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## Unlocking the Mind's Mysteries

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# UNLOCKING THE MIND'S MYSTERIES

Dr. Tracy Bale sheds light on how sex differences and stress influence the brain

BY KATHERINE UNGER BAILLIE

THE BRAIN IS A CURIOUS THING. EMINENTLY MALLEABLE, IT ALSO APPEARS CAPABLE OF BEING PROGRAMMED WITH CERTAIN APTITUDES AND LIMITATIONS, EVEN BEFORE BIRTH.

For Dr. Tracy Bale, Professor of Neuroscience at Penn Vet, the brain has long been an intriguing source of mystery. Her curiosity about this complex organ led her to pursue a career focused on how differences in sex and environment can influence its development.

Her work exemplifies a translational approach to research and underscores the importance of the One Health initiative, connecting human and veterinary medicine. By forming partnerships with clinicians in human medicine, she has broken new ground in understanding how the interplay among heritable traits, life experience, and sex may hold clues as to why and how certain neurological conditions—including autism, schizophrenia, and depression—affect men and women differently.

## WIRED FOR SCIENCE

“As far back as I can remember, I have been drawn to science,” Bale says. “I remember in 10th grade biology, we had to dissect a fetal pig. Most of my friends

thought it was disgusting. I loved every aspect of it.”

Though Bale long felt a natural pull toward science and majored in biology in college, it was during a stint in a government lab after her undergraduate years that she became certain of her career path.

“That was really where I decided I loved research,” she says. “The idea of, ‘Here’s this mystery: What does it mean? How would you solve it? How would you ask the questions? What do the results mean?’” She recalls her advisor at the time telling her, “You need to go to graduate school.”

At the University of Washington, Bale earned her PhD in pharmacology and neurobiology. She wrote her dissertation on oxytocin—the “feel-good hormone”—in rats, investigating how levels of its receptor are regulated differently in males and females and how that expression may relate to sexual behaviors and anxiety.

When she began her graduate work in 1993, her pairing of molecular biology and behavioral studies was somewhat unusual—a



coupling that persists in her lab today. Bale regales students about how she had to log long hours watching female rats strike reproductive postures and performing her own DNA sequencing.

“This was before universities had sequencing cores where the sequencing work is done for you,” she says. “I tell them how I had to pour my own huge gels and sit in a darkroom and go ‘A, T, G...’ and they’re like, ‘No way!’”

After finishing at UW, Bale moved to San Diego to pursue a postdoctoral position at the Salk Institute. She worked under pioneering endocrinologist Dr. Wylie Vale, who focused on how hormones acted in the brain to modulate the body’s responses to stress.

“I brought the sex differences thinking to that project,” Bale says. “To me it seemed the best of all worlds to think about sex differences in the brain and how that manifests into sex biases in diseases like autism, schizophrenia, and depression, which all have huge gender differences in presentation.”

After her postdoc, she briefly considered a career in the pharmaceutical industry. “But I realized that was not for me,” she says. “I really like big-picture, programmatic thinking and giving science a creative spin.”

Instead, Bale joined the Penn faculty in 2003, where, she says, “no two minutes are the same.”

## NEUROSCIENCE PIONEER

In recent years, Bale’s research has examined how events prior to birth—prior even to conception—can shape how the brain develops and how those developments can differ between males and females.

A sprinkling of human studies had hinted that prenatal stress may affect the unborn child—for example, raising the risk of developing schizophrenia. Bale and her colleagues’ work confirmed this in mice, showing that female mice exposed to stress early in their pregnancy had sons with heightened reactions to stress. Remarkably, this result passed on to the subsequent generation: those females’ grandsons also had abnormal stress reactions. Similar responses were seen in the offspring of fathers exposed to stress.

Bale’s search for a mechanism to explain these effects has ushered her into the field of epigenetics, which encompasses how gene expression is regulated by forces outside of the DNA sequence.

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Bale admits to still feeling the challenge of balancing work and family with her now 15-year-old son. But, as she's seen in her work, sometimes exposure to a little bit of stress can build resiliency.

"I remember reading a *Science* article by Dr. Huda Zoghbi [of Baylor University] about Rett syndrome and regulation of a stress hormone by this protein MECP2," she says. "That was back when we had started doing this model of maternal stress and were thinking about how this information is being passed on to the next generation. To me, it was a light-bulb moment."

Since then, Bale and her lab have found a variety of epigenetic markers that arise in both males and females, persisting through generations to influence brain development and behaviors. In addition to looking for markers in sperm and eggs, Bale's team has also examined how the bacterial population of a mother's vagina is passed to a newborn during birth, finding that prenatal stress causes changes in the makeup of the vaginal microbiome that correlate to changes in the developing brains of offspring. Another line of work has identified a protein in the placenta that serves as a biomarker of maternal stress. Levels of this protein differ between male and female placentas, offering a possible explanation for sex differences in stress reactivity in the offspring of stressed females.

Bale's rigorous research has generated some 75 original and review publications, many in top-tier journals. She leads a bustling lab of postdoctoral fellows, graduate students, lab technicians, and research assistants. Her leadership and scientific breakthroughs have garnered her awards from the Society for Women's Health Research, the Endocrine Society, the Society of Biological Psychiatry, and the Society for Neuroscience.

### ONE HEALTH IN ACTION

Bale has joined forces with Dr. C. Neill Epperson, Professor of Psychiatry and Obstetrics/Gynecology at Penn's Perelman School of Medicine, to examine how these effects might manifest themselves in human patients, studying a population of women who have experienced early-life trauma. Bale and Epperson also work together as co-leaders of Penn's Center for the Study of Sex and Gender in Behavioral Health, which was established in 2012 with support from the National Institutes of Health.

"A lot of what this program has done is help us go back and forth from bench to

bedside and back again," Bale says. "Neill will observe something in the clinic and I can help find a way to understand the mechanism behind it."

The Center is part of a rising tide of awareness that sex differences should be explored and accounted for in all aspects of biological research. Bale and Epperson hope to expand the Center on campus, perhaps to the level of an institute, to fold in experts from across Penn, including from the Law School, Wharton, and the School of Arts & Sciences.

### LEADING SCIENTIST, COOL MOM

It is not lost on Bale that a central component of her research—the biological reality of differences between the sexes—also finds application in the workplace. Though she says her career has been largely free of overt bias against women, she has found herself in uncomfortably male-dominated environments, and felt pressure to return to work more quickly than she wanted to after giving birth to her son during her postdoctoral years. She's worked hard to ensure the students and trainees in her lab feel able and supported to pursue both a family and a career in science.

"When my postdoc told me she was pregnant, I let her come up with a plan that made sense to her," says Bale. "I know she's a hard worker and I know she wants to make this work. I think if you want to keep excellent women in science, you have to be accommodating."

As for Bale, she admits to still feeling the challenge of balancing work and family with her now 15-year-old son. But, as she's seen in her work, sometimes exposure to a little bit of stress can build resiliency. And now he's old enough to appreciate the fascinating work his mother has accomplished.

"I was practicing for a talk I was giving to a lay audience the other night with my son," Bale says. "So I was going through some of the slides about a mark on the sperm of stressed males being passed on to their sons. He was like, 'But they knew about that before, right?' And I told him, 'No, no one's ever shown that,' and he was like, 'Mom, that is so cool!'"