

Ignoring Sex Differences Undermines Research

BY SHERRY BOSCHERT

SAN FRANCISCO — Lack of attention to biological differences between males and females may be hurting both sexes in the treatment of health problems.

Research in the past decade has begun to delve into sex differences in depression, pain perception, sleep, stroke, multiple sclerosis, drug responses, and more, speakers said at a meeting sponsored by the Institute of Medicine on sex differences and their implications for translational neuroscience research.

"The advances in molecular biology and in brain imaging make it clear that there's a biological basis to the sex differences," said Rae Silver, Ph.D., who codirected the workshop and is a professor of natural and physical sciences at Barnard College and Columbia University, both in New York.

When researchers don't examine differences between males and females—in basic science on cell biology all the way up to human clinical trials—the resulting lack of data may lead to flawed conclusions. For example, data showing that only 20% of studies on heart disease have included women help to explain why the disease and its treatments are less well understood in women than in men, several speakers noted.

On the other hand, an investigational drug that may have been effective in treating chronic pain in men—but not women—was abandoned after the drug failed in a clinical trial that included both sexes but did not analyze differences in response by sex, another speaker said.

The IOM convened the workshop to follow up on its 2001 report, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" which recommended that sex differences be studied "from womb to tomb" (across the lifespan), across species, and at the cellular level, and that all human diseases affecting both sexes be monitored for sex differences and similarities.

The progress reports at the workshop showed how much remains to be done, and generated lively debate about what the IOM, the National Institutes of Health, and the Food and Drug Administration could do to promote greater attention to sex differences in research and drug development.

Currently, only NIH-funded studies must include some attention to sex differences, and this requirement does not apply to studies funded by industry or other sources.

The NIH and the FDA created an online course on sex differences that offers continuing medical education credits to researchers and clinicians, said Dr. Vivian W. Pinn, director of the NIH Office of Research on Women's Health. The course provides a basic scientific understanding of the major physiological differences between the sexes, the influences these differences have on illness and health outcomes, and the implica-

tions for policy, medical research, and health care. It can be found at <http://sexandgendercourse.od.nih.gov>.

Sex differences in disease susceptibility should be studied whenever there are differences between the sexes in anatomy, in physiology, in the incidence or age of onset of disease, in the symptoms or diagnosis of disease, or in the severity, progression, and outcome of disease, argued Kathryn Sandberg, Ph.D.

"There's growing interest because it's become clear that, in stroke, not only is there a sex difference in incidence, but also a sex difference in symptoms," according to Dr. Sandberg, director of the center for the study of sex differences in health, aging, and disease at Georgetown University in Washington.

A recent study reported sex differences in types of acute ischemic stroke. Men are significantly more likely than women to have lacunar (39% vs. 29%) or atherosclerotic strokes (19% vs. 13%), whereas women are significantly more likely to have cardioembolic strokes than men (30% vs. 23%), she noted (*Women's Health* 2010;6:51-7).

"That's just screaming at you that there's a mechanism that has to be studied," Dr. Sandberg said.

Other speakers emphasized the need for more research on sex differences in major depression, which is twice as common in females as in males, and in multiple sclerosis, which is two to four times more common in females than in males.

Because multiple sclerosis relapses in 80% of women during pregnancy, and findings from animal tests have suggested that estriol protects against multiple sclerosis, a clinical trial is underway of estriol treatment in women with the disease, said Dr. Rhonda Voskuhl, professor of neurology at the University of California, Los Angeles.

Similarly, animal test data showed a protective effect of testosterone in men, and a pilot study of testosterone gel in men with multiple sclerosis showed markers of improvement.

"I'm now primed to do a clinical trial in men," she added.

The problem is that both of these are generic drugs, so it will be difficult to find the \$5-\$25 million needed for phase II/III clinical trials. "It's a shame to drop estradiol and testosterone merely because nobody can make money on it. If you're a patient, you'd rather take estriol, which has been given to hundreds of thousands of people, instead of compound x, y, or z" with unknown side effects, she said.

