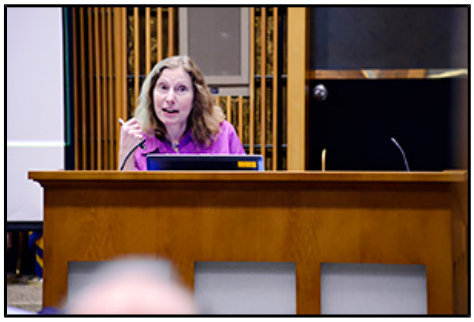
Researcher explores neurobehavioral effects of endocrine disruption

By Simone Otto

Grantee Andrea Gore, Ph.D., energized her audience Jan. 30 at NIEHS with her talk on "Environmental Endocrine Disruption of the Brain: Past, Present, and Future." Gore, *(http://www.utexas.edu/pharmacy/divisions/pharmtox/faculty/gore.html)* a professor at the University of Texas in Austin, has been a moving force in the Society of Endocrinology for many years as well as editor in chief of the journal Endocrinology.



For Gore NIEHS, the third time was the charm. Her two previously scheduled visits were cancelled — in October 2013 by the government shutdown and in February 2014 by snow. (Photo courtesy of Steve McCaw)

"We are really excited to have Andrea here both because of her personal science in the lab, and to acknowledge and thank her for all the work she's done in the field of endocrine disruption that has been very important to help NIEHS with our mission," said Jerry Heindel, Ph.D., program administrator in the extramural division at NIEHS, when introducing Gore.

A long time NIEHS grantee, Gore has collaborated on Endocrine Society-sponsored review articles and conferences on endocrine disruptors. Members of the society have also visited NIEHS this year to discuss collaborations.

"We have contaminated our world and we cannot undo it," Gore said at the beginning of her presentation. "We really need to understand what we've done to try to figure out what the health consequences are and to see whether we can fix some of those problems."

Gene expression and changes in the brain

Like other researchers in the field, Gore's experiments with endocrine disruptors, such as Aroclor 1221 (see text box), turned up reproductive effects, such as timing of puberty. But Gore has taken her work a step further, to also explore nonreproductive sex-specific consequences of exposure in different areas of the brain.

Gore subdivided the hypothalamus, testing different regions for neuroendocrine alterations. One gene strongly affected was the estrogen receptor, a gene that according to Gore is disrupted in the hypothalamus at many different ages and also by many different endocrine disrupters.

Currently, Gore is looking for transgenerational effects on gene expression. Since the exposed F0 dam, the initial parent generation in a multigenerational reproduction study, is pregnant and the F1 embryo and F2 germ cells were also exposed to Aroclor 1221, Gore selected the F3 generation for her studies.

"I think the gene expression work is important because we start to identify targets or networks or pathways that we think are particularly perturbed," said Gore in her lecture.

Exploring sex-linked behaviors affected by endocrine disruption

Gore studied how prenatal exposure to endocrine disrupters affects social behavior. She focused on ultrasonic vocalizations and social novelty. For ultrasonic vocalizations, after 2 days of training rats were paired with a receptive partner across a screen. After the partner was taken away their vocalizations were recorded. The exposed group made a different pattern of calls than controls.

Social novelty was tested by time spent and type of behavior exhibited by rats with a new sexual partner versus a familiar one. While control males touched noses more often, males exposed to Aroclor 1221 touched noses less and spent less time with the novel mate than controls, females touched noses more frequently, showing sexually dimorphic changes.

Gore has also studied the mating preference of male and female rats in the F3 generation of rats exposed to another endocrine disruptor, vinclozilin. The F3 males go on to develop germline transmitted diseases, although at the time of testing they were healthy by all measures used.

Gore found that female rats of both the treatment and vehicle lineages preferred the control males over the males from a treatment background, showing both how profound and how subtle the effects of these chemicals can be even on subsequent generations without direct exposure.

