CALL FOR PAPERS | *Sex and Gender Differences in Cardiovascular Physiology—Back to the Basics*

Why are sex and gender important to basic physiology and translational and individualized medicine?

Virginia M. Miller  
*Departments of Surgery, Physiology, and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota*

Submitted 18 December 2013; accepted in final form 7 January 2014


Sex refers to biological differences between men and women. Although sex is a fundamental aspect of human physiology that splits the population in two approximately equal halves, this essential biological variable is rarely considered in the design of basic physiological studies, in translating findings from basic science to clinical research, or in developing personalized medical strategies. Contrary to sex, gender refers to social and cultural factors related to being a man or a woman in a particular historical and cultural context. Unfortunately, gender is often used incorrectly by scientists and clinical investigators as synonymous with sex. This article clarifies the definition of sex and gender and reviews evidence showing how sex and gender interact with each other to influence etiology, presentation of disease, and treatment outcomes. In addition, strategies to improve the inclusion of female and male human beings in preclinical and clinical studies will be presented, and the importance of embedding concepts of sex and gender into postgraduate and medical curricula will be discussed. Also, provided is a list of resources for educators. In the history of medical concepts, physiologists have provided pivotal contributions to understanding health and disease processes. In the future, physiologists should provide the evidence for advancing personalized medicine and for reducing sex and gender disparities in health care.

behavior; chromosomes; health disparities; hormones; personality

SINCE THE FATHER OF modern physiology, William Harvey, made the landmark observations in 1628 that the heart pumped blood and the blood circulated (23), physiologists have contributed fundamental and critical information for the development of modern medicine. However, physiologists like other scientists have been influenced by several important cultural trends. Possibly because science was traditionally a male-dominated profession, except for the physiology of reproduction, most human physiological studies were focused on and conducted on male human beings. Thus physiological principles contained in classical textbooks and medical curricula were based on the 70-kg healthy male or on male animals. In the United States, the opposition to this restriction of research to “male” bodies resulted in legislation, i.e., the National Institutes of Health (NIH) Revitalization Act of 1993. This law mandated the inclusion of women in research involving humans that was supported by the NIH. Other trends that have influenced our understanding of physiological principles include the rapid expansion of molecular mechanistic studies and the political pressure to reduce the use of whole animals in basic and preclinical experiments. Thus studies using isolated tissues and cultured cells (including cell lines) gained popularity and, unfortunately, without attention to the biology or phenotypic characteristics of the tissue/cell donor with the assumption that the sex of the experimental material was irrelevant. But is it?

Sex is the basic biological variable that distinguishes approximately half of the population from the other. The landmark Institute of Medicine report “Exploring the Biological Contribution of Sex” concluded that sex matters in all aspects of cellular function and physiology from “womb to tomb” (77). One must wonder, then, why is sex of experimental material so often ignored in an era of genomics and personalized medicine?

Epidemiological studies have consistently identified differences in disease incidence and prevalence between men and women. Patient health advocacy groups such as the American Heart Association, American Cancer Society, and the American Lung Association, to name a few, mount targeted campaigns to educate health care providers of sex differences in symptoms, outcomes, and mortality of specific diseases. Moreover, gender, a term that is often used incorrectly by scientists...
and clinical investigators as synonymous with sex, is considered an essential topic in medical curricula related to cultural sensitivity in health care delivery to reduce health disparities among ethnic, racial, and socioeconomic groups. What, then, is the appropriate way to consider sex and gender as research variables and in medical curricula? And why are they important to basic physiology and to translational and individualized medicine? This article will address these questions by clarifying the definitions of sex and gender and by reviewing evidence showing how sex and gender interact to influence etiology, presentation, and treatment outcomes of diseases. In addition, strategies to improve the inclusion of female and males in preclinical and clinical studies will be presented, and discussion will include the importance of embedding concepts of sex and gender into postgraduate and medical curricula with a goal to improve the health of both women and men and thus reduce disparities in health care.

**Sex and Gender: Are We Talking About the Same Thing?**

The Institute of Medicine defines sex as “being male or female according to reproductive organs and the functions assigned by chromosomal complement (XX for female and XY for male)” (77). That is, sex is biology. There are genetic variants in sex chromosomes, but these are rare and are not considered in this review. For example, XXY (or Klinefelter’s syndrome) occurs in about 1 of 580 live male births, X monosomy (or Turner’s syndrome) occurs in about 1 of 5,000 live births, XXX occurs in about 1 of 1,000 births, and XYY occurs in about 1 in 1,000 male births.

