

## **Editorial**

### **But What About Men?**

I couldn't believe my ears when, recently, a very smart man told me, "All you ever seem to think about—and talk about—is women's health." I had thought I always made it perfectly clear that I had a well-balanced interest in both sexes, urging investigators and clinicians alike to think about the *differences* between the two. Contrary to this man's opinion, I believed that "women's health," as it was shaped in the 1990s, was too often shallowly conceived or motivated by commercial, political, or feminist concerns. The only way to keep interest alive in studying women, I was convinced, was to prove that what we were learning about women would lead to better health for all humans.

But as my critic squelched my attempt to explain that he'd misunderstood me, I could only blame myself for any confusion my listeners may have experienced. The term *gender medicine* is almost universally interchangeable with *women's health* in the minds of the lay and professional public—including the most enlightened of my male colleagues. When the program committee invited abstracts for the first International Congress on Gender-Specific Medicine held in Berlin this year, we had to repeatedly remind our faculty that this was not a meeting about women's health and that unless their data were harvested from both sexes, they didn't belong in our lecture series.

The confusion stubbornly persists despite our efforts to explain that men are just as important as women to understanding how human health is best preserved and restored. Whenever I try to justify an interest in women, I find myself too often agreeing to explain only the female side of the equation: how their symptoms of a heart attack can be quite different from the classic male story, whether or not hormone therapy is useful, or how understudied the female patient has been for a whole variety of reasons. Years ago, when Harold Varmus, then director of the National Institutes of Health, asked me if I thought he should establish an Office of Research on Men's Health to balance Vivian Pinn's efforts on behalf of women, I laughed. But I should have listened very carefully and asked him why he was worried about the surge of interest in women. My guess is, he would have said that in our zeal to compensate for our vast ignorance about the unique aspects of women's physiology—and our excitement in finding stunning new facts about them at every turn—we were forgetting that the essence of gender-based investigation was to compare both sexes, not to disregard men. The big payoff in considering the sexes together is that it provides us with a more accurate and detailed model of how the human body works, thus giving us clues that are crucial to improving diagnosis and treatment for both men and women.

Nothing brought home how right my friendly critic was than surveying the current medical literature for the unique features of men's physiology and their experience of disease for this editorial. I now realized how new an exercise this was for me, a genuine paradigm shift, very different from the way I'd explored the literature in the past decade. I had never thought about males at all without reference to what was true (or not true) for females. No wonder my patients often asked me if I only treated women!

I took the Institute of Medicine's landmark monograph on gender-specific medicine, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" from my library shelf.<sup>1</sup> I recalled my anger at not having been chosen to be part of the committee that generated the report, and Theresa Wizemann's reply, "We don't want anyone who already has a position about the value of the importance of sex in scientific investigation and patient care. We want a completely naive group of opinion makers on the subject." She was right. I looked through the monograph again and found that, almost invariably, *the committee had an even-handed emphasis on both sexes*. It was admirable that no one read-

ing the text would label the authors as feminists or even as experts on women's health.

So I perused the literature in a new way for this editorial: I searched for male characteristics that seemed particularly intriguing. One of the most troublesome is the relative (and, it would seem, counterintuitively characteristic) vulnerability of men compared with women. Everyone who cares for patients or, for that matter, comes in contact with the oldest citizens of our society knows that women outlive men. But male vulnerability as they approach older age is far from the whole story—from the moment of conception until they die, men are strikingly less likely to survive than are women. For example, even though there are more male than female embryos, probably because spermatozoa carrying the Y chromosome swim faster than those carrying the X chromosome,<sup>2</sup> there are more miscarriages of male fetuses. Some pundits hypothesize that the gallant Y-bearing sperm is preferentially attracted to immature and imperfectly developed oocytes.<sup>3</sup> (Do men prefer youth even at the expense of age-dependent characteristics like wisdom and stability, even in the womb? Or is it a chivalrous attempt to rescue the most vulnerable ova?) A sad image: an enthusiastic Y-bearing sperm outrunning its less agile X-bearing colleagues, only to choose the object of its affection unwisely once it wins the race.

