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Symposium: Does SexX Really Matter - What a Difference an X Makes: Welcome Remarks

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Welcome Remarks

Phyllis Greenberger*:

I am going to start by giving a little bit of the history of the Society for Women's Health Research (Society) and how we got into the issue of clinical trials and sex based biology. Then I would like to talk about some of the barriers that we still face and some of the solutions that my organization thinks we can offer. For those of you who are not familiar with us, we are the only national non-profit organization whose mission is to improve the health of women through research, education, and advocacy. We were founded in 1990.

We focused our initial work on the inclusion of women and minorities in clinical trials and also on conditions that differently, disproportionately, or exclusively affected women. At that point in time women's health was exclusively defined as reproductive issues. The National Institute of Child and Human Development was the only organization doing research. That research focused on maternal issues. At other institutes and in private industry there was minimal or no focus on the other conditions that affected women differently or disproportionately. A few years after that initial focus, we started getting into the issue of biological differences between men and women. Since our inception we have been very influential at HHS, including at the FDA, NIH, and various other agencies. We have also influenced private industry, which does the bulk of pharmaceutical, device, diagnostic research.

The history of the inclusion of women in medical research is really one of exclusion. In 1977 the FDA banned the inclusion of women in clinical trials. To a great extent this exclusion was motivated by the thalidomide and DES tragedies. Although those tragedies had nothing to do with clinical trials, they had to do with harm to women, creating a feeling that women should not be included in clinical trials. This ban was meant to protect women and their fetuses, but what it actually resulted in was an era of what we refer to as the 'male norm' in clinical research. During that era most research was done on young, white, healthy males. It became common practice to extrapolate results from male subjects to women. I do not think it will come as any surprise that using the 'male norm' was not good for women's health.

In 1985 the United States Public Health Service determined that the lack of information on women in clinical trials was compromising women's health. To address this, in 1986 the NIH urged clinical researchers to include women in their studies and to analyze the results by sex. In 1990, with Congressional support, the Society spearheaded a Government Accountability Office (GAO) study. The study found that NIH was failing to implement its own guidelines. We knew NIH was not doing this, but we needed to make it official. We asked Congress to investigate the issue and discovered that NIH was not following its own mandate.[1] That was the beginning of the Society working with Congress to change laws.

There was not much progress at including women in research until two events took place in 1993. The first was the Revitalization Act, which required the inclusion of women in all clinical research and analysis of results by sex for Phase III trials. Second, the FDA established guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs.[2] These guidelines did not encourage the inclusion of women in safety and dosing studies, which are Phase I and II, but required the inclusion of women in efficacy trials, which are Phase III.

We worked with the GAO again in 2001 to investigate what was being done at NIH and how much progress was being made. The investigation revealed a few things. The audit of the FDA records revealed that the FDA had not effectively overseen presentation and analysis of data related to sex differences and drug development.[3] In fact, there were a number of drugs that had been taken off the market after it was shown that they disproportionately caused adverse reactions in women. The analysis showed that 30 percent of study documents failed to fulfill requirements for

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presentation of outcome data by sex. Nearly 40 percent did not include the required demographic information, demonstrating that the FDA had not effectively overseen the presentation and analysis of data. We believe that if the FDA had studied sex differences either the drugs would have stayed on the market, women would have been monitored, or the drugs would not have been prescribed for women.

In 2001 the board of directors of the Society decided that rather than just looking at conditions that differently, disproportionately, and exclusively affected women and inclusion in clinical trials, we should go more to the basic level and see if we could validate the concept of research looking into sex differences. At first we were not taken seriously. There we were, a group of women, telling researchers and doctors that they were doing research the wrong way and that some of the care they were providing was not appropriate for women. Then we went to the Institute of Medicine to convince them that this was an important study.[4] This process took a number of years, in part because we had to raise additional funds. In 2001, we released our report entitled *Exploring the Biological Contributions to Human Health: Does Sex Matter?* The report concluded that sex does matter. It matters in health and disease from "womb to tomb." It emphasized the need to carefully evaluate sex differences in medical research and incorporate those differences into clinical practice. Biological sex needs to be considered as a variable at all levels of research.

