Women's health and clinical trials

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Women have traditionally been underrepresented in clinical trials. In order to translate recent advances in our understanding of the molecular and physiological bases of sex differences into new therapeutics and health practices, sound sex-specific clinical data are imperative. Since the founding of the Office of Research on Women's Health within the Office of the Director at the NIH in 1990, inequities in federally funded biomedical research, diagnosis, and treatment of diseases affecting women in the US have been reviewed. Discussed herein is the evolution of gender-related research innovations, primarily within the last decade, and strategies and challenges involved in the success of this recent development.

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Medicine is the one discipline in American scientific endeavor in which reforms regarding the role of women as both researchers and research subjects have been institutionalized at the highest level. Adequately addressing women's health issues did not require new technical breakthroughs or simply more female doctors, though the latter helped facilitate change. Nor was women's greater equality in biomedical research a result of the presumed self-correcting mechanisms of objective science. As former director of the NIH, from 1991 to 1993, Bernadine Healy remarked, "research alone cannot correct the disparities, inequities, or insensitivities of the health care system" (1). Reforming certain aspects of how medical research is conducted with respect to the females required new judgments of social worth and a new political will. Even though much has been achieved in addressing issues important to women's health, critics call for continued innovation in medical theories and practices in this field.

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Nonstandard abbreviations used: Multiple Risk Factor Intervention Trial (MRFIT); Food and Drug Administration (FDA).

Gender-biased medicine

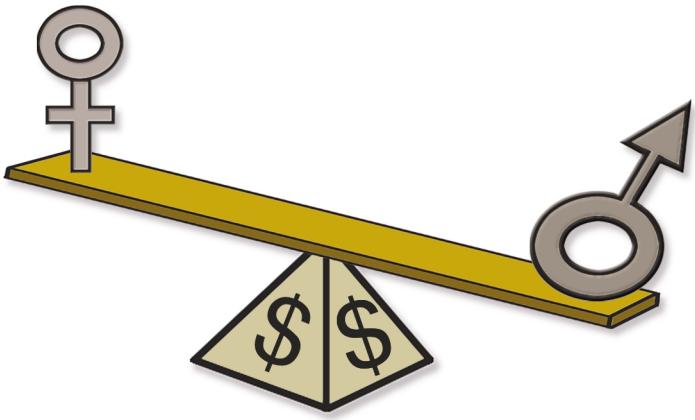
The 1980s saw the great awakening of mainstream medicine to issues of women's health. Researchers, both male and female, began to shower infamy upon several large and influential studies that omitted women as subjects of medical research. These most notably included (a) the Physicians' Health Study of the effects of aspirin on cardiovascular disease, in which 22,071 men and 0 women physicians were enrolled (2); (b) the Multiple Risk Factor Intervention Trial (MRFIT), a randomized trial conducted from 1973 to 1982 to evaluate correlations among blood pressure, smoking, cholesterol, and coronary heart disease in 12,866 men and 0 women (3); and (c) the National Institute on Aging's Baltimore Longitudinal Study of Aging, extending from 1958 to 1975 (4), which excluded female subjects, despite the fact that women constitute two-thirds of the population over age 65. Perhaps most surprising is that the first study of the role of estrogen in preventing heart disease was conducted solely on men, as it was considered a possible treatment (5).

Women's health issues have not been entirely ignored. The well-known Framingham Heart Study, initiated in 1948, has long stood as the benchmark epidemiological study on cardiovascular health and included slightly more women than men (6). The Nurses' Health Study I and II, established in 1976 and 1989, respectively, followed large numbers of registered female nurses, initially to study the long-term use of oral contraceptives, and has been used over the years to look at other health issues, such as the correlation between low-dose aspirin administration and risk of heart attack in women. Unlike the Physicians' Health Study, the Nurses' Health Study was an observational investigation, not a more costly, randomized clinical trial (7). Like the study of male physicians, the study of female nurses evaluated predominantly white, health-conscious populations.

Is what's good for the gander good for the goose?

