

Discrimination by Good Intention: Gender-Based Medicine

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Gender-based medicine is probably one of the most important universal changes affecting medicine today. Yet, the general public and most medical professionals are surprisingly unaware of the ongoing fundamental changes in the perception of the differences in bodily functions between men and women. Even the mention of the notion "gender" evokes usually embarrassing confusion with biological sex. Being male or female is the result of our chromosomal constitution. Being masculine or feminine is a different category and the result of the function we play in society, the sociological fabric of our environment, roles, functions and habits assigned by the society on men and women, and expectations which a given society has set for its members. None of these emanates from the biological differences between the sexes. The sometimes profound health implications of this environmental gender role are fascinating, yet remain beyond the realm of this discourse. "Gender-based medicine" deals with the physiological and pathophysiological differences in bodily functions between men and women, and for better differentiation from "Environmental gender-based medicine" it should probably be termed "Biological gender-based medicine."

WHY MOST DISEASES AND DRUGS HAVE BEEN STUDIED IN MEN ONLY

Both physiologically and pathophysiological, women are generally viewed

as something akin to *small men*, albeit with different genitals and the capability to deliver babies. Most diseases have been studied almost exclusively in men, the majority of medications have been evaluated in men only, and in terms of pharmacokinetics the large variability of the physiological changes in a cyclic women are neglected. On the surface, the exclusion of women from clinical studies appears as yet another aspect of gender discrimination. However, a closer look reveals that this is not necessarily so and can better be understood as "discrimination by good intention" – the roots of which date back to the mid-20th century. In the 1940s and 1950s it was common practice to treat threatened abortion in pregnant women with the synthetic estrogen diethylstilbestrol. It took many years until the catastrophic consequences of this treatment became evident when genital malformations, including cancer in the offspring of treated mothers, were diagnosed and a causal relationship to DES was established. Soon thereafter, in the 1960s, another medical catastrophe shook the medical world – the thalidomide disaster. Over 12,000 phocomelic babies were born after their mothers had been treated during pregnancy with the anti-nausea drug thalidomide. Consequently and mainly in order to protect women, the U.S. Food and Drug Administration published a guideline in 1977 that demanded the exclusion of women from phase II-III trials. This guideline was almost universally and probably gladly accepted by researchers and sponsoring companies who a

DES = diethylstilbestrol

priori preferred male research subjects to the physiological variations of cyclic women. Thus, women largely disappeared as research subjects. A decade later, in 1986, the National Institutes of Health attempted to correct this unbalanced state of affairs by declining funding of research projects that did not include both sexes. This effort was ill-fated mainly due to the fact that most clinical research has and is being conducted without NIH funding. As late as the mid-1990s less than-one third of published research included women and even those data were often incomplete.

The NIH went to great lengths to promote research on women and in 1990 founded the Office of Research on Women's Health. Bernadine Healy, as chairperson of the NIH, launched the Women's Health Initiative in 1991, a monumental research project on approximately 160,000 women with a budget of over 600 million US dollars. In 1994 the NIH issued a guideline requiring the inclusion of women in clinical trials, again with only modest results [1]. Ramasubbu et al. [2] reviewed all randomized controlled trials published in the *New England Journal of Medicine* between 1994 and 1999 with mortality as an endpoint. The inclusion criteria of the authors were met by 120 of 442 randomized controlled trials. On average, 24.6% included women and only 14% provided gender-specific analysis. Interestingly, it was only in 1998 that the FDA reversed its 1977 guideline that had explicitly excluded women from clinical trials. Given the long time span

NIH = National Institutes of Health
FDA = Food and Drug Administration

required for drug development, clinical trials and marketing, it is obvious that our knowledge on most currently used drugs derives almost exclusively from male-centered research. Consequently, women are often prescribed drugs that may be less effective or even harmful. As late as 2005, Simon reported in an editorial in *Science* [3] that 8 of 10 prescription drugs had to be withdrawn from the U.S. market because of issues related to women's health.

DIFFERENT BODILY FUNCTIONS IN MEN AND WOMEN

The fundamental functional differences between men and women are related to virtually all bodily systems. The gastrointestinal system, for example, functions differently between men and women. Compared to men, women have colitis or Crohn's disease twice as often, 4 times more gallbladder stones, suffer 5 times more often from irritable bowel syndrome and 20 times more often from functional bowel disease. This can partly be explained by different composition of gastrointestinal fluids including saliva and bile and from the significantly lower passage time of fluids and food through the stomach and intestines. Moreover, both estrogen and progesterone inhibit gall bladder contractions, and the emptying process is therefore even slower at ovulation and during pregnancy.

