

Editorial: Sex Matters in Preclinical Research

Stephen R. Hammes, MD, PhD

Chief, Division of Endocrinology, Diabetes, and Metabolism, University of Rochester Medical Center, Rochester, New York 14642

In recent months, there has been a flurry of discussion regarding the importance of considering the sex of animals, primary cells, and even cell lines when performing preclinical studies. These conversations were highlighted in a recent editorial in *Nature* by Janine A. Clayton, Director of the National Institutes of Health Office of Research on Women's Health, and Francis S. Collins, Director of the National Institutes of Health (1). In their editorial, Drs Clayton and Collins point out that sex differences can be tremendous with respect to many diseases, including multiple sclerosis, Parkinson disease, and other neurological disorders. Specific to endocrinology, diseases such as autoimmune thyroid disorders and thyroid nodules are significantly more common in women than in men. The editorial in *Nature* serves as a well-needed call to arms for preclinical researchers that they must pay more attention to sex and gender when both performing and reporting their research. The authors make specific suggestions regarding how the National Institutes of Health (NIH) plans to help the scientific community better equalize studies in males and females. These include a requirement for grant applicants to "report their plans for the balance of male and female cells and animals in preclinical studies in all future applications, unless sex-specific inclusion is unwarranted" (1). In fact, the Research for All Act of 2014 is now making its way on Capitol Hill. This legislation calls for an increase in the study of female animals, tissues, and cells in basic research conducted or supported

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by the NIH. One goal is that, "within 1 year, the NIH shall determine when it is appropriate for basic research projects to include both sexes and issue guidelines to ensure the inclusion of both sexes."

These are great principles and the NIH should be commended for bringing them back to the forefront. It is important to note, however, that these concepts and sentiments are nothing new to basic research. In fact, the National Academies of Sciences hosted a workshop in 2012 entitled "Sex-Specific Reporting of Scientific Research," which was sponsored by the Office of Research on Women's Health (2). At this meeting, most participants felt that the sex of the animals and cell lines was being neglected and therefore should be clearly indicated in the Methods section of an article.

In response to this 2012 workshop, the Endocrine Society led the charge to

elicit change. This movement was spearheaded by then Editor-in-Chief of the journal *Endocrinology*, Dr Jeffrey Blaustein. In his 2012 editorial (3), Dr Blaustein discussed the importance of sex and gender in research, and the journal instituted a new policy whereby "all manuscripts submitted to *Endocrinology* must indicate the sex of animals used, or in the case of primary cells or cultures, the sex of the animal from which they were derived." The policy did not go so far as to require identification of the sex of cell lines used in culture, but disclosure of this information was strongly encouraged. Although *Molecular Endocrinology* has not formally instituted a similar

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policy, the editorial board holds its manuscripts to a similar standard, and reviewers and editors are encouraged to consider the issues of sex when reviewing manuscripts.

This history clearly demonstrates the Endocrine Society's strong support of efforts to specify sex when doing research, whether basic or clinical. Clearly, when the NIH, the Endocrine Society, or any scientific organization is generating its general research portfolio, every effort should be made to give equal time to both sexes. However, requiring equal representation of sex for individual research projects can be tricky and should be approached with caution. Many lines of investigation would clearly not require adherence to such a rule, such as studies of reproduction, prostate cancer, or ovarian cancer. Even in the study of biology that involves both sexes, the commonality of sexual dimorphism means that results in males and females will often be different and will need to be reported separately. It is not obvious that researchers will be able to afford performing studies in both males and females, and to require them to do so could severely hamper productivity. The NIH has made efforts to help with the costs through administrative supplements on sex differences (PA-14-027); however, these have been awarded on a year-by-year basis (2013 and 2014). Given the already limited research dollars available, long-term solutions will require thorough planning and consideration. Finally, it is not always clear where to draw the line when it comes to sex differences. Does it even stop with the experimental subjects? A recent report in *Nature Methods* found that male researchers elicited significantly more stress on rats and mice than their female counterparts (4), suggesting that even the sex of the experimenter can alter the results of an animal study.

Given the complexities of considering sex in basic research, the Endocrine Society encourages researchers of all disciplines to follow the full-disclosure policies already initiated by the journal *Endocrinology*. All published articles should identify the sex of the animals and cells so that the results can be properly interpreted and reproduced by the scientific community. Although ensuring appropriate representation for both sexes in preclinical research is also clearly important, it will require a careful and thoughtful approach by the NIH and the scientific community to ensure that quality, originality, and productivity are not compromised.

Stephen R. Hammes, MD, PhD
Editor-in-Chief, *Molecular Endocrinology*

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Address all correspondence and requests for reprints to: Rebecca Kelly, Managing Editor, Endocrine Society—Publications Department, 2055 L Street NW, Suite 600, Washington, DC 20036. E-mail: molendo@endocrine.org.

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