In pursuit of scientific excellence: sex matters

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THE YEAR 2012 MARKS the 125th anniversary of the American Physiological Society (APS). Throughout its history, APS has been a leader in innovation and excellence in scientific technology, discovery, education, and publication. Consistent with this history, APS is leading the scientific publication community by requiring the reporting of the sex of experimental animals and material derived from experimental animals or humans, as well as the sex (or gender where appropriate) of humans used in studies published in their journals. Upon reading this statement, your reaction might be, “How can this change in policy be a groundbreaking action? Sex is such a basic biological variable that influences physiology and disease. Hasn’t it been obvious for a long time that it should be reported in the Methods section of scientific papers?” Well, it has been obvious that sex is a biological variable affecting experimental outcomes, but it has been far from obvious to journals and investigators that it should be routinely reported in the scientific literature!

Recent reviews of basic science journals (3), of studies of cells in culture from high-impact cardiovascular journals (18), and of basic and clinical scientific literature (5, 22) suggest that sex of experimental material is not consistently reported in the scientific literature. Indeed, overall less than 40% of studies using experimental animals and only about 25% of studies using cells in culture identified the sex of the experimental material. This percentage is low given the growing knowledge base that physiology and pathophysiology differ between male and female animals and humans beyond reproductive function to include all physiological systems [i.e., cardiovascular, respiratory, musculoskeletal, immunological, gastrointestinal, neurological, renal (23)]. Furthermore, intracellular signaling pathways may be differentially expressed in cells, tissues, and animals, including humans, depending on their sex and hormonal status (1, 2, 4, 6–11, 14–17, 19–21, 24, 25), to mention only a few studies.

In the era of physiological genomics and individualized medicine, the presence of an XX or XY chromosomal complement is fundamental to the genome of an individual person, animal, tissue, or cell. Every cell has a sex.

Therefore, based on existing knowledge, it is inappropriate to assume that results from studies conducted on only one sex apply to the other (13). For some studies of neonates and embryos, cells derived from males and females are mixed in a single culture and should be reported as such. The scientific community needs to determine whether this technique is valid by providing sufficient data to control and confirm survival, differentiation, and function of cells of each sex. Similarly, cell-based therapies need to validate survival and function of the cell graft in the same- and opposite-sexed recipients.

Validation through replication of results is one hallmark of excellent science. For other investigators to reproduce your experiments, information regarding the type of experimental material that was used in the original experiment is required. Sex of the experimental material is a critical piece of that information.

How then should the sex of experimental material be reported? Use of the terms “sex” and “gender” has evolved over the last decade. According to definitions proposed by the Institute of Medicine (23), “sex” is a biological construct dictated by the presence of sex chromosomes and in animals and humans the presence of functional reproductive organs. “Gender” is a cultural construct and refers to behaviors that might be directed by specific stimuli (visual, olfactory, etc.) or by psychosocial expectations that result from assigned or perceived sex. Gender, thus, can influence biological outcomes. In most studies conducted on isolated cells, tissues can be classified as male or female by the sex chromosomal complement and for experimental animals by the sex chromosomal complement and anatomical features. Similar information may be available for humans. However, humans may self-report their sex according to gender and some studies in animals can be designed to address influences of psychosocial (gender) constructs on physiological outcomes (12). The new editorial policy for all APS journals requires the reporting of sex for cells, tissues, and experimental animals and humans (i.e., male and female) or gender where appropriate. The investigator must decide based on the experimental design which terms are most appropriate for a given study.

As a member of the APS for over 30 years, I am pleased that our professional society is a leader in instituting and enforcing a policy for reporting sex of experimental material. As President of the Organization for the Study of Sex Differences, I am honored to help educate my colleagues on the importance of sex as a biological variable in our collective efforts to strive for scientific excellence. This new editorial policy for APS journals will lead the way for changes in editorial policies of other scientific journals. Implementation of the new policy by reviewers, associate editors, and editors will improve communication of scientific results and perhaps assist in more rapid translation of information from basic science to clinical medicine. Yes, in our pursuit of scientific excellence, sex matters.

DISCLOSURES
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REFERENCES