Every cell has a sex, which is determined by the presence of the complement of sex chromosomes. The nongonalad functions directed by the sex chromosomes are critical to the physiology of the organism (53, 70a) and include such important functions as coagulation (65), innate immunity (10, 12), synthesis of norepinephrine (4, 17, 49), androgen sensitivity (36), energy metabolism (adiposity) (72), blood pressure (29), and apoptosis (32). These nongonalad effects of the sex chromosomes coupled with gonadal effects through genomic actions of the sex steroids result in sex differences in gene expression in every cell (28, 31, 51, 56, 66, 76, 78, 79). Thus the sex of cells in culture, in isolated tissues, and in whole animals cannot be ignored in the design of experiments.

Whereas sex is biology, as defined by the Institute of Medicine, gender is everything else (77), including psychosocial and cultural factors. According to Ristvedt (62), the term “gender” evolved over time being originally used in linguistics. In linguistics, gender was used to designate words as masculine and feminine, or neutral. This concept was exported into “sexual science” where it was used to define masculinity/femininity (46) and then psychoanalytic writers used it to encompass “socially constructed” male/female differences (62). Thus sex and gender became incorrectly synonymous. In the 1990s, even the author of this review published papers addressing “gender differences” in vascular function when in reality the studies were about “sex differences” (1, 6–8, 43, 75). Fortunately, the Institute of Medicine report clarified the definitions, and there are steady and consistent efforts to adopt and apply the term “sex” to biological factors and “gender” to psychosocial and cultural factors.

**Interaction of Sex and Gender in Translational Science**

Sex differences in physiology and pathophysiology can be classified in three general categories. First are conditions or diseases unique to one sex, such as conditions associated with reproduction. Second are conditions or diseases that have greater prevalence in one sex compared with the other. Third are conditions that have different age of onset, symptomatology, or response to treatment in one sex compared with the other. Examples of conditions related to cardiovascular diseases in each of these categories are shown in Table 1. Other areas of physiology can generate similar lists that encompass diseases of the respiratory system, musculoskeletal system, immunological system, gastrointestinal system, renal/urological system, development, and behavior.

Sex is a basic variable in every cellular and integrated physiological experiment. Because sex is based on two distinct chromosomal configurations, analysis of data to determine sex differences should treat sex as a dichotomous variable.

Although gender is related to sex, gender is not a dichotomous variable even though it is often considered as such when data are collected from self-declaration of gender as male and female. Gender defines behavioral, psychological, and cultural characteristics that are expressed on a continuum. For example, masculine and feminine behaviors may be defined by sociocultural expectations (37). What may be considered a neutral behavior in one culture, for example, driving or smoking, may be considered a masculine behavior in another culture. When behaviors are classified as aggressive or stoic for males compared with nurturing or expressive for females, males and females exhibit a range of scores that are distinct but overlap, i.e., a continuous variable (62). Thus analysis of outcome data by self-reported gender alone may not provide all of the information needed to draw conclusions about behaviors that could affect disease risk factors, treatment efficacy, or outcomes if self-reporting of gender differs from the biological sex of the individual.

**Table 1. Examples of cardiovascular pathophysiological conditions showing sex differences**

<table>
<thead>
<tr>
<th>Conditions unique to one sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disorders of pregnancy</td>
<td>Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td>Vasovagotropic symptoms of menopause</td>
<td>Myocarditis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions with sex-specific prevalence</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>Hypertension, myocardial infarction, stroke</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s disease</td>
<td>Ventricular apical ballooning (Tako Tsabo)</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>Microvascular angina</td>
<td></td>
</tr>
<tr>
<td>Postural orthostatic tachycardia syndrome</td>
<td>Heart failure with reduced ejection fraction</td>
<td></td>
</tr>
<tr>
<td>Heart failure with preserved ejection fraction</td>
<td>Heart failure with reduced ejection fraction</td>
<td></td>
</tr>
</tbody>
</table>