In the growing field of sleep medicine, "We still lack some basic understandings about sex differences and their consequences for disease," added Roseanne Armitage, Ph.D., professor of psychiatry at the University of Michigan in Ann Arbor.

Jeanne Duffy, Ph.D., director of the Chronobiology Core at Brigham and

Women's Hospital, Boston, described profound differences between the sexes in subjective and objective measures of sleep quality. For example, women are more likely to subjectively report not having good sleep even when objective measures would suggest they slept better than men. "We don't understand these differences," she said.

In other sleep research, men report better daytime functioning after getting less than 7 hours of sleep, though objective measures suggest they're functioning no better than women on the same amount of sleep, said Rachel Mamber, Ph.D., director of the Sleep Medicine Clinic at Stanford (Calif.) University.

Progress has been limited since the Institute of Medicine issued its report in 2001 calling for all human diseases affecting both men and women to be monitored for both sex differences and similarities.

On a preclinical level, a review of studies in rodents found that 87% either used only male rodents, didn't specify sex, or didn't examine sex differences in the few studies that included males and females, Jeffrey S. Mogil, Ph.D., said (*Pain* 2005;117:1-5).

There's an assumption among scientists that data from female mice are more variable and thus are harder to work with, but research by Dr. Mogil and his associates found that this is not true. If anything, data are more variable from male mice, although not significantly more so than data from females, said Dr. Mogil, professor of psychology at the center for research on pain at McGill University in Montreal.

Moreover, a once-radical hypothesis has been proved to be true—that males and females have qualitatively different pain processing mechanisms that are genetically and neurochemically distinct from males, Dr. Mogil's mice studies have shown.

All of that could explain why more than 100 promising studies in mice suggesting that dextromethorphan (a common ingredient in cough syrup) potentiates the analgesic effects of morphine resulted in a failed clinical trial in humans of the drug combination, Dr. Mogil said. The mice studies undoubtedly focused on males, and later studies by Dr. Mogil showed that dextromethorphan boosts morphine's effects in males but not in females. The pharmaceutical company that sponsored the human trial and later abandoned the drug combination had not analyzed sex differences.

"That was an example of a flaw in the NIH policy. They included women but didn't do anything with them" in the analysis of results, Dr. Mogil said.

At the basic science level, it's now understood that the three main causes of sex differences are activational and or-

ganizational effects of testicular and ovarian hormones and direct sex chromosome effects, Arthur P. Arnold, Ph.D., said.

The differences between these have clinical implications, yet in almost no cases have these "big three" causes of sex differences been studied systematically and comprehensively in preclinical studies, said Dr. Arnold, professor and chair of physiological sciences at the University of California, Los Angeles.

In a discussion at the end of the workshop, more than one participant suggested adopting some kind of mandate to push harder for inclusion of sex differences—perhaps, for instance, requiring that basic scientists or clinicians who do not plan to include female subjects in studies at least provide a rationale for that decision.

Other attendees pushed back against the idea of a mandate, however, and argued instead that making money available for sex difference research would stimulate the desired work.

Dr. Pinn said she'd take back to the NIH the idea of educating program officers who handle grant decisions about sex differences, in hopes of developing some of them into advocates or champions of sex differences research.

She added, "We may think of doing a small pilot program to look at incorporating sex differences in basic research."

Neuroendocrinologist Jon Levine, Ph.D., argued that scientists and physicians need earlier education on sex differences. "Our brightest and best are going into graduate and medical school programs that don't recognize that there are sex differences in brain function" and other areas, said Dr. Levine, professor of neurobiology and physiology at Northwestern University, Chicago. "At my own institution, there is one day's class within one course on sex differences in brain function and disease. That has to change." ■

Disclosures: The speakers included in this article reported having no relevant conflicts of interest.

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