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Gender Medicine: “In a perfect world...”

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This focus group of papers for the Women’s Health/Gender Medicine section highlights a topic that is near and dear to my heart as a researcher who studies sex and gender differences in cardiovascular and renal disease and hypertension. It is also timely since the National Institutes of Health (NIH) and the Office of Research in Women’s Health (ORWH) have recently come together to require that NIH applicants consider sex as a variable in biomedical research involving animals and cells. In a commentary published earlier this year in *Nature* (1), Janine Clayton, Director of the ORWH, and Francis Collins, Director of the NIH, suggest that this initiative is the equivalent in animal and cell research as the NIH Revitalization Act of 1993 that required the inclusion of women in NIH-funded clinical research (2).

In 2001 the Institute of Medicine published a white paper that defined “sex” as “being male or female according to reproductive organs and the functions assigned by chromosomal complement (XX for female and XY for male)” (3). This includes any physiological process that is directly mediated by the presence or absence of sex steroids (3), and includes but is not limited to reproduction. In contrast, “gender”, a word that is often misused not only by the scientific community but also the lay press, includes “everything else” (3), and is mainly how one sees oneself as male or female, and how society therefore responds to the person as male or female. Thus gender encompasses psychosocial issues and environment that are not included in the definition of “sex”.

It is very true that most pre-clinical research is done using male animal models (4). The reasons are myriad, including the notion that the cost of including females in the study doubles the cost that may be prohibitive in these times of reduced funding levels and cutbacks at NIH. In addition, there is the misconception that the presence of the estrous cycle in the female makes them a more difficult and variable model to study. To date there have been very few physiological or pharmacological effects that have been shown to vary by the day in the estrous cycle, especially in rodents, the most commonly used animal model for pre-clinical research. Certainly women are not treated differently for their hypertension, heart disease or hypercholesterolemia based on whether they are in the follicular phase or the luteal phase of their menstrual cycles, or even based on the lack of a menstrual cycle after menopause. Of course, with regard to hypertension, the guidelines for treatment of women are not different than for men. Unfortunately, this is in spite of the fact that many studies around the world are now showing that hypertension is not as well controlled in postmenopausal women as men (5,6), suggesting, among other causes, that the mechanisms responsible for the hypertension in women may be different than for men.

While it is also true that the NIH has required the inclusion of women in all clinical trials since the Revitalization Act, the numbers of women actually recruited for clinical trials range from 20–60% of the cohort (7). For example, for hypertension, the clinical trials are fairly good at an average of 60% women, but for heart disease, the numbers are much lower, closer to 20% women. Importantly, while women are included in the trials, very few of the studies are powered statistically to find gender differences. Furthermore, there are no adverse consequences for investigators funded by the NIH who do not recruit enough women and men to evaluate the role of gender in their studies whether there is a gender effect or not. It is just as important to show that there is no effect of gender on a physiological outcome as to show there is an effect, and these data should be published.

In a perfect world we would recommend to NIH to announce financial incentive programs paid for by specific percentages of the portfolios in each institute, including Requests for Applications (RFA), to perform pre-clinical studies to evaluate sex differences, and require documentation that this is accomplished in the yearly progress reports required of funded investigators. That, more than anything else, would change the culture of research in which only males are used. These changes would impact not only NIH then, but also other foundation-supported funding as well, since as we all know, what happens at NIH has a ripple effect throughout many other funding agencies. We would also recommend that NIH encourage training in how to perform studies using both sexes, and set aside a portion of T32 training grant funding that is directed and focuses on this training. Finally, both study section members and administrators will need training in how to scientifically evaluate applications that incorporate sex as a tested variable in animal studies.

Finally, in a perfect world both women and men in equal numbers would be recruited in clinical trials when appropriate, and the principal investigators would be held accountable by NIH if these equal numbers were not met, and the data were not analyzed for gender.

While I have focused on the new initiatives by NIH to include sex as a variable in pre-clinical studies, this is a common problem being addressed by many governmental research agencies around the world (8–10).

These are exciting times for gender medicine going forward, and we hope that these proposed initiatives by NIH will improve the health of both men and women.

In the current issue of *Clinical Therapeutics*, we have included several review articles that incorporate the use of animal models to study various diseases. Tipton and Sullivan discuss the role of T cells and the immune mechanisms responsible for hypertension (11). This is a growing area of research based on findings several years ago now that replacement of T cells but not B cells in mouse models that are null for both T cells or B cells, causes them to have a hypertensive response to the vasoconstrictor angiotensin II (12).

While heart disease is the leading cause of death among women, they are typically approximately 10 years older than men at diagnosis and thus the consequences of the disease are complicated by aging in women. Thus pre-menopausal women have been thought to be protected since the incidence of heart disease is lower in them than age-matched men.

Garcia and colleagues provide data to suggest that pre-menopausal women may not be protected against heart disease especially in the face of diabetes (13).

The cardiovascular disease that accompanies systemic lupus erythematosus (SLE) is a focus of the review by Gilbert and Ryan (14). Women have a 9 fold higher incidence of developing SLE, as is the case with most autoimmune disorders. This has lead many investigators to propose that estradiol may promote the incidence of the disease and cardiovascular disease complications associated with the disease. This article examines the data supporting an etiological and permissive role of estrogen in women with studies utilizing animal models that show that estradiol may be protective as they age in females with SLE.

Preeclampsia is another immune associated disease that is the focus of the review by Eric George (15). Preeclampsia is the leading cause of morbidity and mortality of both the mother and fetus during pregnancy. In fact, the children of women who have preeclampsia are born small for gestational age and may even be subjected to premature birth to save the child and the mother in extreme cases. Finding the mechanisms responsible for preeclampsia is a field of intense research. In his comprehensive review, George covers the diagnostics, the treatment and potential mechanisms responsible for preeclampsia based on both human studies and studies in novel animal models.

The Barker hypothesis proposes that children born with low birth weight are at increased risk for cardiovascular disease. In her review, Barbara Alexander, a leader in the field of developmental programming of cardiovascular disease, describes what led Barker to this hypothesis in England in the early 1900's, and recent evidence supporting the hypothesis from both human studies and animal models (16).

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