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MONOGRAPHIC SECTION

A SEX AND GENDER PERSPECTIVE IN MEDICINE: A NEW MANDATORY CHALLENGE FOR HUMAN HEALTH

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Preface

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The analysis of the biology of sex differences as well as the development of gender specific medicine is a milestone in the advancement of our knowledge in different fields of life sciences [1]. Among these fields are included those aimed at the improvement of our knowledge in all the aspects of human health dealing with the differences between men and women: from the policy and public health analyses to the clinical practice, from the basic sciences to the detection of diagnostic gender-specific markers [2, 3]. This could lead to the comprehension of the pathogenetic mechanisms of human diseases and the appropriateness of the medical intervention in the clinical practice [4, 5]. In fact, the development or the improvement of the cures could take advantage from the knowledge of the sex and gender disparity in order to ascertain and develop differential interventions between women and men. As concern the terms sex and gender, they are usually referred as to the biological or to the socio-cultural issues, respectively. These definitions, at least as originally proposed, are quite clear if applied to humans but are quite complicated by the typical approaches of the experimental medicine. This field of investigation takes in fact advantage from three different bodies of study: the use of *in vitro* systems, *e.g.*, cultured cells, the classical *in vivo* preclinical studies carried out with experimental animals and *ex vivo* analysis of cells from humans. All these approaches, in our opinion, often comprise either biological or "social" dimension. In fact, even *in vitro* studies should take into account the "social" behavior of cells. A good example in this respect is represented by studies on lymphocytes in which the interactions among different subpopulations are of great relevance and the relevance of the X chromosome has been underscored [6, 7].

The number of human pathologies displaying a significant gender disparity is rapidly growing up so that the need for the investigations specifically devoted to point out sex or gender differences appear as mandatory [8]. The growing number of works published in the field and taking into account sex/gender disparities is really impressive (*Figure 1*). However, it should also be noted that the great majority of published works do not consider both sexes, *e.g.* male and female animals in preclinical studies or women and men in human studies. For example, the great majority of experimental works, either in animals or in culture cells, do not take into account the biology of sex differences: more than 95% of *in vivo* studies do not consider males and females but one sex only. Very often the sex of the studied animal species is unspecified (in more than 20% of studies). The scenario in *in vitro* or *ex vivo* studies is even worse: the sexual origin of the isolated cells is considered as a negligible issue in more than 99% of the experimental works. Furthermore, the experimental studies are often carried out irrespective to the predominance of the disease in one sex or another so that it can be observed that a disease with high predominance in women is analyzed, *e.g.*, in pharmacological studies, in male mice or XY cells exclusively. This is striking but, in line with this, a further aspect must be taken into account: phase 1 studies (the first step of pharmacological studies in humans usually based on *in vitro* screening and animal studies) in humans very often do not include women. It has been observed that: i) a quarter of the drug manufacturers in an industry survey did not deliberately recruit representative numbers of women as participants in drug trials; ii) women, when included in clinical trials, are generally under represented: iii) in USA, the Food and Drug Administration (FDA) often does not analyze trial data to determine whether women's responses to a drug differ from men's; iv) many drug manufacturers do not study whether their drugs specifically interact with sex hormones. Nevertheless, women are high drug consumers in comparison with men (reports say: 42.1% *vs* 32.2%, respectively) and adverse effects of drugs are essentially suffered by women. All in all, this scenario seems to suggest the need of a reappraisal of

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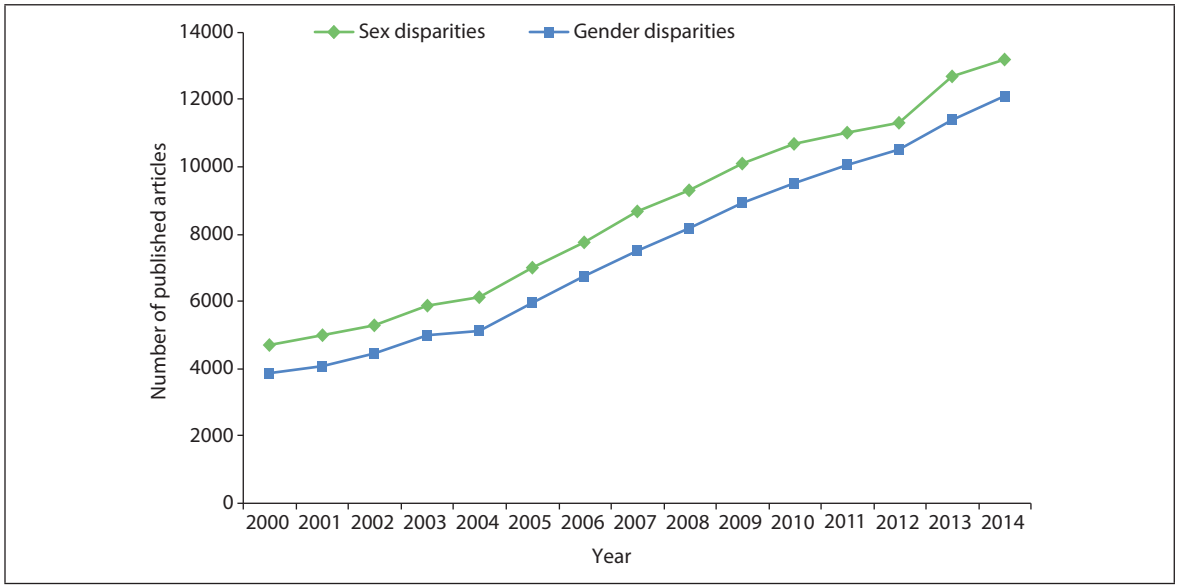

Figure 1
Number of published articles on sex and gender disparity from year 2000 to year 2014.

the scientific medical approach that could improve our knowledge and, consequently, the appropriateness of the intervention on our health.

