Mars and Venus

For decades, researchers and doctors have relied on data gleaned from studying men to understand and treat health problems in women. New efforts to tease apart physiological differences between the sexes promise to improve health care for women—and for men.

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Much of current medical practice uses research on men to guide treatment for women. But many illnesses don’t hit both sexes equally hard. For example, at any particular age, the incidence of heart disease for men exceeds that for women. Moreover, heart attack symptoms aren’t the same for both sexes. Researchers are uncovering unique aspects of women’s physiology that might underlie their particular disease profiles and potentially lead to sex-tailored therapies.

Women today head labs, build bridges, and fly fighter jets, whereas men dust and bake and parent. Equality at work or home, however, shouldn’t necessarily translate into equality at the doctor’s office. Men and women have different propensities for certain diseases, particularly age-related ones, and some of these maladies manifest themselves differently in the two sexes. Yet most medical treatments for women are based on studies of men. Now, researchers are making inroads into understanding these differences. Such discoveries could lead to therapies customized for men or women, improving everyone’s health in old age.

Medical science has suffered from “the cult of the typical 70-kilogram man,” says Sherry Marts, vice president of scientific affairs for the Society for Women’s Health Research (SWHR), a nonprofit organization based in Washington, D.C. “Anything you didn’t find in a 70-kilogram man was somehow atypical, and women were just small men with different plumbing and a hormone problem. But the more scientists look for sex differences, the more they find.”

Researchers have excluded women from health studies for a variety of reasons. They’ve been reticent to risk putting a fetus in harm’s way, should a female subject become pregnant during the course of a study. Scientists have also been concerned that women’s cycling hormonal patterns would complicate data analysis. Including enough women to account for these fluctuations and allow for subjects who drop out due to pregnancy would make studies expensive and time-consuming.

Over the past 20 years, however, a movement to include women in clinical research and develop sex-specific treatments has gained momentum. A 1985 United States Public Health Service report called attention to the fact that most health recommendations for women were based on studies of men, and in the ensuing years, the National Institutes of Health (NIH) made policy changes in response. In 1986, NIH began encouraging scientists to submit research proposals that included women as study subjects, and a 1993 law mandated inclusion of women in all clinical studies; moreover, phase III clinical trials, the final stage of drug approval, should include sufficient numbers to permit analysis of women as a separate group, unless doing so is impossible or unnecessary because other data suggest that men and women respond similarly. By 1997, more than 50% of participants in clinical studies funded by NIH were women.

These efforts have yielded important results. For instance, research has revealed that some painkillers work better in women than in men. And findings from the Women’s Health Initiative, a randomized trial that includes more than 100,000 women, have shown an increased risk of heart attack in elderly women on hormone replacement therapy (see “Weathering the HRT Storm”). Although questions remain about how to interpret the findings, the study has provided the first rigorous, large-scale test of the treatment, which doctors have prescribed to women since the 1970s. “We’ve made a lot of progress,” says Vivian Pinn, director of NIH’s Office of Research on Women’s Health. “There’s a lot more recognition of the value of [investigating sex differences].”

But researchers can do more, some analysts say. A 2000 report from the General Accounting Office (the investigative arm of Congress, now known as the Government Accountability Office) praised NIH for increasing the inclusion of women but found that the requirement wasn’t rigorously applied to all clinical studies. And SWHR the same year reported that few NIH-funded studies carried out and published the sex comparison. That criticism was unfair, says Pinn, because few studies proposed after the inclusion law passed had been finished by then. In addition, NIH can demand that researchers consider sex when submitting proposals, but they don’t have power over journals to require publication of analyses by sex, she says, although she notes that in 2001 the Journal of the National Cancer Institute began pushing researchers to analyze and report analyses by sex in submitted manuscripts. Other organizations encouraged studies of sex differences to extend beyond humans. For instance, a 2001 report by the National Academy of Sciences’ Institute of Medicine (IOM) advised that efforts to understand sex discrepancies should include laboratory animals and cells. Pinn agrees that consideration of sex needs to infiltrate basic research as well as the clinical realm. Scientists are already taking this approach to clarify mechanisms that underlie health differences between men and women.

Heart to Heart

Clues have been surfacing for decades that men and women aren’t the same when it comes to disease. For instance, until menopause women are at far lower risk of developing heart disease than men are. Data from the Framingham Heart Study, initiated in 1948 to uncover risks for heart trouble and one of the few long-term studies to include women (see “Taking the Long View”), reveal that premenopausal women lag behind men in incidence of heart disease by about 10 years; that gap begins to close after menopause.

† sageke.sciencemag.org/cgi/content/full/2004/26/ns3

‡ sageke.sciencemag.org/cgi/content/full/2003/38/nf18
Playing catch-up. Heart disease rates in women approach those in men only at old ages.

