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Sex and Gender Analysis in Medical and Pharmacological Research

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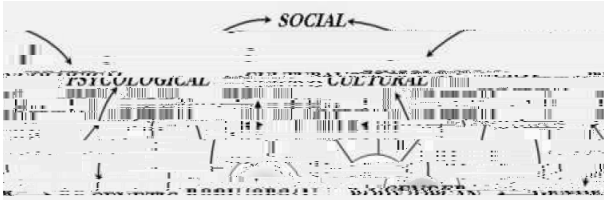
Gender is an essential determinant of social outcomes, including health. Besides, gender can be separated neither from biology nor from other social identifiers as ethnicity, culture, age or social economic class (United Nations,1995). The concepts of '*sex*' and '*gender*' are a face of the nature–culture debate, with the presumption that sex is unchangeable, whereas gender is constructed and can change. Recently, evolutionary psychologists have proposed biological explanations of behaviour by arguing that social constructions may have a biological origin (Taylor et al, 2000). The phenotype is the result of complex interactions between genotype and environment, leading to a lifelong remodelling of our epigenomes, and numerous dimorphic genes expression might be under the control of sex-specific epigenetic marks (Gabory et al, 2009).

Environmental factors (social behaviour, nutrition or chemical compounds including drugs), especially during crucial windows of life, can influence health and diseases, in a sex/gender-related manner. Thus, developmental programs, for each sex, may be more sensitive to specific environmental challenges either during developmental programming and gametogenesis or throughout the individual's life, as well as under the influence of sex steroid hormones and/or sex chromosomes. Variation in programming could thus lead to various defects and different

Historically, *men have been the investigators*[1] *of and the participants*[2] *in health research*. Data arising from these studies, mainly conducted on men have been extrapolated to represent the experiences of both sexes (Uhl K et al, 2007; Franconi, 2007; Schiebinger, 2003). Nevertheless, it is indisputable that there are substantial biological and social differences in the lives of females and males. Despite the multitude of health inequity problems, little systematic research has been done on the social causes of ill-health.

Indeed, research has overwhelmingly focused on biomedical research at the level of individuals. Researchers focused on the health of groups and the determinants of health inequities that are outside individual control have received a smaller share of research resources and attention. Östlin and Paraje (unpublished data, 2004) scrutinized worldwide health-related scientific literature using the ISI database[3] for the period 1992–2001. They found that only 0.2% of the total of 3,361,298 health-related articles dealt with health and social connections. *Ignoring factors such as, race and gender leads to biases in both the content and process of research.*

The recognition of the differences and similarities between men and women can impact on the prevention, diagnosis, development of diseases and outcomes, and



(the social construction of masculinity and femininity)

Gender bias in education

All somatic cells contain all chromosomes, including the sexual ones. Receptors for sexual hormones are present on a wide variety of cells. Thus, cells also have a sex. Although it is hard to examine the sex of cells, organelles, and cellular fragments, sex differences have been found in animal and human materials (Berkley, 1997).

Animal studies

Female mammals have long been neglected in biomedical research. As a consequence, our understanding of female biology is compromised. A recent survey shows that male bias is present in eight biomedical disciplines, with single-sex studies of male animals outnumbering those of females 5.5 to 1. (Beery and Zucker, 2010). The exclusion of females in much of non-human animal research limits our knowledge and the value of research. In consequence, it is crucial to change this situation.

It is important that international organizations such as the United Nations, the World Health Organization (WHO), regulatory agencies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and granting agencies adopt initiatives, similar to that of the National Institute of Health of the United States of America (NIH) wseq.022 8(i Tw -34.0the)9(erenrol(

2001; Gijsbergs van Wijk et al, 1996). It is, however, not sufficient to include both sexes in the sample; a gender analysis also needs to be carried out.

Regarding pharmacological treatments, a 2005 study of 300 new drug applications between 1995 and 2000 found that even those drugs that showed substantial differences in how they are absorbed, metabolized and excreted by men and women had no sex-specific dosage recommendations on their labels (Kim et al, 2010). This may be part of the reason why women are 1.5 -1.7 times more likely to develop an adverse reaction to prescription drugs than men (Franconi et al, 2007). However, it is unlikely that these drugs will be studied again. As many drugs are now generic (without patents), there is little economic incentive for studying them. To overcome this lack of knowledge, alternative strategies could be adopted, such as revising the original studies by retrospectively applying a sex/gender-based analysis (Johnson et al, 2009). The advantage of this approach is that it could be performed without lengthy time investments. It is important to recall that a sex/gender-based analysis is generally not applied in Cochrane systematic reviews on cardiovascular diseases (Doull et al, 2010). Moreover, a secondary analysis of data could be done when a gender analysis was not originally considered (Burns and Grove, 2001). The optimum would be the incorporation of sex/gender analysis at the beginning of a study, which would comprise both male and female animals.

Pregnancy

Although the Council for International Organizations of Medical Sciences clearly stipulates that pregnant women are eligible to participate in biomedical research, they are routinely excluded because of possible harm to the fetus.[4] This is ethically and medically unacceptable because pregnant women use many drugs, and they have the right to receive safe and effective care. Drugs should be studied in pregnancy, because the physiological changes induced by pregnancy make it impossible to calculate the appropriate dose and develop safety information by extrapolation from data on men and non-pregnant women. Thus, pregnant women often do not receive evidence-based medicine due to lack of information. Persuading pregnant women to take part in research can be difficult because of the perception that trials are riskier than taking prescribed medication (Baylis and Kaposy, 2010). *Correcting the current situation should become a priority.*

Gender bias in translational medicine

Translational medicine, which is currently defined as the translation of basic research into practical clinical applications, has great potential to develop and deliver new tools that may assist prevention, diagnosis, and treatment of disease. Before clinical trials are carried out, the safety and effectiveness of new drugs are usually tested in animal models (Sibbald, 2000).