Notwithstanding, the pathological conditions that have been demonstrated to display a gender disparity are really impressive: transmissible and non-transmissible diseases have been investigated in this respect in a series of studies aimed at the analysis of the incidence, progression or outcome of very important diseases such as infections, cardiovascular, neurodegenerative, metabolic, respiratory, autoimmune diseases and several forms of cancer. In addition, a number of works underscored sex/gender differences in response to therapy either for infections, *e.g.* antiviral therapy, or for non-transmissible diseases such as cancer response to therapy. Moreover, disparity has been described as concern the adverse effects of pharmacological therapies and iatrogenic diseases. On the basis of this huge mass of data, some scientific Journals included sex/gender in their aims and ask the authors to consider this issue, and some Journals devoted to the analysis of differences between males and females have been released. Among these are: the American journal named *Biology of Sex Differences*: a journal dedicated not only to the study of gender medicine but, as one can expect from its title, also to the study of experimental biology and medicine, *i.e.* biological differences between XX and XY cells or male and female animals. More recently, the *Italian Journal of Gender Specific Medicine* (www.gendermedjournal.it/) has also been published. This is an interdisciplinary European journal aimed at the publication of social and biomedical aspects of gender disparities.

Since many years a research group at the Istituto Superiore di Sanità (ISS, Italian National Institute of Health, Section of Gender Medicine) is already operating in the field of gender medicine publishing a number of original works and collaborating with the Italian network operating on this matter. In particular, with the Centro Studi Nazionale su Salute e Medicina di Genere (National Center for Gender Health and Medicine) founded in 2009 in Padua and headed by Giovannella Baggio created an active and intertwined series of contacts including several working groups spread all over our Country. For example, various Italian regions contributed to this networking: in Puglia the Gruppo Italiano Salute e Genere (GISeG, Italian Group for Health and Gender) and in Veneto the Società Italiana di Medicina Generale (SIMG). Many other active working groups operate in other regions, *e.g.*, in Emilia-Romagna and Lombardia (*i.e.*, the Lorenzini Foundation in Milan was the first organization operating in the field in Italy). Several further groups specifically working in the field of gender medicine have been created within some medical associations, such as the Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI, Internal Medicine Association), the Federazione Nazionale degli Ordini dei Medici Chirurghi e degli Odontoiatri (FNOMCeO, Italian Federation of all Medical Doctors). Finally, several efforts have been made by the two main Italian stakeholders in the field of safety and risk assessment – the National Institute against the work-related injury, INAIL, and the ISS – in order to develop a gender-biased risk assessment at the workplaces [9].

A specific reference Center for the study of the biology of sex differences as well as gender medicine is now established at the ISS. In this issue of the *Annali dell'Istituto Superiore di Sanità*, some of the research groups working at the Institute and collaborating with other research groups operating in Italy and abroad provide a brief overview of the state of the art of their field of investigation. Several important areas of study and intervention have thus been covered: from the life styles and prevention to the validation of specific biomarkers, from the pathogenesis and manifestations of human diseases such as autoimmune and cardiovascu-

lar diseases, cancer and infections, to the psychological stress, addiction and pain relief. The scenario is thus wide enough to warrant assorted and diverse competences and skills. Hence, the efforts of the Italian National Institute of Health are still at the beginning but we are sure there is room enough to contribute to the development of an evidence-based medicine that takes into account sex and gender disparity.

REFERENCES

1. Putting gender on the agenda. *Nature* 2010;465(7299): 665. DOI: 10.1038/465665a
2. Schiebinger L. Scientific research must take gender into account. *Nature* 2014;507(7490):9. DOI: 10.1038/507009a
3. Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. *Clin Chem Lab Med* 2013;51(4):713-27. DOI: 10.1515/cclm-2012-0849
4. Ortona E, Matarrese P, Malorni W. Taking into account the gender issue in cell death studies. *Cell Death Dis* 2014;5:e1121. DOI: 10.1038/cddis.2014.73
5. Del Principe D, Ruggieri A, Pietraforte D, Villani A, Vitale C, Straface E, Malorni W. The relevance of estrogen/estrogen receptor system on the gender difference in cardiovascular risk. *Int J Cardiol* 2015;187:291-8. DOI: 10.1016/j.ijcard.2015.03.145
6. Markle JG, Fish EN. SeXX matters in immunity. *Trends Immunol* 2014;35(3):97-104. DOI: 10.1016/j.it.2013.10.006
7. Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. *Nat Rev Immunol* 2010;10(8):594-604. DOI: 10.1038/nri2815
8. Regitz-Zagrosek V. Sex and gender differences in health. *EMBO Rep* 2013;7:596-603. DOI: 10.1038/embor.2012.87
9. Giammarioli AM, Siracusano A, Sorrentino E, Bettoni M, Malorni W. Integrating gender medicine into the workplace health and safety policy in the scientific research institutions: a mandatory task. *Ann Ist Super Sanità* 2012;48(3):311-8.