The female lungs are more vulnerable than lungs of men to disease. Pulmonary hypertension, asthma and chronic obstructive lung disease are usually more severe in women than in men. Lung cancer in women is on a steady rise and is currently regarded as the most fatal cancer in women, accounting for 25% of all cancer deaths with a higher incidence rate than breast cancer. In Europe there are annually about 400,000 new lung cancer cases, 30% of which occur in women. Alarmingly, 80,000 out of 400,000 new lung cancer patients never smoked and most of these were women. While the

incidence of lung cancer in men is constant, the incidence in women is rising. The man-to-female ratio 10 years ago it was 4:1 and in 2007 was 2.5:1 [4].

Even more striking is the paucity of data related to cardiovascular disease in women. The common assumption is that men are more likely to suffer from heart disease than women. This is true only for women before menopause due to heart protection by sex steroids. After menopause women have taken over the lead and currently more women die annually from cardiovascular disease than from all cancers combined. U.S. data from 2005 reveal that 143,000 women died from stroke and 650,000 from cardiovascular disease, while the death toll from all cancers combined amounted to 560,000 [5]. Yet, until the 1990s, almost all research on the cardiovascular system was done exclusively in men. More than 20 years ago, Tobin et al. [6] reported that the relative risk for women with heart attack to be misdiagnosed was twice as high as for men, that women with an abnormal thallium test were 10 times less likely to be referred for catheterization, and that treatment was more conservative for men than for women. Moreover, many anti-arrhythmic drugs are less effective in women than in men, and some of these drugs have been shown to be actually harmful for women. The female heart responds differently to continuous stress like hypertension than the male heart, and diagnostic tools like the customary stress test are substantially less significant and less specific in women than in men.

Another important area of gender differences is pain. Women experience pain differently, have different thresholds for pain, and react differently to analgesics [7]. Moreover, the menstrual phase, segmental sites and tissue depth have interacting effects on pain thresholds [8]. Kappa-opioids (i.e., pentazocine) produce significantly greater analgesia in women than in men [9], while μ -opioid receptors (i.e., morphine) are

more active in men. Non-opioid drugs elicit a stronger response in male laboratory animals than in female animals. Therefore, specific analgesics may have different effects in men and women. Yet analgesics, like most other drugs, are usually prescribed disregarding the sex of the patient.

BOTH SEXES ARE AFFECTED BY GENDER BIAS

It needs to be emphasized that gender-based medicine, which aims to address and to study all these differences, is not female focused, although very much ground has to be covered in order to generate badly needed scientific data on the physiology and pathophysiology, specifically of female bodily functions. There are also many issues where crucially needed data related to men's health is missing. Male breast cancer is rare, accounting for only 1% of all breast cancers, i.e., 100 times rarer in men than in women. This is a relatively small number but, at a rate of 1:100,000 it cannot be deemed negligible in absolute terms. Yet, this cancer has hardly been studied in men. Osteoporosis is regarded as a female disease with a lifetime risk of 1:2 women but men also suffer from osteoporosis with a lifetime risk of 1:5. Again, research on osteoporosis has focused almost exclusively on women. From the onset, men are at a health disadvantage. Male gender is independently associated with adverse pregnancy outcome [Submitted for publication] and male neonates are twice more likely to die at birth [10]. Men are more susceptible to disease than women throughout their life cycle and their life expectancy is also shorter. Men are also at a disadvantage in cancer survival [11]. Very little research has been done to study these basic health disadvantages in men. Gender-based medicine therefore has to deal with health issues in both women and men.

Thus, gender-based medicine is not about creating a new medical discipline but rather about introducing new perspectives and creating a nexus between

existing disciplines. Pediatrics emerged as a separate medical discipline approximately 200 years ago as a result of our understanding that children are not merely small adults. As a result, most medical disciplines had to be redefined to accommodate the medical need and requirements of children. Feto-maternal medicine is probably the first medical discipline where the gender-based approach has been implemented. It is generally accepted that most diseases are expressed differently in pregnant women than in non-pregnant women or in men. Also, today it is largely undisputed that systemic diseases like hypertension, diabetes or various autoimmune diseases in pregnant women should be managed by obstetricians rather than by respective specialists. Yet, once pregnancy is over, the woman, still suffering from her systemic disease, is again treated as the typical 70 kg Caucasian male.