The usefulness of animal testing has, however, been questioned because animal models are dissimilar to humans in numerous ways, which limits the generalizability of results to human biological systems (Croce, 1999). Discordance between animal and human studies could arise a) from the fact that many animal studies are of low quality (poor blinding, small groups with inadequate power, simplistic statistical analysis, selection of a variety of outcome measures, which may be disease surrogates or precursors and which are of uncertain relevance to the human clinical

[4] Thalidomide's teratogenic effects in the 1960s ledEt m9Ath

condition etc; Horn et al, 2001), or b) from the failure of animal models to mimic clinical disease adequately (Franconi et al, 2008).

It is clear that there is a gender bias in preclinical test because male animals dominate the samples. There are, however, more subtle gender biases, such as the selection of disease models. For example, in humans, many gender differences have been described in diabetes mellitus. Diabetic women have a higher cardiovascular morbidity and mortality (Legato, 2004), whereas in rodent models, females became less diabetic than male (Franconi et al, 2008). It is extremely important to identify suitable animal models for

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the dearth of information on how gender interacts with other social determinants continue to limit the content of health research.

Implementation in education
Until now sex/gender has not been well incorporated in health care provider curricula. As our understanding of sex/gender differences continues to expand, sex/gender-based medicine should become a primary consideration for all health care providers. Thus, curricula should change to overcome gender inequalities in health and gender bias in medicine through an integration of gender competencies, which would lead to gender-sensitive health services and equity in health.

Elimination of bias or ambiguity in selection criteria, and of barriers to returning to work after a break
This could help attain a critical mass of women in research, which in turn may increase the probability that existing research cultures will be transformed, and thus create a more conducive environment for sex/gender issues to be addressed in research.

Integrating women's input to research and policies, especially at high level
This could lead to the selection of different themes in research and to the adoption of different experimental design that may help to resolve gender bias, considering that women often have different priorities, needs, interests and resources (United Nations, 2002).

Overcoming potential pitfalls.
Gender research is complex, requires long-lasting evidence, and is full of potential pitfalls because there is not enough data and/or scholarly techniques to arrive at any conclusion. It is emerging that, in order to have results that can been extrapolated to humans and compare males and females, it is important to determine the age at which testing will occur, the time of the day, and the appropriate method of measurement of the trait. One must also know the diet or the housing condition before the testing. For female gestation, lactation and parity, the use of oral contraceptives should also be considered. Descriptive studies should be complemented with studies that try to elucidate the underlying pathways leading to observed health outcomes for both genders. When differences are found, further analyses should be required to explore the contributing factors. Detection of modest differences may require studies with more complex experimental designs, more complex model systems and more subjects to achieve statistical power, and thus may require additional financial resources.

It appears that the quickest action may come from the academic journals, which are moving toward adopting a common set of guidelines for studies using animals, which would require scientists submitting manuscripts to provide details including the sex of the animals, estrous phase, etc. Weighting data obtained from female animals and systematic reviews of animal experiments could be useful to determine similarities between animal models. It is accepted that systematic reviews of animal experiments could facilitate the translation of research findings from animals to humans (Macleod and Sandercock, 2005).

In summary, there is an urgent need for recommendations on the inclusion of female animals in experiments, and for guidelines on experimental designs that include a gender approach.

Identifying and understanding sex-based characteristics, particularly in the diseased state
This remains a great need in research at all levels, from the single cell to animal models to human subjects (Wald and Wu , 2010; Franconi et al, 2007).

Translation to the clinical practice

The usefulness of identifying and understanding sex/gender-related characteristics is undermined if the results of these endeavours are not translated to clinical practice.

Integrating social and biomedical sciences
The scientific community has evidenced numerous physiological and behavioral disparities between the sexes/genders, and they deserve to be integrated into research selection and design. In male and female mice, hundreds of genes have different expressions (Yang et al, 2006), suggesting that there is an inherent difference at the very basic level of our biological makeup. Moreover, these differences are influenced by sexual hormones, but they extend beyond sex hormones and involve imprinting (Tilghman, 1999), and developmental plasticity (Loizzo et al, 2010). The understanding of epigenetic factors in sex/gender differences should be enhanced in order to understand the degree of sex and gender interactions, and how they influence health and diseases.

Establishing sex/gender differences research centres
Sex/gender specific centres that encourage balanced representation of both sexes in preclinical and clinical studies are still critically needed. The centres should be characterized by an integration of different disciplines.

Implementing gender diverse research teams through a number of incentives
Diversity is linearly related to research quality. Because men and women have a different perspective and apply different approaches and questions into research, they can also be more creative.

Implementing gender-related research grants
This would be useful to encourage the scientific community to increase its efforts in understanding pathogenetic mechanisms of diseases, and to bolster gender-sensitive therapies.

Harmonizing normative issues among countries

Sensitizing the general public about gender issues
Gender blindness is pervasive among the general population, and is a barrier to overcoming gender bias. Gender issues should be taught from primary school, and should also include an emphasis on "great women", who tend to be neglected.

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