**Conditions with sex-specific onset, symptoms, and response to treatment**

- Hypertension, myocardial infarction, stroke
The question then becomes, how does gender interact with sex to influence health and disease? Both sex and behaviors influenced by gender will affect physiology and pathophysiology. The relative contribution and interaction between biological sex and external sociocultural influences of gender is an ongoing topic of scientific inquiry. Sophisticated imaging modalities coupled with computational analysis showed sex differences in distinct connectivity between cerebral hemispheres and cerebellum of adolescent males and females of various ethnicities from the Philadelphia region of the United States (27). These data provide additional support for the hypothesis that conceptual and motor behaviors develop at an early age and reflect underlying differences in biology of the sexes. This conclusion should not be surprising given that every cell has a sex and cellular function that is influenced by the genome and sex steroid milieu to which the cell is exposed (2, 3).

For physiological studies using material derived from experimental animals, the issue of “gender” is mostly irrelevant, except for specific studies of behavior (22), as the environment in which experimental animals are bred and raised is controlled. However, gender will impact results of experiments in which tissues and cells are derived from humans, clinical human studies, as well as those studies of health disparities and health outcomes in humans. For example, risk of death from cardiovascular disease was lower in men with a high “femininity” behavioral score, compared with men with a high “masculinity” behavioral score (25). Some risk factors associated with gendered behaviors, such as smoking history and alcohol consumption or occupations, are captured on inclusion criteria or evaluations for clinical studies or in the medical record by a quantitative scale such as pack years of smoking. Gene expression and cellular regulatory pathways in isolated cells obtained from such individuals may reflect epigenetic changes brought about by lifelong tobacco use or exposure or exposure to xenobiotics or other environmental pollutants (herbicides, industrial and automotive smog, radiation, industrial or occupational-related chemicals, e.g., organic solvents, dyes, aerosols, asbestos). For cells and tissues obtained from commercial sources and biobanks, such information may not be available. However, at a minimum it is critical for the accurate interpretation of experiments to acknowledge that the sex of the cells or tissues may matter and could influence the results and to consider the hormonal status of the tissue donor which if unknown, could be surmised in part by age of the donor (sexually immature child, adolescent, adult of reproductive age, or senior).

In addition to sex differences in potential exposure to disease risk factors, differences in sociocultural attitudes such as ethnicity, occupation, marital/partner status, income, years of education, etc., may affect access to medical care and compliance with treatment. Furthermore, the type of cardiovascular pathology, symptoms (Table 1) and response to treatment including response to therapies (48), i.e., aspirin (61) and statins (21) and to modifiable cardiovascular risk factors such as smoking cessation, diet, and exercise are influenced by the underlying biology, i.e., sex (13, 50, 55, 60). In an era where health outcomes will be assessed from “big data” sets, it may be appropriate to exclude the category of gender and to include the category of sex together with more specific criteria that capture continuous and quantifiable variables constituting behavioral and cultural aspects of gender that are considered risk factors for disease. In Europe and Canada, the term gender-based medicine or gender differences is used more consistently to define medical conditions and health outcomes than the term sex-based medicine. Neither of these terms sex-based or gender-based medicine incorporates the totality of parameters influencing an individual’s health status. However, their use represents a critical first step in acknowledging and quantifying parameters that influence health and movement toward embedding concepts of sex and gender into all aspects of health care, i.e., “individualized medicine” that encompasses both sex and gender.

Sex, Gender, and Policy in Scientific Publication and Research Funding

As mentioned in the Introduction, the NIH Revitalization Act of 1993 mandated the inclusion of women in studies of humans. However, the number of women included in drug and device trials remains low (14, 15, 19, 26). The reasons for low participation of women are many (38), including that some trials investigate conditions that are more common in men, for example heart failure with reduced ejection fraction. However, even in studies of conditions occurring with similar prevalence in women and men, participation by women ranged from 25–45% (40). Some studies inadvertently exclude women because of restrictive inclusion criteria based on parameters that have a sex differential, such as size or normative blood parameters (16, 59) or that women are simply not asked to participate (57).