External disasters hurt the male embryo's chances of survival too. One concept is that sperm generated during times of major environmental stress have a selectively damaged Y chromosome.<sup>4</sup> Another proposal cites the "extra" X chromosome as an exceptional resource for the female embryo; the X chromosome chosen for lyonization may not be completely silenced and is a potential resource for rescue or repair of flawed genes on its surviving partner. Reading this, I wondered if there might be some means of selectively supplying the vulnerable male with those X-related genes to increase his chances of survival.

Industrial countries are witnessing a little-appreciated decline in male-to-female births since the 1950s,<sup>5</sup> for which several explanations have been offered. One of the most interesting

is that the probability of a male conceptus declines with increases in parental age.<sup>6,7</sup> Another study suggests that the *difference* in parental age is a significant predictor of the sex of the first child.<sup>8</sup> Pesticides, which produce an increase in birth defects in male children, have also been incriminated.<sup>9</sup> One of the most poignant reasons advanced for the change in the numbers of males conceived is that just after World War II, coital frequency escalated. Increased sexual activity seems to result in earlier fertilizations in the reproductive cycle, which produce more males.<sup>10</sup> Presumably, as peace wore on, the push to propagate lessened. Whatever the reason, the numbers of blighted male fetuses are increasing: fetal male deaths in Japan, for example, have been steadily climbing from a male/female ratio of 1.34 in 1972 to 1.72 in 1996.<sup>11</sup>

Even when the male manages to exit the womb successfully, he is still behind the survival eight ball: he is 3 to 4 times more likely to have developmental disorders than his sisters.<sup>2</sup> Kraemer, pointing out that boys develop motor and cognitive aptitude later than girls, believes that societies compound the problem by treating boys more roughly, expecting them to be much less vulnerable than girls: "Where caregivers assume that from birth a boy ought always to be tougher than a girl, his inborn disadvantage will be amplified."<sup>2</sup>

On the other hand, the fact that most societies offer boys more nutritional, educational, and vocational advantages than girls receive may compensate in part for the vulnerability of males and an almost evolutionarily selected effort to ensure a boy's survival. However, these efforts to favor males are apparently not sufficient—throughout the world, men's suicide and death rates far exceed those of women's.<sup>12,13</sup>

Men's larger stature may work against them as well. One theory of why women live longer than men do (7 years longer in most developed countries) negates the value of hormones, because same-aged men have higher estrogen levels than untreated postmenopausal women. The ends of chromosomes (the telomeres) are gradually eroded as life goes on, and several studies have shown that men have shorter telomeres than women do.<sup>14</sup>

Kraemer advances the intriguing notion that larger size requires a more frequent doubling of cells to keep tissues intact, thus ensuring earlier death:

“...the replicative history of male cells might be longer than that of female cells, resulting in the exhaustion of the regeneration potential and the early onset of age-associated disease predominantly in large-bodied males.”<sup>2</sup>

As much as I would have resisted the idea before my friend asked me about research in men, I believe there’s merit in modifying our approach to gender-based medicine from time to time to embrace a concentrated look at just one sex. For those of us who began this journey motivated by the conviction that more information about women would improve our capacity to sustain and prolong human life, it’s worth a try. There is something about an undiluted effort to consider the singular characteristics of the needs and vulnerabilities of one sex that sends us back to the drawing board with a new point of view about how best to help them. Serendipitously, it prompts us to consider how to convey the unique advantages of one sex onto the other. Research into the comparative vulnerability of men, for example, (instead of always concentrating on how we have neglected women’s biology) will doubtless uncover new ways to improve any human’s ability to survive. In the last analysis, isn’t that what gender-specific medicine is all about?

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