It’s not just the towels that need to be labeled his and hers—there are also his and her livers, neurons, immune systems, and a host of other differences between the sexes that are cropping up in the most unexpected places, researchers are finding. The latest additions to the *Men Are from Mars. Women Are from Venus* saga have important implications for the practice of both medicine and research, because they not only help explain why women or men are more prone to certain disorders, but also suggest that many treatments should be tailored according to sex.

Unlike the picture of sex differences that was painted with broad brush strokes in previous decades, recent findings reveal how the sexes diverge down to the level of genes and molecular pathways. The wealth of these more detailed findings reveal that sex hormones foster a wide range of different biochemical pathways in men and women throughout the body, affecting such processes as drug metabolism, injury response, and inflammation. That these hormones influence so many basic facets of physiology suggests we humans come in two distinct functional models, putting a whole new spin on sexual dimorphism. “There are surprisingly dramatic differences in physiology between the sexes in certain areas,” said geneticist Aldons Lusis, Ph.D., of the University of California, Los Angeles. He was one of several experts who expressed their views to *Endocrine News* on this topic.

**Sex Hormones’ Role in Gene Expression**

A few years ago, Dr. Lusis and his colleagues used microarray technology and mice to reveal sex differences in the expression of thousands of genes in liver, fat, and muscle tissues. In all these, more than half of the active genes were expressed to a different degree in male- versus female-derived samples. Strikingly, many of these differentially expressed genes had no obvious connection to X or Y chromosomes. This led Dr. Lusis to suspect that sex hormones were behind the differences.

He and his colleagues have now confirmed this suspicion in a study to be published in the March 2009 issue of *Endocrinology*. Researchers compared gene expres-
Molecular pathways that diverge by sex aren’t unique to neurons, but occur in many other cell types and tissues and appear to determine major responses in the body, such as the immune response to injury or infection. Both sexes produce the dozen-plus different T cell types and linked cytokines and regulators, but mounting evidence suggests that females lean more heavily on the antibody-laden Th2 immune response, whereas males tend toward a mostly cell-mediated Th1 response that fosters inflammation.

Sex Hormones Affect Immune Response

The opposite effects of estrogens and androgens, which can directly latch on to hormone receptors of immune cells, explain much of this divergent immune response, as revealed by both in vitro and in vivo studies. The balance of these hormones might elucidate why women are more susceptible to autoantibody-mediated disorders such as rheumatoid arthritis and lupus, postulated immunologist DeLisa Fairweather, Ph.D., of the Johns Hopkins Medical Institutions in Baltimore. In a recent review article in the American Journal of Pathology, she noted that one study found that free estrogen levels in the synovial fluid of men with rheumatoid arthritis were twice those of men without the condition, and on par with those of women with rheumatoid arthritis.

But the influence of sex hormones on the immune system isn’t all bad news for women. The pro-inflammation Th1 response in males tends to foster atherosclerosis and may explain, in part, why premenopausal women are protected to a large degree from coronary artery disease, suggested Doris Taylor, Ph.D., director of the University of Minnesota’s Center for Cardiac Repair in Minneapolis. To assess the role that male or female immune cells have in fostering heart disease, Dr. Taylor and her colleagues injected atherosclerosis-prone male mice with bone marrow cells from females. After eating a high-fat diet for several months, these males had significantly less plaque on their heart arteries than either control males or males that received bone marrow cells from other males. The males with the female bone marrow also showed a heightened Th2 immune response, which tends to suppress inflammation. These recent findings reinforce the notion that what is good for the goose may not be good for the gander, and that sex differences are far more omnipresent in the body than originally thought. “You have to look before you can say there are no sex differences in basic processes,” said Dr. McCullough. “No one really looked for these sex differences before. But now that we’re looking, we’re seeing them.”

References