The percentage of women enrolled in a trial may affect interpretation of the results. For example, the incidence of type II diabetes with the use of statin therapy was found to be proportional to the percentage of women enrolled in the trial: in a woman-only trial, the risk was 42%, whereas the risk was negligible (14%) in trials enrolling only men (21). Thus, to individualize treatment options, a discussion between the health care provider and patient should include discussion of risk versus benefits that are specific to the sex of the individual. Therefore, it is critical that data from mixed sex trials be analyzed by sex and those results reported even if they are negative. It is just as critical to identify under what conditions, systems, responses, mechanistic pathways, etc., are the same between the sexes as to identify those which are not. However, reporting results by sex in clinical trials remains low (27a). It is critical that data be reported by sex rather than only accounting for sex as a confounding variable so that sex-specific outcomes from multiple studies could be evaluated by meta-analysis. Such sex-specific analyses form the basis for evidence-based medical decisions and are necessary to optimize individualized treatment strategies for men and women (48).

The inability to reproduce many basic science experiments and to translate those results to the clinical arena is a concern (74). Solutions proposed to improve reproducibility of results have focused on statistical issues in experimental design and analysis (go.nature.com/ooloep) and the lack of consistent quality systems such as reagents and assays used in different laboratories: http://gbsi.org/sites/default/files/uploads/pdf/the_case_for_standards.pdf (77a). Methods sections of papers should provide sufficient information, including the sex of the experimental animal, so that another investigator can reproduce the experiment. Reporting of sex in basic science studies is abysmal and in many cases the sex of the material is not
reported at all (66, 70, 81). Given the lack of reporting of the sex of experimental material, an additional consideration would be for more rigorous monitoring and requirements for reporting of sex of the biological material. Gene expression and cellular processes vary by sex as discussed above, thus analyzing data from mixed groups of males and females in human studies or mixed groups of male and female cells or genetically manipulated mice may mask a treatment effect if the particular response is upregulated or positive in one sex and downregulated or negative in the other. As with the reported results with side effects of statin medications (21), other results derived from mixed populations of males and females may be influenced by the relative proportion of each sex used in the experiment.

Table 3. Specialized centers of research on sex differences from 2002–2016

<table>
<thead>
<tr>
<th>Theme</th>
<th>Institution</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes, hormones, and environment</td>
<td>Northwestern University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Genes, androgens, and intrauterine environment in polycystic ovarian syndrome</td>
<td>University of Maryland</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Genes, androgens, and intrauterine environment in PCOS</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Genes, androgens, and intrauterine environment in polycystic ovarian syndrome (PCOS)</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Identifying the genes that put women at risk for osteoporosis</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Genetic and environmental origins of adverse pregnancy outcomes</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Substance Abuse/Pain</td>
<td>Northwestern University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex differences in pain sensitivity</td>
<td>University of Maryland</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex and gender influences on addiction and health: a developmental perspective</td>
<td>University of Michigan, Ann Arbor</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Role of sex and gender differences in substance abuse relapse</td>
<td>Medical University of South Carolina</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex and gender differences in addictions and stress response</td>
<td>Yale University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex, stress, and cocaine addiction</td>
<td>Yale University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex, stress, and substance use disorders</td>
<td>Yale University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Gender-sensitive treatment for tobacco dependence</td>
<td>Yale University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex and gender factors in the pathophysiology of irritable bowel syndrome and interstitial cystitis</td>
<td>Yale University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>A coordinated study of stress, pain, emotion, and sexual factors underlying the pelvic visceral</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>disorders of irritable bowel disorder and interstitial cystitis</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Center for Neurovisceral Sciences and Women’s Health (sex differences in pain)</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex differences and progesterone effects on impulsivity, smoking, and cocaine stress</td>
<td>University of California, Los Angeles</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Emory University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Pharmacology of antiepileptic and psychotropic medications during pregnancy and lactation</td>
<td>Emory University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Mechanisms by which drug transporters alter maternal and fetal drug exposure during pregnancy</td>
<td>Emory University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Birth, muscle injury, and pelvic floor dysfunction</td>
<td>University of Michigan, Ann Arbor</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Mechanisms underlying female urinary incontinence</td>
<td>University of California, San Francisco</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Lower urinary tract function in women</td>
<td>University of California, San Francisco</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Molecular and epidemiologic basis of acute and recurrent urinary tract infections in women</td>
<td>Washington University</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Metabolism</td>
<td>University of Chicago</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex steroids, sleep, and metabolic dysfunction in women</td>
<td>University of Colorado</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Metabolic consequences of loss of gonadal function</td>
<td>University of Colorado</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>University of California, Davis</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex differences in musculoskeletal conditions across the life span</td>
<td>University of California, Davis</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Brain/Mental Health and Cardiovascular</td>
<td>Brigham and Women’s Hospital</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Fetal antecedents to sex differences in depression: a translational approach</td>
<td>Brigham and Women’s Hospital</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Prepubertal stress, windows of risk and sex bias for affective disturbance</td>
<td>University of Pennsylvania</td>
<td>2002–2007</td>
</tr>
<tr>
<td>Sex-specific risk for vascular dysfunction and cognitive decline</td>
<td>Mayo Clinic</td>
<td>2002–2007</td>
</tr>
</tbody>
</table>
tory pathways in cells of female origin and to understand differences in integrated physiological control mechanisms in male and female experimental animals. Granting agencies, such as NIH, should consider improved mechanisms for investigators to more completely address issues of sex and gender in their grant applications. For example, the Canadian Institutes of Health Research (CIHR) requires grant applicants (http://www.cihr-irsc.gc.ca/e/32019.html) to respond to specific questions about sex and gender in research (Table 2). Currently, there are no requirements to include or address rationale for use of material from only one sex in applications funded by the NIH. Although identification of the number and sex of animals used in basic science studies and other conditions relative to their husbandry are required in the “Vertebrate Animal” section of NIH applications, it is not required to discuss sex and gender relative to outcomes of long-term goals of the research plan or to the scientific validity of choice of the experimental material. For example, would it be scientifically appropriate to develop an animal model of pulmonary hypertension only in male animals when in humans, pulmonary hypertension is more prevalent in females than males.

