The ladies need more attention

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GIRLS AND BOYS ARE DIFFERENT. The accompanying article[1] details meticulously, in scientifically unassailable fashion, the embarrassing flaw in generations of scientific inquiry that male cells, male animals, and male patients have been overrepresented disproportionately in scientific research. It is difficult to condone this obvious oversight. An acknowledgedly staid and traditional Victorian man like Charles Darwin might reason that the evolutionary conservation of fundamental proteins like phosphatases and kinases confirm the similarities in the cellular machinery as divergent as drosophila, mice, monkeys, and men (and women). We scientists also have been lulled into the acceptance of the male experimental animal knowing that the genome of George Romney and George Washington are 99.99% identical. But how about Betsy Ross?

SO, ARE BOYS AND GIRLS REALLY DIFFERENT?

Betsy Ross and Abigail Adams did boast a full strand of additional operational chromosomal material relative to George and John, and that extra X does span more than 150 million base pairs, comprising more than 2,000 genes. Although we have made huge recent progress in molecular biology, the dream that our base nucleotide sequences dictate our lives has proven a broken promise. Altshuler and Gates summarize our conceptual plight: "A small proportion of genetic variants that influence diseases or traits are common in some places and rare in others…even where such variants exist, they appear to explain only a small fraction of the variation in the trait within the population." Indeed, we have declared previously that "Genes don't count."[2] So, is the male animal different only because of the manner in which our environment treats him? Is a buff biker dude likely to process external or even paracrine signals in a fashion similar to Beyoncé, or are these differences dwarfed by the chasm distinguishing Beyoncé from Mother Teresa?

WHO BELIEVES IN ESTRADIOL?

Estrogen binds to and transcriptionally regulates DNA and also influences nongenomic activities.[3] Membrane surface estrogen receptors in both sexes have been confirmed for cardiac, pulmonary, hepatic, dendritic, hematologic, and endothelial tissues in addition to the more "classic" female breast, uterine, and ovarian cells.[4] Estrogen receptors activate rapidly the mitogen-activated protein kinases and phosphatidylinositol-3-kinase pathways, which promote expression of protective heat shock proteins and endothelial nitric oxide synthase. This receptor-mediated process results in increased flux through ion channels, thereby enhancing growth factors and the coupling of G-proteins that activate cyclic adenosine monophosphate and increase intracellular calcium.[4] So, estrogens do talk to cells unconstrained by gender.

CAN WE PUT IT ALL TOGETHER?

For many biologically documentable reasons, we know that females of all ages and species survive hypovolemic shock, sepsis, and trauma better than do the males.[5,6] Although estrogen is protective,[7] we know that testosterone is trouble.[8] Indeed, when putting the whole package together, women outlive men by an average of 6 years in every culture.

IS IT THE NUMERATOR OR THE DENOMINATOR?

So, we all acknowledge that girls are tougher; however, is part of the problem that guys are just prone to blundering into battles that provoke ischemia/reperfusion injury, hypotension, and sepsis? Traditionally, surgeons are more interested

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in incorporating therapeutic advances (the numerator) than in studying epidemiologic and cultural shifts (the denominator). In every society, men suffer penetrating and even blunt trauma with unpardonably embarrassing prevalence compared with the women. We have explored previously the physiologic status that extends the phenotype of "being a lady" well beyond that of just "being female."[9,10] We agree wholeheartedly and endorse the premise of the authors of the accompanying article[1] and applaud the efforts of those who would decrease effectively the risky behavior of males (the denominator). Equally important, however, we encourage consideration of our previously published therapeutic proposal.[9,11] Again, we acknowledge that girls are both different and tougher than boys. In our previous reports,[9,11] we suggested harnessing the estradiol receptor in patients at risk for multiple organ failure. This strategy may, of course, confer the maximum advantage to "at-risk" males.

BEING FEMALE AS THERAPY

We are in favor of assaulting the denominator by attacking global issues with a "Hillary Clinton Doctrine" of female empowerment involving microfinance, agricultural investments, and a more civilized society.

At the acute care level, however, we know that estrogen receptors on the membrane surface have been identified and confirmed in essentially all organs of both sexes.[6] In addition, in animals after injury, expression of immunologic proteins is altered and enhanced within 90 minutes of the administration of 17-beta-estradiol. It seems both reasonable and logical that we should harness this constructive therapeutic energy. Although we are disappointed that our previously proposed intervention[9,11] appears to have been ignored, we happily imagine confronting the androgen-powered buff biker dude with a liver lac in our trauma bay: "Big Daddy, I am going to give you a shot that will help you to survive by turning you into a girl." We are, however, fully cognizant of the classic black box warning on the bottle of estrogen that states: "May provoke an overwhelming urge to go shopping," but, we suggest, conversely, that this might also be good for the economy.

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