In addition, women don’t have the same kinds of heart attacks as men do. “Women in general prefer the milder version of coronary disease,” says public health researcher William Kannel of Boston University. They tend to get angina—squeezing chest pain—rather than the massive myocardial infarctions that often lead to sudden death in men, although MIs increase in prevalence as women age and are more often fatal in women than in men. And women frequently experience heart attack symptoms that aren’t typical for men. Rather than the classic “crushed chest” sensation and numb left arm, they often feel jaw and shoulder pain and experience nausea and heartburn. “Women are much less likely to get the Hollywood heart attack,” says Marts. Those differences have hampered diagnosis. As a result, conventional wisdom holds that heart disease is a man’s ailment, yet more women die from heart disease or stroke than from cancer. “For a long time, if you were a woman in your late 30s to early 60s, … it was very hard to get anyone to consider that you may be having a heart attack,” she says. “There are stories of women showing up in the emergency room complaining of symptoms like this, being given a bottle of Maalox, and dropping dead in the parking lot of a heart attack.”

Awareness of the range of symptoms associated with heart problems has improved treatment for women, says Marts, but researchers also want to understand why men and women have different tendencies to get heart attacks and experience them differently. Women lose their protection against heart disease after menopause—when estrogen quantities plummet—when estrogen quantities plummet—at which time their rates of heart attack begin approaching those of men. So researchers have implicated a dearth of estrogen in heart attacks. At the cellular level, that idea has merit. Estrogen softens and relaxes plaques by helping bodies maintain a healthy balance of cholesterol-carrying molecules. Yet hormone replacement therapy increases the risk for heart attack in women over 65, suggesting that something else is at work, says Kannel.

That something could be mechanical, says cardiologist Marianne Legato of Columbia University in New York City. For instance, they are smaller and tend to beat faster because they can’t push as much blood with each pump, she says. In addition, they take longer to return to the resting state after a contraction. These features can render them susceptible to abnormal rhythms and also might explain why such stutters are a more common side effect of certain drugs in women than in men. “I really would like to understand what it is that protects women until they get to menopausal age, especially looking at things other than estrogen,” says Kannel. And scientists want to sort out an important diabetes—heart disease connection: Diabetes raises the risk of heart disease in premenopausal women, negating their usual protection, says Legato. “If we understood why diabetes increases women’s risk fourfold, we’d understand a lot more about physiology and coronary artery disease,” she says.

Different Strokes
Another cardiovascular problem—stroke—also hits women and men differently. Because women live longer, they experience more total strokes—and stroke deaths. Yet for most of their lives, women suffer strokes at lower rates than do men of the same age; the rates don’t start to converge until people reach their 70s.

Researchers are uncovering disparities between the sexes that alter how brain cells respond when they lose their blood supply, which happens during the most common kind of stroke. Gender biologist Patricia Hurn of Oregon Health and Science University in Portland and colleagues have caused strokes in rodents and found that a larger area of the brain dies in male animals than in female ones. Although extent of damage might not strictly translate to a worse outcome, the finding is consistent with statistics indicating that death rates from stroke are slightly higher for men than for women (although overall, more women die of stroke). Removing the ovaries from female animals increases the damage they sustain, and treating ovariectomized animals with estrogen reduces it, suggesting that hormones contribute to the contrast between the sexes. Yet, as with heart disease, hormone replacement in people exacerbates rather than reduces stroke incidence, hinting that other factors are at work.

To uncover these other contributors, scientists have begun looking at the differences between the cells of males and of females. Males’ cells carry one X chromosome, whereas females’ carry two; conventional wisdom has held that one X chromosome in females’ cells shuts down, and that the Y chromosome carries few genes aside from those that dictate male sex. Because both types carry one active X chromosome, the cells of either sex should be genetically similar, the argument goes. However, new work is uncovering key differences in how the cells of each sex operate.

Robert Clark, a cell biologist at the University of Pittsburgh School of Medicine in Pennsylvania, and colleagues grew separate cultures of brain cells from male and female rats and dosed the cells with the neurotransmitter glutamate. This molecule normally helps brain cells communicate, but in high doses—which the brain suffers during a stroke—it can overstimulate cells to death. More cells from males succumbed to glutamate and other stroke-related compounds than did those from females. On the other hand, molecules that induce classic cell-suicide pathways disproportionately killed cells from females. Further analysis revealed that the cells of each sex activate different death mechanisms. Males’ cells released a molecule called apoptosis-inducing factor from their mitochondria, whereas females’ cells disgorged one called cytochrome c; both kill, but they recruit different cellular machinery to do so. The different paths to ruin mean that males’ cells die in a less controlled, messier manner, says Clark: “The male cells explode and female
cells shrivel.” Moreover, girls who suffer traumatic brain injury carry more cytochrome c in their spinal fluid than boys do, suggesting that the cellular results apply to people, his team reported in the March issue of the *Journal of Cerebral Blood Flow and Metabolism*. Clark focuses on head injuries in children, but the findings might also be relevant for older people, he says. For instance, understanding variations in death mechanisms between males’ and females’ cells might help explain incongruities in neurodegenerative diseases, such as the observation that men are more likely than women to develop Parkinson’s disease, and that women respond less well than men do to some PD treatments. Hurn’s group has similarly found that males’ cells die more readily when starved of glucose and oxygen, conditions that mimic a stroke. “There’s something different about XX cells and XY cells,” says Hurn.

