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VIEWPOINT

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Including women in research. It's necessary, and really not so hard to do

In this issue of *Experimental Physiology*, Sims and Heather (2018) have written an important paper to clarify methods and help researchers as they continue to, or begin to, include women in their research. Sex and sex hormone exposure should be considered as carefully as any other variable in the research environment. Their paper is a useful guide and demonstrates that controlling these variables has complexity but can be accomplished when prioritized.

In the USA, The National Institutes of Health (NIH) Revitalization Act of 1993 (https://grants.nih.gov/grants/funding/women_min/guidelines.htm) directed all NIH-supported investigators to ensure the inclusion of women in all human research studies unless 'a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research'. This Act went on to insist that women of childbearing age not be excluded from scientific research without a compelling reason. The goal of this mandate was to ensure that health information gathered in the course of research was as relevant to women as to men. Before this mandate, most clinical and basic science research focused on men or males (or tissues derived from males); therefore, the challenge for scientists was to update their laboratories to accommodate women, to consider how female physiology might impact their findings and to learn how to test women. The NIH Revitalization Act has had an extraordinarily positive impact for women's health and equity because at present slightly more than half of NIH-funded human research participants are women.

The NIH has extended this mandate to animal and basic physiology research (Clayton & Collins, 2014), because dependence on male animals and cells in preclinical research has obscured sex differences, limited research progress into understanding female physiology in varied fields (Beery & Zucker, 2011; Mogil & Chanda, 2005) and limited the efficacy of drugs. The NIH now requires that sex be considered as a biological variable (SABV), and guidelines specific for these considerations have been published (Clayton, 2016). Considering SABV is not the same as looking for differences between the sexes, but rather indicates that sex is an important consideration (Clayton & Collins, 2014). Although this is the beginning of a long process, because SABV does not require the inclusion of female animals, cells or tissues, the SABV step by NIH is an essential one. These decisions by NIH continue to create significant challenges for investigators. Investigators now need to control or at least understand hormonal effects during human physiological studies.

Although the primary roles of oestrogens and progestogens are to create an environment hospitable for conception and the developing fetus, gonadal hormones have important influences on organs and systems outside of reproduction. Estradiol is the predominant biologically active oestrogen in young, healthy women and can exert a strong influence in physiological studies. Both estradiol and progesterone vary widely across the menstrual cycle in young women. Furthermore, >90% of European and US women are currently taking or have taken hormonal contraceptives, indicating that hormonal exposure in this form has an important influence on research design. The hormones found in these contraceptives are not the same as endogenous hormones, which adds a layer of complexity to the design of physiological studies.

As the paper by Sims and Heather (2018) in this issue makes clear, physiological systems function differently in women compared with men, and sometimes these sex differences are attributable to their different hormonal milieu. A major research challenge, therefore, is to control or consider reproductive steroid hormone exposure to examine a physiological system of interest. In young women, often the challenge is consideration or understanding of these hormonal changes over the course of the menstrual cycle or during hormonal contraception. The paper by Sims and Heather (2018) provides clear, concise guidelines to assist investigators as to when it is best to test women during the menstrual cycle or when they are taking hormonal contraceptives, and how best to control for hormone exposure when the primary interest is sex differences. This paper also provides guidance about how to handle data when these variables cannot be controlled adequately.

Including women in physiological research is essential for women's health, but investigators cannot simply pool men and women into one group when both sexes are included in studies. Even though the changing hormonal milieu in women across the menstrual cycle creates challenges for the design of controlled studies, these challenges are necessary and are well worth the effort. Regardless of methodology, the same attention to detail used to control the physical, external or internal environment for physiological studies should be paid to the hormonal environment. Sims and Heather (2018) address these details within this paper and provide a roadmap for researchers to proceed in this endeavour.

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