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In pursuit of scientific excellence – sex matters

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28           The year 2012 marks the 125<sup>th</sup> anniversary of the American Physiological  
29 Society (APS). Throughout its history, APS has been a leader in innovation and  
30 excellence in scientific technology, discovery, education and publication.  
31 Consistent with this history, APS is leading the scientific publication community  
32 by requiring the reporting of the sex of experimental animals and material derived  
33 from experimental animals or humans, as well as the sex (or gender where  
34 appropriate) of humans used in studies published in their journals. Upon reading  
35 this statement, your reaction might be, “How can this change in policy be a  
36 ground breaking action? Sex is such a basic biological variable that influences  
37 physiology and disease. Hasn’t it been obvious for a long time that it should be  
38 reported in the Methods section of scientific papers?” Well, it has been obvious  
39 that sex is a biological variable affecting experimental outcomes, **but** it has been  
40 far from obvious to journals and investigators that it should be routinely reported  
41 in the scientific literature!

42           Recent reviews of basic science journals (4), of studies of cells in culture  
43 from high impact cardiovascular journals (19), and of basic and clinical scientific  
44 literature (1, 6) suggest that sex of experimental material is not consistently  
45 reported in the scientific literature. Indeed, overall less than 40% of studies using  
46 experimental animals and only about 25% of studies using cells in culture  
47 identified the sex of the experimental material. This percentage is low given the  
48 growing knowledge base that physiology and pathophysiology differs between  
49 male and female animals and humans beyond reproductive function to include **all**  
50 physiological systems (i.e. cardiovascular, respiratory, musculoskeletal,

51 immunological, gastrointestinal, neurological, renal (23)). Furthermore,  
52 intracellular signaling pathways may be differentially expressed in cells, tissues  
53 and animals, including humans, depending upon their sex and hormonal status  
54 (2, 3, 5, 7-12, 15-18, 20-22, 24, 25), to mention only a few studies.

55         In the era of physiological genomics and individualized medicine, the  
56 presence of an XX or XY chromosomal complement is fundamental to the  
57 genome of an individual person, animal, tissue or cell. Every cell has a sex.  
58 Therefore, based upon existing knowledge, it is inappropriate to assume that  
59 results from studies conducted on only one sex apply to the other (14). For some  
60 studies of neonates and embryos, cells derived from males and females are  
61 mixed in a single culture and should be reported as such. The scientific  
62 community needs to determine if this technique is valid by providing sufficient  
63 data to control and confirm survival, differentiation and function of cells of each  
64 sex. Similarly, cell-based therapies need to validate survival and function of the  
65 cell graft in the same and opposite sexed recipients.

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

71         How then should the sex of experimental material be reported? Use of the  
72 terms “sex” and “gender” has evolved over the last decade. According to  
73 definitions proposed by the Institute of Medicine (23), “sex” is a biological

74 construct dictated by the presence of sex chromosomes and in animals and  
75 humans the presence of functional reproductive organs. “Gender” is a cultural  
76 construct and refers to behaviors which might be directed by specific stimuli  
77 (visual, olfactory, etc) or by psychosocial expectations that result from assigned  
78 or perceived sex. Gender, thus, can influence biological outcomes. Most studies  
79 conducted on isolated cells, tissues can classified as male or female by the sex  
80 chromosomal complement and for experimental animals by the sex chromosomal  
81 complement and anatomical features. Similar information may be available for  
82 humans. However, humans may self-report their sex according to gender and  
83 some studies in animals can be designed to address influences of psychosocial  
84 (gender) constructs on physiological outcomes (13). The new editorial policy for  
85 all APS journals requires the reporting of sex for cells, tissues and experimental  
86 animals and humans (i.e. male and female) or gender where appropriate. The  
87 investigator must decide based on the experimental design which terms are most  
88 appropriate for a given study.

89         As a member of the APS for over 30 years, I am pleased that our  
90 professional society is a leader in instituting and enforcing a policy for reporting  
91 sex of experimental material. As President of the Organization for the Study of  
92 Sex Differences, I am honored to help educate my colleagues on the importance  
93 of sex as a biological variable in our collective efforts to strive for scientific  
94 excellence. This new editorial policy for APS journals will lead the way for  
95 changes in editorial policies of other scientific journals. Implementation of the  
96 new policy by reviewers, associate editors and editors will improve

97 communication of scientific results and perhaps assist in more rapid translation of  
 98 information from basic science to clinical medicine. Yes, in our pursuit of  
 99 scientific excellence, sex matters.

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