Until 1988, clinical trials of new drugs by the US Food and Drug Administration (FDA) were routinely conducted predominantly on men (8), even though women consume approximately 80% of pharmaceuticals in the US. The results of male-only clinical trials have led to the development of diagnoses, preventive measures, and treatments that are commonly extrapolated to women, yet the reverse is rare. In 1992, a survey by the US General Accounting Office, the body responsible for the audit, evaluation, and investigation of Congressional policy and

funding decisions, found that less than half of publicly available prescription drugs had been analyzed for sex-related response differences (9). A consequence of extrapolating the results of male-only clinical data to female consumers is that women were (and still are) typically prescribed dosages devised for men's average weights and metabolisms. For example, it is now known that acetaminophen, an ingredient in many pain relievers, is eliminated by the female body at approximately 60% the rate of elimination documented in men (10). The administration of drugs to women at dosages designed for men can place women at risk for overdose. Furthermore, while little is known about the effects of aspirin on heart disease in women, postmenopausal women, like men, have been encouraged to take aspirin daily. The effects of other widely used drugs, such as Valium, were never tested in randomized clinical trials with female subjects, although 2 million women per year consume this drug to control conditions such as anxiety, epilepsy, muscle spasms, and alcohol addiction.



Investigators have defended their choice of males as research subjects on the grounds that men are cheaper and easier to study. The estrous cycle is viewed as a methodological complication during analysis that increases research costs because many more control groups are required. Researchers have also feared that the inclusion of women of childbearing age in clinical trials might endanger fetuses. FDA guidelines restricting research on women of childbearing potential were first implemented in 1977 in reaction to the birth defects resulting from thalidomide and diethylstilbestrol administrated during pregnancy, and the FDA only revised these guidelines to include this population of women in early-phase clinical trials in 1993. These protective restrictions, however, can support the portrayal of women as "walking wombs," unable or unwilling to control their fertility. These guidelines also overlooked the pharmacologic needs of many pregnant women, three-quarters of whom require drug therapy during pregnancy and currently use prescription or over-the-counter drugs for chronic conditions such as diabetes or depression (11).

The net effect of gender bias in medical research is that women are at risk for adverse drug reactions and may suffer unnecessarily and die. Such adverse reactions occur approximately twice as often in women as in men. For example, some antithrombotic agents used to break up blood clots immediately after a heart attack, while beneficial to many men, may cause significant bleeding problems in women (12). Commonly prescribed drugs used to treat high blood pressure tend to lower men's mortality from heart attack but have been shown to increase cardiac-related deaths among women (12). Emerging evidence also suggests that the effects of antidepressants can vary over the course of the menstrual cycle. Subsequently, drug dosage may be too high at some points during estrous and too low at others. Besides that, drugs developed for men and untested on women may be dangerous for women, drugs that are potentially beneficial to women may be eliminated in early phases of clinical testing when the test group does not include women and no benefits are manifest in male subjects (13). Concomitantly, while women tend to be undertreated in many areas of medicine, they are also at risk for overtreatment in the area of reproduction, such as unnecessary cesarean sections and hysterectomies (14).

Much has now been made in the US of the need to depart from the "usual male model," where testing is routinely done on males, and from the "usual white model," where test subjects are of white European origins, in medical research and health (15, 16). Researchers are now wary of developing a "usual female model," where females are assumed to conform to a unitary category of sex, and racial and ethnic differences remain unanalyzed. Whereas the women's health movement of the 1970s sought to solidify sisterhood through the commonalities of female childbirth experiences, there is now an emphasis on the differing health needs of different racial and ethnic groups of women. Only very limited conclusions can be drawn about a patient's disease from her biological sex. This is revealed in the variation of disease morbidity and mortality in different ethnic populations. African-American women are, for example, more at risk for stroke, heart attack, and hypertension than European-American women. While African-American women have a lower incidence of breast cancer than European-American women, they die more often as a result. Hispanic women's rates of cervical cancer are twice as high as those of non-Hispanic white women. In addition, non-Hispanic white women have higher rates of osteoporosis than Hispanic or African-American women; however, because osteoporosis is considered a white disease in the US, African-American and Hispanic women may not be properly screened and educated about it (17).