(Simone Otto, Ph.D., is an Intramural Research Training Award fellow with the NIEHS Ion Channel Physiology Group.)

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Heindel oversees the NIEHS grant portfolio supporting Gore's work on endocrine disruption, including research that supports the Endocrine Society scientific statement on endocrine-disrupting chemicals, which she coauthored with several other grantees. (Photo courtesy of Steve McCaw)

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Among members of the audience with questions for Gore was NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D. Birnbaum's lab at NIEHS focuses on endocrine disruption by fire retardant chemicals. (Photo courtesy of Steve McCaw)

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NIEHS Deputy Scientific Director Bill Schrader, Ph.D., asked about experiments related to timing of exposure. "Have you ever given these compounds at a different time and shown that there is no effect because you have avoided that developmental window?" (Photo courtesy of Steve McCaw)

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Endocrinologist Janet Hall, M.D., who is involved in clinical research at NIEHS, asked about Gore's future plans to

examine interactions among different endocrine disruptors. “Moving into the mixture field is going to be harder than it ought to be,” Gore responded. (Photo courtesy of Steve McCaw)

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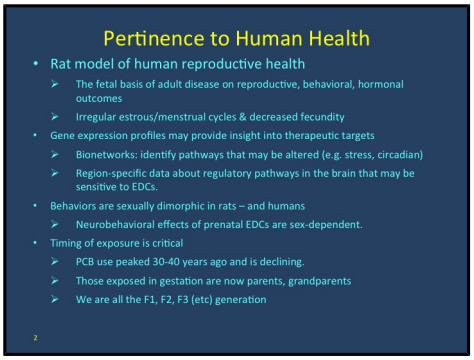
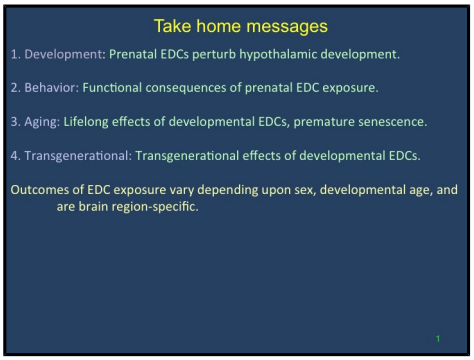
Interested scientists from across NIEHS research divisions included, from left, NTP alternative methods expert Warren Casey, Ph.D.; reproductive and developmental biologists Wendy Jefferson, Ph.D., and Retha Newbold; and grant program manager Cindy Lawler, Ph.D. (Photo courtesy of Steve McCaw)



(Photo courtesy of Andrea Gore)



(Photo courtesy of Andrea Gore)

Effects of endocrine disruption on gene and protein expression

Gore used as model pregnant Sprague Dawley rats exposed to vehicle, 3 percent dimethyl sulfoxide in oil; estradiol benzoate, a positive control; or Aroclor 1221, a mixture of polychlorinated biphenyls (PCBs), in 1 or 2 doses at the beginning of the third trimester of pregnancy on day 16 and day 18. PCBs are endocrine disrupters, and endocrine disrupters are defined by the Endocrine Society as an exogenous, or nonnatural, chemical or mixture of chemicals that interferes with any aspect of hormone action. Male and female pups were studied to determine the sexually dimorphic effects of this prenatal exposure.

Gore measured expression of 48 genes in various brain regions and ages. Her work revealed that female genetic expression patterns were masculinized after exposure. Protein expression was altered to an even greater magnitude.

"I think that epidemiological studies in the last few years have come a very long way in contributing to our understanding of relationships or correlations," Gore said of her new research directions. "Therefore, animal models such as ours are critical for directly testing the cause-and-effect relationships between early life exposures and the manifestation of a dysfunction. Since the hormones and brain pathways that we study in rats are highly conserved with humans, as well as other mammals, we believe that our results will help identify targets for possible interventions."

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, Office of Communications and Public Liaison. We welcome your comments and suggestions. *(bruskec@niehs.nih.gov)*

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