

STATE YOUR PURPOSE

TO INVESTIGATE THE ORIGINS OF HEALTH AND DISEASE

EARLY IMPACTS

NEUROSCIENTISTS DISCOVER THE ORIGINS OF WELL-BEING IN THE FIRST YEARS OF LIFE

By Rhea Maze

Why do more women suffer from depression, the leading cause of disability in the world, while more men suffer from cardiovascular disease, the No. 1 cause of death globally for both sexes?

Robert Handa, a Colorado State University biomedical sciences professor, and Stuart Tobet, a biomedical sciences professor and director of CSU's School of Biomedical Engineering, are longtime collaborators with joint research interests in sex differences and the co-occurrence of conditions such as depression and cardiovascular disease.

"Part of that is looking at development, and the other part is looking at particular places in the brain," Tobet said. "And the tie that binds it all together is that what might happen during prenatal development may have a long-term impact on an individual's health and well-being."

FROM PREGNANCY THROUGH ADULTHOOD

More than a decade ago, Handa and Tobet began collaborating with Jill Goldstein, a professor of psychiatry and medicine at



Harvard Medical School and director of research at the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital. The three researchers connected over their shared interest in sex differences in the development of the brain and how disruptions in fetal and early development can set the stage for psychiatric and medical disorders later in life.

For more than 20 years, Goldstein has followed a unique cohort of individuals from the historic New England Family Study, formerly known as the National Collaborative Perinatal Project that began in 1959 with the enrollment of approximately 60,000 pregnant women. A wealth of information about each mother's health and pregnancy, including blood and placental samples, was collected and stored, and their children were closely followed until age 7.

Goldstein and her team re-recruited offspring from this study over the past two decades to conduct ongoing work with them, including brain imaging, as they move through their 50s. This provided the team with a valuable opportunity to investigate the early origins of why men and women are at different risks for disorders of the brain, and how problems during prenatal development and childhood may contribute to brain abnormalities in adulthood and the development of these disorders across the lifespan.

A DREAM TEAM

"Handa and Tobet are two of the leading experts in the world on the sexual differentiation of the brain," Goldstein said. "They've taught

me a great deal about the specific mechanisms of how hormones and genes regulate brain development and how these early exposures can have lasting effects on sex differences in the brain throughout life. Seeing how their work in animal models translates to the human brain and vice versa informs and stimulates the work that my team does at the clinical level. One of the first things we studied together was the fetal programming of sex differences in depression-like behaviors in animal models, which led to some really interesting findings about how the brain talks to the heart."

A key value of the team is that Handa and Tobet can use results from Goldstein's human studies to guide experiments in animal models and test mechanisms that may cause potential disorders. The team found that prenatal exposure to glucocorticoids (hormones secreted by the adrenal gland in response to stress and controlled by the brain) and inflammation can set the stage for things to go awry in adulthood. "One of the most common symptoms in neuropsychiatric disorders, particularly major depressive disorder, is problems with the stress response," Handa said.

Their models showed that exposure to glucocorticoids in mid-to-late gestation can result in changes in cardiovascular and brain function in adulthood. In their studies on prenatal stress, they

discovered that some of the same brain regions that regulate mood also regulate the heart. Their ongoing collaborative efforts include trying to identify specific processes in fetal development that contribute to the co-occurrence of depression-like behaviors and cardiovascular disease risk in animal models.

THE FUTURE OF HEALTH CARE

"We know that a pregnant woman's health and nutrition influences a lot of what happens to her child in adulthood," Handa said.

The team hopes their research will help lead to the development of better strategies for prenatal care and counseling and identifying people who might be at greater risk for disorders, as well as treating patients with various disorders and advancing the emerging field of precision medicine, a model of customized health care tailored to suit a patient's unique needs.

"In this day and age of precision medicine, incorporating the impact of sex differences in medicine is absolutely critical," Goldstein said. "Taking the lifespan perspective of looking at how development may have lifelong consequences is a very optimistic approach to thinking about intervention – because the earlier we can intervene with people who are high risk, the more likely we are to be successful." ■

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