task force sponsored a 1993 public hearing and a workshop that addressed critical issues of inclusion.<sup>6</sup> Issues of risk versus benefit were considered and juxtaposed against the ethical and legal factors that might arise in this process.

The ORWH also contracted with the Institute of Medicine (IoM) to consider ethical and legal issues of including women of childbearing age in biomedical and behavioral research. The emphasis of the deliberations presented in the published report<sup>7</sup> is on inclusion

rather than exclusion. The report stresses the need to fill gaps in knowledge about how to manage disease and illness in pregnant women. It advises that women of childbearing age should not be excluded because of the risk that *some* will get pregnant. It also stresses that diseases of pregnant women need to be studied.

The NIH staff have prepared a notebook, *NIH Outreach Notebook on the Inclusion of Women and Minorities in Biomedical and Behavioral Research*, which addresses both recruitment and retention of women and minorities in clinical studies, provides relevant references and case studies, and discusses ethical issues. It is not intended as a definitive text on this subject, but should assist investigators in their consideration of an appropriate plan for recruiting and retaining participants in clinical studies.

The Act and the policy changes it has indicated should result in a variety of new research opportunities to address significant gaps in knowledge about health problems that affect women and men of diverse racial-ethnic groups.

#### PROMOTING PARTICIPATION OF WOMEN IN BIOMEDICAL CAREERS

Women still face many obstacles that prevent them from entering and advancing in a variety of biomedical research careers. Barriers of entrenched social attitudes, institutional systems, financial constraints, maternal responsibilities, and discrimination affect women in their efforts to achieve and contribute according to their potential as health care professionals, academicians, and researchers.

The NIH and the ORWH are challenging the status quo by identifying the barriers and attempting to create pathways for women to overcome the barriers to their entrance and advancement in biomedical careers. Recognizing the actual and potential contributions of women to the advancement of scientific knowledge is a priority for the ORWH. We at the ORWH are convinced that the best

means of ensuring that research related to women's health remains a visible and active priority into the twenty-first century is to increase the number of women in leadership and policy-making positions in research institutions, including the federal government, universities, and the private sector.

While at one time it could be suggested that the lack of women in advanced academic positions or senior positions in biomedical research was related to the low numbers entering medicine and graduate science programs, this no longer can be held to be the only, or even the major, contributing factor. Recruitment of women into both science and biomedical careers has increased steadily. Enrollment of women in medical schools is up, with women well represented in doctoral studies overall. Yet these statistics can be misleading, because women, and especially minority women, are not proportionately represented in advanced scientific and academic leadership positions.

In order to address the participation of women in biomedical careers, the ORWH held a public hearing, followed by a workshop, to determine the barriers and recommend solutions to nurture the participation of women in science careers.<sup>8</sup>

#### BARRIERS TO WOMEN IN BIOMEDICAL CAREERS

The major sentiments expressed at the ORWH's public hearing were well expressed by one woman scientist who stated, "One rule of thumb is I have to be twice as smart and work three times as hard to get three-fourths the pay and one-half the credit."<sup>8</sup> From nearly 70 testimonials, the following nine general issues emerged that are common to women biomedical professionals:

- Obstacles to recruiting women to biomedical sciences
- Visibility and the need for more role models and mentors
- Career paths and rewards
- Re-entry into a biomedical career
- Family responsibilities

Sexual discrimination and sexual harassment  
 Research initiatives on women's health  
 Sensitizing men  
 Minorities and racial discrimination

## ORWH INITIATIVES FOR TRAINING OF WOMEN IN BIOMEDICAL CAREERS

The ORWH has already begun to increase opportunities for women in biomedical careers. The ORWH has initiated an extramural pilot program, which is now in its second year, for the re-entry of women and men whose biomedical research careers have been interrupted by child or family care responsibilities. The response has been encouraging, with great interest in such opportunities. The NIH is now developing a similar re-entry program to be based in the intramural community.

The ORWH has several other major initiatives under way: it supports ongoing projects and has initiated specific training projects that include opportunities for high school students, college faculty and students, and minority students to obtain research experience or exposure to current scientific concepts through the NIH.

## CONCLUSION

Now, as never before, our society has an opportunity for real progress in improving women's health. Yet no scientific advances in women's health can guarantee continued equity of interest in women's health issues unless women of all races and cultures become full participants in relevant biomedical and biobehavioral research as researchers and as research subjects.

The health care community must be able to provide care based upon sufficient understanding of gender, racial, and cultural differences and the influences of hormones on health and disease. The NIH is committed to providing that understanding through biomedical and behavioral research. Scientific advances and developing biomedical technologies must then be appropriately translated to application and intervention with full knowledge that persons of different genders, races, and backgrounds may be affected in different ways.

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