**Guest editorial** 

## Sex and gender: chromosomes, gonads, history, and society

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The first two decades of the 21<sup>st</sup> century have witnessed an unprecedented development in transgender medicine.<sup>1-5</sup> I predict that transgender medicine will transform our understanding of the effects of sex and gender on human health and disease during the entire life course. Prompted by these epochal transformations, I will try to clarify some general concepts related to sex and gender as they apply to medicine and public health in the Western medical tradition. However, I will not discuss sexual orientation.

With some simplification, we can now distinguish sex as a biological concept from gender as a more social and cultural concept. As defined by the US Institute of Medicine, sex is "the classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement." Gender is "a person's self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual's gender presentation. Gender is shaped by environment and experience".<sup>6,7</sup>

We can assume that the biology of sex has not changed over historical time. Until the end of the last century, the dogma was that all of the biological differences between men and women are mediated by the gonads and by the production of sex steroids.8 At the time of conception, the fertilized ovum receives either two X chromosomes or one X chromosome and one Y chromosome (with rare exceptions in sex chromosome disorders). The sex chromosomes are responsible for the development of ovaries or testes which begin to secrete sex steroid hormones in utero. The circulating sex steroids transform the fetus in the direction of male or female, and the appearance of the genitalia is the basis for sex assigned at birth (with rare exceptions in disorders of sex development and genital ambiguity). In adolescence, the bodies of boys and girls are further transformed into adult men and women by the increased secretion of sex steroids.4,8

However, starting around the beginning of the 21<sup>st</sup> century, a more complex model has emerged, in which some of the effects of the sex chromosomes are not mediated by the gonads. There are three recognized mechanisms for a chromosomal effect not mediated by the

gonads.8 First, men have genes coded on chromosome Y that are not present in women. Second, women have two doses of the genes coded on chromosome X. One of the two chromosomes in each cell is inactivated; however, some genes escape inactivation, so that women have a double dose of some genes.<sup>9,10</sup> Third, women receive one X chromosome from the mother and one from the father. The pattern of chromosome X inactivation is complex and variable within a given tissue or organ. For example, the hepatocytes in the liver of a women are a mosaic of cells expressing either the maternal or the paternal genes coded on chromosome X. This mosaic can range from almost completely maternal (e.g., 90% maternal) to almost completely paternal (e.g., 90% paternal). All of the intermediate percentages are possible. The same is true of other tissues and organs.<sup>11</sup>

In contrast to sex, gender-related factors have varied over history. Gender includes both a subjective component of self-representation (or gender identity) and a societal component related to the social, cultural, and legal contexts in which men and women live.5-7 Historically, individuals have been treated as male or female based on the sex assigned at birth (appearance of the genitalia). Different religious, cultural, and political systems have determined the role of men and women in the family and in all aspects of social life. Some of the norms are implemented through family pressure, education, media, and peer-pressure. Some other norms are implemented legally and are enforced. In most countries of the world, it is legally impossible to be anything but male or female.12 The personal aspects of gender (e.g., psychology, personality, or behavior) and the social and political aspects of gender (e.g., legal system, religious practices, or social norms) are tightly related to the biology of sex, and it is sometimes difficult to separate the effects of sex (biology) from gender (culture) on the body in conditions of health and disease.5-7

The interactions of age and sex have become more complex by the recognition that some persons do not identify themselves with the sex assigned at birth but with the opposite sex, and are considered transgender. Less commonly, persons may identify themselves with both sexes, or with neither sex (non-binary identity).<sup>12</sup> As of 2017, data collected by the US Centers for Disease 2

Control and Prevention (CDC) estimate that approximately 1.4 million adults of age 18 and older and 150,000 persons age 13 to 17 identify as transgender in the United States.<sup>1,5</sup> The concept of gender has emerged to separate anatomical sex assigned at birth from gender identity. Some of these transgender persons have the desire to modify their appearance to be congruous with their gender. The modifications may range from simple behavioral changes, cosmetic changes, or changes in dressing to the request for gender affirming medical therapies. Gender affirming therapies, in turn, range from receiving hormones of the opposite sex to surgical removal of the gonads (removal of ovaries or testes) or other tissue modification (e.g., removal of the breast, removal of the penis).

The short-term effects of these therapies have been studied and appear to be beneficial, especially in treating the gender dysphoria manifested by many, but not all, transgender persons (distress caused by the incongruency of sex and gender).<sup>2,3</sup> However, these therapies may cause an increased risk of cardiovascular disease within approximately 10 years of follow-up.13 In addition, the long-term effects of gender affirming therapies beyond 10 years remain unknown. Transgender men and women who have undergone gender affirming therapy can be considered living human experiments in which the hormonal milieu has been modified medically; however, the sex chromosomes have remained incongruent. The genetic effects of sex that are not gonadally mediated will remain incongruent.5,8 Therefore, important new areas of research are the interactions between gonadally mediated effects (modifiable by hormonal treatment or surgery) and non-gonadally mediated sex effects, and their impact on health and disease. Long-term cohort studies of transgender persons with and without gender affirming therapies through midlife and aging are needed to inform future transgender medicine.

Keywords. Sex, gender, chromosomes, gonads, history, society.

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