The feminist sea change

Beginning in the late 1980s and 1990s, feminist calls for reform in federally funded biomedical research in the US were taken up by the federal government. The 1990s saw what could only be called a revolution in biomedicine for women in the US. In

Reform of investigation without representation

The NIH Revitalization Act of 1993 requires the following:

- Women and minorities and their subpopulations be included in all NIH-supported biomedical and behavioral research
- Women and minorities and their subpopulations be included in phase III clinical trials in numbers adequate to allow for valid analysis of differences in intervention effect
- Cost not be accepted as a reason to exclude these groups
- The NIH initiate and support outreach programs to recruit and retain women and minorities and their subpopulations as participants in clinical studies

This act ensured that the NIH could not and would not fund any grant or project thereafter that did not comply with this policy. Grant applications with unacceptable rates of inclusion are barred from receiving funding until the NIH is satisfied with revised proposals. Grantees are subsequently required to report annually on the gender, race, and ethnicity of accrued subjects (20).

September 1990, the US federal government founded the Office of Research on Women's Health within the Office of the Director at the NIH. This office has two primary missions: to develop opportunities for and to support women's recruitment and reentry into, and advancement in, biomedical professions, and to ensure that research conducted and supported by the NIH adequately addresses diseases, disorders, and conditions that affect women. In 1991, the federal government announced the establishment of the Women's Health Initiative, a major 15-year research program coordinated among 40 clinical centers nationwide, in conjunction with the Department of Health and Human Services, the NIH, and the National Heart, Lung, and Blood Institute, to which $625 million was budgeted toward the study of the most common causes of death, disability, and poor quality of life in postmenopausal women. Between 1990 and 1994, Congress enacted no fewer than 25 pieces of legislation to support advancements in the understanding and management of the health of American women. The most important of these was the NIH Revitalization Act of 1993 (18). Also significant was the publication of the *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research* (19). The act reinforced existing NIH policies, with a number of major differences (see *Reform of investigation without representation*) (20), ranging from requiring that females and minorities be adequately represented in clinical trials to establishing new federal regulations for mammography (21, 22). In 1994, the FDA also created an Office of Women's Health, which oversees correction of gender disparities in drug research and administration policies (23).

Taxation without representation

Much of the impetus for the women's health movement came from the feminist idea that women should get their fair share of research dollars, both as researchers and as research subjects. Attention was drawn to the failure to include women in publically funded research. Quite appropriately, many people supported the idea that since women pay taxes that contribute to federally funded health research, they deserve to derive benefit from that research. Simply taking women seriously as researchers and including them as research subjects in areas other than reproduction — a base-line liberal approach — has had a tremendous impact on medicine. The reforms have been simple in their conception — inquiry should include female subjects — but dramatic in their realization: the right of females to be included in basic medical research is now secured by federal law.

Beyond the liberal approach to gender equity in biomedical research, which emphasizes equal attention to the health needs of men and women, a reconceptualizing of sex-related differences in the human body has been crucial to advances in women's health (24). When the General Accounting Office reviewed NIH policies in 1989, there was still no uniform definition of research specific to women's health. Medical researchers had long assumed that the phrase "women's health" referred to reproductive health — involving attention to birthing, contraception, abortion, breast and uterine cancer, premenstrual syndrome, and other maladies distinctively female. Definitions of women's health now treat the whole array of women's distinctive biology. Florence Haseltine, founder of the Society for Advancement of Women's Health Research and a powerhouse for reform at the NIH, has identified this shift from reproductive health to more general female health issues as being crucial for ongoing reforms in women's health research (25). The NIH now defines women's health research as the study of diseases unique to women (such as breast cancer), or diseases with a higher prevalence in women than in men (such as osteoporosis), or diseases that present differently in women than in men (such as heart disease). Working from this conceptual base, the Women's Health Initiative has focused attention on the prevention of osteoporosis in addition to the leading causes of death in women: cardiovascular disease and breast and colon cancer. The NIH Office of Research on Women's Health has also funded understudied areas of research, including women's occupational health, sex-related differences in autoimmune diseases, and female urologic health.