The inclusion of women in clinical research and the fact that scientists have begun finding differences between men and women in terms of susceptibility, prevalence, time of onset, severity, and response to treatment of various diseases and conditions, has led us to redefine women's health. Today's definition of women's health moves beyond the reproductive system and encompasses every disease and condition that affects women disproportionately or differently. Biological sex differences result from a combination of genetic, hormonal, physiological, and environmental factors. These differences have real world consequences for the diagnosis and treatment of diseases.

First let us look at heart disease. It was not until the Society had their first Sex Differences Conference on cardiovascular disease that anyone really started thinking that cardiovascular disease affects women. Heart disease kills 500,000 American women each year, over 50,000 more women than men, and strikes women, on the average, 10 years later. Women are more likely than men to have a second heart attack within a year after the first one. No one knows why. We do know there are significant sex differences in the anatomy and physiology of the heart and how heart disease manifests itself.

Another example of sex differences arises with neurological disorders. We have always known that men and women's brains are different, structurally and functionally. This may result from the effects of estrogen and testosterone during brain development and differences in response to steroid hormones in localized regions of the brain later in life. These differences can result in differing rates of certain neurological disorders in men and women. For example, women have higher rates of depression and anxiety disorders while men have higher rates of autism and ADHD.

The list goes on. In almost every category of disease – autoimmune, bone diseases, etc. – there are differences between men and women. While science has made great strides in understanding the basic biological differences, there is still a great deal to learn. We have reached a crossroads at which we need to examine how medical research is conducted and support programs and policies to promote the study of biological sex differences. We have spent more than a decade trying to raise awareness of the importance of sex differences in health and disease among research scientists, clinicians, funders, legislators, and the public. We have put together expert panels on various topics, published reports, and funded four interdisciplinary research networks. These four networks look at sex differences in cardiovascular, metabolic, neurological, and musculoskeletal diseases.

About two and a half years ago we launched a new scientific membership organization, the International Organization for the Study of Sex Differences, which brings together scientists to look at sex differences. We still face a lot of barriers. While there are a growing number of investigators doing research on sex differences and the literature is expanding, many scientists are still unaware that sex differences exist at every level. There are no consistent efforts among the NIH to encourage studies that elucidate sex differences of the basic biological mechanisms underlining these differences. By requiring that all grant proposals include plans for data by sex, the NIH could ensure that sex difference becomes a de facto priority in medical research. When the NIH interpreted the 1993 legislation, they interpreted it to require that women be included only in Phase III. We believe that inclusion needs to occur in Phase I and II, looking at toxicity and dosages.

There is also a problem in terms of the medical research. Scientific and medical journals do not require that authors report the sex of their studies' subjects, human or animal, or that results are analyzed by sex. As a result many published studies do not contribute to our knowledge of sex differences. If all scientific journals required analysis by sex, researchers would have to design their studies to detect sex differences. We believe that funders and institutional review boards should require that all research include women at all phases. Analysis of sex differences is not done routinely and in some cases the number of female participants is too small to obtain statistically significant data.

The 2007 review of published data from cardiovascular disease trials shows that, of the 628 reviewed studies, three-quarters did not include sex difference analysis, forty-one trials did not provide the sex of participants, and seventeen did not include women at all. At the basic research level, studies on animal models do not routinely include both sexes as subjects. We have been told that female animals are more expensive and more complicated, but that does not mean they should not be used.

Barriers to progress also exist at the health care provider level. Physicians need to be informed about sex differences to treat their patients effectively. In 2005 an American Heart Association national study of physician awareness showed that physicians remain largely unaware of sex differences in cardiovascular disease. Only eight percent of primary care physicians, thirteen percent of OBGYN's, and seventeen percent of cardiologists were aware that heart disease kills more women than men every year.

Currently how sex affects health and disease is not part of nursing and medical school curriculum. It is important that health care providers be trained in sex differences so they can appropriately evaluate, treat, and educate their

patients. Similarly, continuing medical education does not always include research that looks at sex differences. There is still physician bias. Female and male patients showing up at a clinic with the same symptoms may be treated differently. Doctors often fail to recognize women's risks for conditions such as heart disease, lung cancer, and osteoarthritis. Even when a physician diagnoses a condition such as heart disease, he or she is less likely to refer a female patient to diagnostics and treatment. Women get less aggressive treatment. Two alarming studies showed that even when male and female patients had the exact same conditions and symptoms the physicians' diagnoses were more aggressive for men.