A typical reason cited for not including both male and female animals in preclinical and mechanistic basic studies is cost. However, the cost of identification of sex differences in discovery experiments may be minimal compared with the cost and time wasted by developing an experimental model or therapeutic approach based on one sex that does not reflect disease expression in humans, fails clinical testing, or has to be withdrawn from the market due to adverse events in a mixed study population of men and women. For example, 8 out of 10 drugs withdrawn from the market between 1997 and 2001 were due to adverse events in women (24). The first medications intended for use in both sexes to have different dosage recommendations for women and men came in May 2013 for zolpidem-containing drugs. The Federal Drug Administration approved labeling changes lowering the recommended dosage of these drugs for women due to increased side effects in women. One proposal to eliminate sex discrimination in basic research for conditions that are not sex specific would be to adopt principles of Title IX directed to eliminate sex discrimination in education to biomedical research (63).

Scientific review panels for funding agencies usually do not respond favorably toward studies that explore sex differences, classifying such studies as “descriptive.” There is some limited attention to this problem by the federal government. The Office of Research on Women’s Health (ORWH) developed and designed an innovative, interdisciplinary-targeted funding mechanism that integrates basic, clinical, and translational investigation into sex and gender differences: Specialized Centers of Research (P50 SCOR mechanism). The range of topics for the Centers was derived from three sources: the Institute of Medicine report “Exploring the Biological Contributions to Human Health, Does Sex Matter?” (77), the ORWH 2000 “Agenda for Research on Women’s Health for the 21st Century,” and the NIH Strategic Plan for Women’s Health and Sex Differences. Since the inception of the program in 2002, only 33 awards have been made to 26 academic centers (Table 3). Requirements for the SCORs include a minimum of three

Table 4. Professional resources

NIH funded Specialized Centers of Research on Sex Differences
- Available at: http://orwh.od.nih.gov/interdisciplinary/scor/index.asp

Textbooks:
- Regitz-Zagrosek, V. ed. Sex and Gender Differences in Pharmacology. Springer-Verlag 2012.