Critics of the Women's Health Initiative

Not everyone, of course, agrees that women's health requires special attention. Critics deny that it has been improper to leave women out of randomized clinical trials, such as the MRFIT studies. According to this view, since men die from heart disease at earlier ages than women, they are an appropriate group for study (26).

The Women's Health Initiative currently receives approximately 6% of the NIH annual budget, and critics charge that the funds earmarked for the study of female-specific disorders is excessive. They argue that 13% of the NIH annual budget is already devoted to health issues directly related to women, while only 6.5% of the budget contributes to the study of diseases unique to men. Their trump card is that the life expectancy of an American female, at 78.6 years, substantially outstrips that of the American male, at 71.8 years, suggesting that women are currently well cared for.

Other critics deny that feminism has now adequately addressed women's health in medical research and charge that the Women's Health Initiative and the poorly funded Office of Research on Women's Health are merely efforts to diffuse the explosive politics surrounding federal funding of women's health research (12). What is equal or fair in this instance? Is the solution to equalize spending on men's and women's health research? One could argue that research that uses the male body as the norm serves men better even when fewer dollars are spent on male-specific diseases. One might also argue that the greater role of women in human reproduction warrants more research on female reproductive health. But surely the goal of US biomedical research is to study both men and women of various classes, races, and backgrounds to maximize their long-term health and well-being.

A call for broader reform: beyond the biomedical model

Feminist reform within the NIH has been critical in improving health care for women. But some feminists suggest that it may not be enough simply to include women in clinical studies already in progress or to take into account their distinctive physiology. Study populations can be reconfigured and women's diseases can be given research priority within existing medical practices, they claim, without dramatically improving women's health. These feminists contrast the dominant "biomedical" model of research with a "community" or "social" model of the investigation and evaluation of women's health. They challenge approaches that focus narrowly on disease management and biochemical processes in organ systems, cells, or genes (27). Broad social models that seek to ground health in the community do not ignore genetic or biological aspects of health — certainly the genetic components of Tay-Sachs disease, sickle-cell anemia, cystic fibrosis, and β-thalassemia require study. Nor do advocates of the community or social models deny the importance of personal lifestyle (attention to nutrition, exercise, relaxation, and restraint from smoking and drug abuse). They do, however, see as equally important an understanding of how health and disease are affected by an individual's daily life, access to medical care, economic standing, and relation to his or her community. Advocates of relating health and disease to broader social factors see health as embedded in communities, not restricted to individual bodies.

What brought about change at the NIH?

It is commonly assumed that increasing the number of female physicians is sufficient to bring about change in medical theories and practices with respect to women (28). Increasing the number of women in the medical profession is, of course, important. The NIH Office of Research on Women's Health has rightly set women's recruitment and reentry into, and retention in, biomedical careers as one of its goals. But to see this as the decisive factor in promoting better health care for women oversimplifies and depoliticizes a complex cultural process. It is not just women but feminists — both men and women — inside and outside the medical field who have driven reform in medical research policies. The changes discussed here in the study and practice of medicine in the US have resulted from a multidimensional process of social change that has included (a) a broadly based women's movement; (b) fundamental changes in attitudes toward women; (c) the collaboration of men opposed to the apparent inequality in research policies; (d) the institutionalization of academic research on women and gender in universities; (e) strong congressional lobbies on emotional issues such as breast cancer research; (f) a reasonably strong economy; and (g) action by Congress to legislate gender equality in health research. The same forces and changes that successfully increased the number of women in the medical profession have also facilitated a change in attitudes and policies regarding the conduct of research relating to women's health. The reform of gender-related medical research may now serve as a model for correcting gender bias in other sciences. Most importantly, including an analysis of significant sexual differences in biomedical research has facilitated the development of reliable databases upon which physicians and other health professionals can base informed clinical decisions and health recommendations for both women and men.

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