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Other recent studies also support the view that the two sexes’ cells aren’t as similar as once thought. According to work published in *Nature* on 17 March, 15% of genes on an “inactive” X chromosome aren’t quieted. The extra dose of X chromosome genes could underlie sex-specific behavior of cells, write the authors. “We thought we understood X chromosome inactivation,” says geneticist Mary-Lou Pardue of the Massachusetts Institute of Technology, who chaired the IOM committee that issued the 2001 evaluation of research into sex differences. But “the X chromosome is more important than we originally thought.”

Because the epidemiology of heart disease in women began in earnest with the Framingham study almost 60 years ago, research in that area leads the charge in understanding sex-specific health nuances. But researchers are also making great strides in solving secrets of male and female brains, says Marts, which could help explain susceptibility to mental illness: Women are more likely to suffer from depression, for instance, and men might be more likely to develop schizophrenia. Further work should illuminate sex disparities in other diseases: Osteoporosis hits women earlier—and harder—than men because falling estrogen quantities make bone vulnerable (see “The Plot Thickens on Thin Bones”2 and “More Than a Hot Flash”), but further research might reveal additional mechanisms that shape bone-loss patterns in each sex.

**Drug Disparity**

Physiological and molecular distinctions between men and women—and their cells—suggest that for some diseases, treatments should be customized according to sex. Brain damage in particular probably requires sex-specific therapy, given discoveries of sex differences in brain-cell death, says Clark. Hurn agrees. “Stroke trials typically don’t stratify by sex,” she says, because the incidence of stroke is higher in men and because strokes hit without warning, which complicates attempts to recruit substantial numbers of subjects. That limitation hampers efforts to tease out whether an agent would act differently in men than in women.

Other work adds to the idea that strokes have different triggers in the two sexes and should be treated differently. A protein called PARP heightens stroke damage, studies on male animals have revealed, and blocking PARP quells destruction, suggesting that the molecule is a promising target for stroke drugs. However, although PARP-blocking drugs preserve male brains, such compounds worsens strokes in female animals, Hurn’s team reported in the April issue of the *Journal of Cerebral Blood Flow and Metabolism*. She says that scientists should use animal experiments to discern when a clinical investigation warrants separating men and women or when the data can be combined.

**Bad medicine.** Long used for heart attack prevention, aspirin doesn’t protect women, although new findings suggest that it guards them against stroke.

1 sageke.sciencemag.org/cgi/content/full/2002/44/ns8

2 sageke.sciencemag.org/cgi/content/full/2002/10/ns3
Additional recent studies call into question long-standing approaches to preventing disease. For more than a decade, doctors have advised patients—both male and female—to take an aspirin a day to keep a heart attack away, yet that therapy originated from findings in men. Later trials showed that aspirin fed off stroke in women as well as in men. But a paper published in the 31 March New England Journal of Medicine revealed that aspirin did not prevent heart attack in women. Thus doctors shouldn’t apply a blanket policy for women based on the data from men. “We’ve waited 15 years [for a study on women] to find that out,” says Marts.

Not only do some drugs work differently in men and women, but each sex also breaks them down in a distinct manner. For instance, humans as well as laboratory animals exhibit sex-specific variation in the production of drug-metabolizing enzymes (see “Just a Little Bit”). “You could imagine that for a drug where the [difference between a therapeutic dose and a toxic dose] is narrower, you might say, yes, gender is important enough to pay attention to,” says molecular endocrinologist David Waxman of Boston University. However, he notes that humans show greater variation among individuals—regardless of sex—than between males and females, and the importance of intersex discrepancies requires further investigation.

Women aren’t the only ones who can benefit from studies that analyze the sexes separately. For instance, researchers halted trials in the 1990s of one promising stroke drug called tirilizad because the drug didn’t perform better than a placebo did. But later analysis suggested that the drug failed because women did exceedingly poorly on it—they frequently suffered seizures, for instance. “It’s a drug that could have been good in men but didn’t work particularly well in women,” Hurn says.

As researchers further explore unique facets of male and female physiology, they hope to improve health care for everyone. “Men and women are different enough to study both sexes,” says Legato, “and they are different enough that we should change the practice of medicine.” Such progress should enhance quality of life from the kitchen to the cockpit.

R. John Davenport is an associate editor of SAGE KE. He’s waiting for the pills that will force him to ask for directions.

Further Reading
NIH Revitalization Act of 1993
grants.nih.gov/grants/olaw/pl103-43.pdf
2000 GAO report
www.gao.gov/new.items/he00096.pdf
2001 IOM report
www.iom.edu/report.asp?id=5437
American Heart Association Heart Disease and Stroke Statistics
www.americanheart.org/presenter.jhtml?identifier=1200026
Framingham Heart Study
www.nhlbi.nih.gov/about/framingham
NIH Office of Research on Women’s Health
www.od.nih.gov/orwh
Society for Women’s Health Research
www.womenshealthresearch.org

References