ACHIEVEMENTS SO FAR AND WHAT NEEDS TO BE DONE

Modern medicine should not only be evidence-based but also gender-based. To accomplish this objective there is a dire need for extensive basic and clinical research and also for changes in the curricula of medical studies and of residencies. The essential prerequisite for these actions is the awareness of the necessity and the willingness to question existing paradigms. These preliminary but crucial goals have already been met. The World Health Organization has established the "Department of Gender, Women and Health." At Monash University in Australia, Gender-Based Medicine is an integral part of medical studies, Georgetown University has established a "University Center for the Study of Sex differences in Health, Aging and Disease." NASA has done pioneering work in studying the physiological differences between men and women as related to space travel. Fellowships in women's health are offered by various universities, such as Columbia, MacNeall in Illinois, East Carolina

University, Brigham and Women's Hospital in Boston and many others. In 1997, Prof. Marianne Legato created at Columbia University in New York the "Partnership for Gender Specific Medicine," and departments for gender-based medicine have been established at prestigious universities and hospitals worldwide, including the Karolinska in Stockholm, the Medical University in Vienna, the Charité in Berlin and many others. Dozens of books have been written related to the topic and textbooks are available [12,13]. There are scientific journals devoted to Women's health (*Gender Medicine*, Elsevier) and Men's health (*Men's Health and Gender*, Elsevier). An International Society for Gender Medicine has been established and gender medicine-oriented national and international congresses are being held worldwide. The amount of research projects conducted and published is mushrooming. The silent revolution of Gender Medicine has broken through the first great wall on its path, and is being accepted as an undeniable and necessary shift of paradigms. But this is only the beginning. Now it is time to embark on a truly interdisciplinary journey and to invest academic and clinical efforts in order to establish gender-based medicine as an integral part of how we teach and apply modern medicine for the benefit of women and men alike.

THE ISRAELI SETTING

In Israel, we have covered some ground in this direction during the past year. At Tel Aviv University, gender-based medicine has entered the curriculum and will be taught to sixth year students and is slated to commence in the coming academic year. In June 2008, at Rabin Medical Center, a gender-based medicine Interest group has been established, which today includes over 40 members, among them two hospital directors and 27 department heads from 11 hospitals. Within a few months, over 20 gender-oriented research projects have been

launched at different departments and on 26 February 2009 a Scientific Congress will be held during which the Israeli Society of Gender-Based Medicine will be established. It is time to join.

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References

1. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. *Fed Reg* 1994; 14: 508-13.
2. Ramasubbu K, Gurm H, Litaker D. Gender bias in clinical trials: do double standards still apply? *J Women's Health Gend Based Med* 2001; 10: 757-64.
3. Simon V. Wanted: women in clinical trials. *Science* 2005; 308: 1517.
4. Grohe C. Lungenkrebs und Geschlechterunterschiede: 5. Berliner Symposium Geschlechterforschung in der Medizin, Berlin, 2008.
5. <http://webappa.cdc.gov/cgi-bin/broker.exe>
6. Tobin JN, Wassertheil-Smoller S, Wexler JP, et al. Sex bias in considering coronary bypass surgery. *Ann Intern Med* 1987; 107: 19-25.
7. Wiesenfeld-Hallin Z. Sex differences in pain perception. *Gender Med* 2005; 2: 137-45.
8. Giamberardino MA, Berkley KJ, Lezzi S, de Bigontina P, Vecchiet L. Pain threshold variations in somatic wall tissues as a function of menstrual cycle, segmental site and tissue depth in non-dysmenorrheic women, dysmenorrheic women and men. *Pain* 1997; 71: 187-97.
9. Gear RW, Miaskowski C, Gordon NC, et al. Kappa-opioids produce significantly greater analgesia in women than in men. *Nat Med* 1996; 2: 1248-50.
10. Christensen K, Orstavik KH, Vaupel JW. The x-chromosome and the female survival advantage. An example of the intersection between genetics, epidemiology and demography. *Ann NY Acad Sci* 2001; 954: 175-83.
11. Micheli A, Ciamichini R, Oberaigner E, et al. The advantage of women in cancer survival: an analysis of Eurocare-4 data. *Eur J Cancer* 2008, ahead of print doi:10.1016/j.ejca.2008.11.008
12. Legato M, ed. Principles of Gender Based Medicine. Elsevier, Academic Press, 2004.
13. Rieder A, Lohff B, eds. Gender Medizin. Vienna/New York: Springer, 2008.