Educating women about the importance of participation in clinical trials is another area that we continue to work in and fund. The only time we ever hear about clinical trials is when something goes wrong and it is on the front page of the paper. If our goal is to learn what works better in women and men, or children, or the elderly, or minorities, we need diverse participation in clinical trials. We need to educate women and physicians. Often physicians discourage people, both men and women, from entering clinical trials.

In a nine-year cardiovascular disease study, which asked women what is the greatest health problem facing women today, only eight percent identified heart disease. The number went up to thirteen percent in 2003 and twenty-one percent in 2006. Women fear breast cancer more than heart disease, but in reality they are much more vulnerable to heart disease and in many respects it is preventable. There are problems with how the media interprets scientific data from the published literature and reports study findings incorrectly. This contributes to patient confusion and lack of confidence. One example of this that is still controversial is the way in which the Women's Health Initiative (WHI) study was halted. We believe it is a perfect example of miscommunication leading to confusion. The WHI was a federally funded study to determine whether hormone replacement therapy reduces the risk of heart disease in post-menopausal women. Since the release of the initial results, contradictory information has come to light. Women are still confused as to whether hormone therapy is safe, whether taking calcium helps their bones, and whether low fat diets are beneficial for their health.

We are faced with a system where in many respects patients are forced to be their own health advocates as consumers in a complicated health care system. This works for only a fraction of educated consumers. For the majority of us it is extremely difficult enough to figure out the health care system, much less to develop a relationship with a provider. If a patient asks too many questions or appears to question the authority of the physician, the patient is often labeled as difficult.

Research teams need to think broadly about research questions, including sex as a variable in both basic and clinical research and requiring analysis in reporting results by sex. Journals also need to report by sex. Sometimes when an article is too long a journal will cut out the portion having to do with women or will simply refer to women as 'patients'. Often readers do not know whether women were included. Imagine you are a cardiologist reading an article in the popular journal, *Circulation*, about a major trial on cardiovascular disease, but the article only refers to males. Then there might be in a smaller journal, less popular among healthcare providers, in which the part on women is included.

Blood and tissue samples that are stored in repositories should indicate the sex and hormonal status of the donor. For women, this would include pre-pubescent, reproductive, pregnant, menopause, post-menopause statuses. As the Institutes of Medicine suggest, research needs to be conducted in individuals from womb to tomb. We need faster translation of basic research results into the clinic, not just in terms of better drugs and diagnostics, but in the adoption of new technologies that are affordable. We need to develop guidelines to educate providers on how sex differences impact the health and health care of women.

In closing we believe that the study of sex differences is the strongest approach to improve women's health. As sex differences research evolves and is translated into more personalized medical treatments, both sexes will equally benefit. Understanding the differences in how diseases manifest themselves in women also helps us understand the mechanism in men. We will all equally benefit from better health and health care.

Corrine Parver:

If you were to emphasize to policymakers that sex differences research benefits both men and women, rather than just women, would they be more responsive to the issue?

Phyllis Greenberger:

For many years we have been trying to convince the pharmaceutical industry that if they do not do testing on women in the early stages of drug development, we will find problems once the drugs are on the market. The industry would rather have a drug that is out there for everybody and worry about problems later, than spend more time and money doing complicated and costly trials that will only allow them to market the drug to half the population. Obtaining funds from Capitol Hill is a long shot. It is up to the NIH directors. Some NIH directors get it and are doing the right thing, but the majority of them do not.

We did a study a number of years ago looking at the percentage of proposals that were funded by the NIH. At that time only three percent related to sex difference research. The institutes that one would think would have more of a focus on women's issues, such as the Cancer Institute and the Heart Lung and Blood Institute, were the worst. Nobody is against knowing what works best and there are a lot of things that could be improved. We are still learning about sex differences in diagnostics, devices, and pharmaceuticals. We are concerned that if the NIH starts looking at comparative effectiveness without taking into consideration sex differences we may end up backtracking from the progress we have made so far.

1 *NIH Guide for Grants and Contracts,* National Institutes of Health, Bethesda, MD, 1986.
2 *Women Sufficiently Represented in New Drug Testing, But FDA Oversight Needs Improvement.* Rep. GAO-01-754, United States General Accounting Office, Washington, DC, 2001.
3 *Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women.* Rep. GAO-01-286R, United States General Accounting Office, Washington, DC, 2001.
4 Wizemann, T.M. M.-L. Pardue, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Eds. 2001. Board on Health Sciences Policy, Institute of Medicine, Washington, DC.