Web-based Continuing Medicine Education Courses:
- NIH ORWH Sex and Gender Differences in Health and Behavior. Available at: http://sexandgendercourse.od.nih.gov
- NIH ORWH The Basic Science and the Biological Basis for Sex and Gender Differences. Available at: http://sexandgendercourse.od.nih.gov
- Women’s Health Info Site: Sex and Gender Differences for Clinicians and Trainees. Available at: http://whedscomosspot.com
- National Association of Women’s Health Medical Educators Faculty Guide (NAWHME).
- Resource listing of various educational modalities to use in integration efforts. Available at: http://www.drexelmed.edu/Home/OtherPrograms/WomensHealthEducationProgram/Resources.aspx

Web-based Research and Educational Resources:
- Sex and Gender Women’s Health Collaborative. Available at: www.sgwhc.org
- Stanford University’s Gendered Innovations. Available at: http://genderedinnovations.stanford.edu
- Canadian Institute of Gender Health. What a Difference Sex and Gender Make. Available at: http://www.cihr-irsc.gc.ca/e/44082.html
- Articles Outlining Experimental Design Methodology:

Professional Membership Organizations:
- Organization for the Study of Sex Differences. Available at http://www.ossdweb.org
- International Society of Gender Medicine. Available at http://www.isogem.com
- Journal of Women’s Health. Available at http://www.lieberpub.com

AJP-Heart Circ Physiol · doi:10.1152/ajpheart.00994.2013 · www.ajpheart.org
projects that encompass basic, clinical, and translational investigation.

ORWH is the major funder of the SCORs, but the ORWH is only a small fraction of the overall NIH budget. Although funding for SCORs is also provided by six National Institutes of Health Institutes and Centers and the Federal Drug Administration, the major portion of the NIH budget focuses predominantly on basic biomedical research in males. The SCORs represent initial steps in bringing attention to the need for research on sex differences in physiological processes and translational medicine. Clearly, there is a need for expansion of this program to reflect a broader range of diseases showing sex differences and for development of new funding sources directed at understanding basic and preclinical biological mechanisms for sex differences to advance translational, individualized medicine.

Embedding Concepts of Sex and Gender into Postgraduate and Medical Curricula

Evidenced-based medicine is built on results from basic, human, and clinical studies. Results of these studies need to be included in postgraduate and medical curricula to ensure development of sex-based evidence for individualized medical decision making. In a small case study conducted at Mayo Clinic, although fourth year medical students were aware of some sex differences in drug metabolism, they reported that such information was not translated into patient care (42). A consensus statement from thought-leaders in medical education agrees that concepts of sex and gender will best be embedded throughout the postgraduate training and not as discrete units (44). The challenge is to provide sufficient mechanistic data and outcome data in all aspects of training which is a work in progress. Educators are reluctant to begin a time and labor-intensive process of developing entirely new programs and materials. However, resources are beginning to accumulate that can be incorporated and customized to fit into existing programs (Table 4). Efforts to expand these resources are under way and should hasten curricula change.

Conclusion

Individualized medicine requires viewing the patient through a sex and gender lens as a first step toward personalizing care and potentially improving outcomes. However, the evidence upon which to base sex-specific decisions needs to be improved. The first step toward accomplishing this goal is for basic scientists to provide more data regarding mechanistic and regulatory processes which are similar and which differ between males and females. In addition, there is continued need for more scientific journal editors to institute editorial policies and for those who do, to enforce these policies that require reporting and analysis of data by sex and gender. Furthermore, increased support of sex difference research by funding agencies is needed, and funding agencies should develop requirements for inclusion of female animals in basic science and women in translational studies and clinical trials. Physiologists have consistently made pivotal contributions to understanding regulatory processes in health and disease. In the future, their contributions will continue to form the basis for advancing personalized medicine. As educators, they will pass on their discoveries to future basic and clinical researchers and health care providers by embedding concepts of sex and gender differences throughout revised curricula. When sex and gender are included as essentials for scientific excellence in research and education, health disparities between women and men will be reduced.

ACKNOWLEDGMENTS

V. M. Miller is immediate past president of the Organization for the Study of Sex Differences.

GRANTS

V. M. Miller’s research program is funded by National Institute of Health Grants AG-44170, HD-65987, HL-83947, and HL-90639.

DISCLOSURES

My funding and association with the Organization for the Study of Sex Differences could be considered conflicts of interest since they are focused on sex differences. However, all are reported above, and I will leave it to the reader to determine whether three is a conflict. I do not receive personal financial benefit from any of these activities.

AUTHOR CONTRIBUTIONS

V.M.M. drafted, edited, revised, and approved final version of manuscript.

REFERENCES

4. Arnold AP, Chen X. What does the “four core genotypes” mouse model tell us about sex differences in the brain and other tissues? Front Neurolendocrinol 30: 1–9, 2009.