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NEWS RELEASE

Environmental toxins poisoning epigenetic inheritance

Depiction of epigenetics and environmental toxicant exposure

In a study that signals potential reproductive and health complications in humans, now and for future generations, researchers from McGill University, the University of Pretoria and Université Laval have concluded that toxins in the environment, notably DDT, modify the sperm epigenome at sites potentially transmitted to the embryo at conception.

The study reveals that fathers exposed to DDT- may produce sperm that could have health consequences for their children. Epigenetic changes were found to occur at genes that are involved in fertility, embryo development, neurodevelopment and hormone regulation. These alterations correspond to the higher levels of birth defects and increased incidence of diseases, including neurodevelopmental and metabolic, that occur in DDT-exposed populations, including in Canada's North.

While it is generally understood that women should avoid exposure to environmental contaminants because toxins make their way into the embryo, the research on how a father's exposure and his sperm might also be changed through the epigenome has been scant, that is until the publication January 31 of *The Association*

between Long-Term DDT or DDE Exposures and an Altered Sperm Epigenome—a Cross-Sectional Study of Greenlandic Inuit and South African VhaVenda Men in the Journal Environmental Health Perspectives.

Nearly two decades ago, the first research study using a rodent model, showed that exposures to a toxicant endocrine-disrupting chemical altered the heritable layer of biochemical information in the sperm, the epigenome. This changed fertility and led to disease across rodent generations in unexposed animals. In the years following, millions of dollars have been poured into animal studies to better understand how such exposures can transmit disease through the epigenome across generations. These studies confirmed the phenomena known as 'epigenetic inheritance,' whereby environmental exposures alter the sperm epigenome, a biochemical layer of information that controls how the DNA is used to express genes during sperm production and in the developing embryo. This epigenetic control of gene use includes DNA methylation and histone proteins. Whether such exposures act similarly in humans was unknown.

"We identified regions of the sperm epigenome that are associated with the serum levels of DDE (chemicals that form when DDT breaks down) and this association follows a dose-response trend and I think that's quite striking, in that the more DDE you're exposed to, the higher the chromatin, or DNA methylation defects are in the sperm," said Ariane Lismer, PhD, the study's lead author, who completed the work while pursuing her PhD at McGill's Department of Pharmacology and Therapeutics.

"Secondly, there was an enrichment of regions that were changed in sperm that are predicted to retain some of their chromatin marks in the pre-implantation embryo, and that led us to think that these regions might escape epigenetic reprogramming and have a direct role in regulating embryo gene expression. So, if they're altered in sperm and they're transmitted to the embryo, which is something that I've shown is possible in mice, the regions that are DDE-sensitive in sperm might be having an impact directly in the embryo," Lismer added.

"We demonstrate the sperm epigenome's response to toxin exposures may be linked with disease in the next generation," said Sarah Kimmins, PhD, who led the research as Professor of Pharmacology and Therapeutics at McGill and is also now a professor in the Department of Pathology and Cell Biology at Université de Montréal. "This is a critical new step for the field because while there are many studies of animals demonstrating toxin effects on the sperm epigenome, studies in humans have not comprehensively demonstrated this."

"Instinctively it's long been accepted that the environment is critical to child health and the well-being of the mother because she carries the baby and she lactates, et cetera," added study co-author, Janice Bailey, PhD, formerly Professor of Animal Sciences at Université Laval and now the Scientific Director at Fonds de Recherche du Québec en Nature et Technologies (FRQNT). "But fathers have been excluded from that equation. We tend to think all they have to do is fertilize. But in fact, we forget that half of that genome and epigenome comes from the fathers, and half of it comes from the mothers. What that epigenome does in embryo development is critical for normal development."

The decade-long research examined the impact of DDT on the sperm epigenome of South African Vhavenda and Greenlandic Inuit men. Despite the existence of the Stockholm Convention, a global treaty that aims to protect human health and the environment from the effects of persistent organic pollutants, the South African government has special permission to use DDT for malaria control. According to Tiaan de Jager, PhD, Dean of the Faculty of Health Sciences and Professor in Environmental Health at the School of Health Systems and Public Health at the University of Pretoria, "The use of DDT for indoor residual spraying for malaria vector control has been very controversial. Although most endemic provinces now use alternative chemicals, DDT is still used in some areas when needed."

These pollutants can move across vast distances from the southern hemisphere to the northern hemisphere by what is called the 'grasshopper effect.' This means they evaporate with warm air and return to Earth with

rain and snow in the colder areas of the globe where they persist in the Arctic food chain. With global warming, the exposure of human and animal populations to DDT is reportedly increasing.

“There really is a pressing need to find alternative ways to control for malaria and to put those in place, such as vaccines and alternative pesticides, because here we're showing the DDT is impacting not only the health of the exposed generation but potentially the next generation as well,” Kimmins noted.

South Africa is currently moving towards malaria elimination, by introducing alternative strategies. “I always say that while we, and other countries, are still dependent on the use of DDT, we should look at safer alternatives and be innovative in our approach to get to elimination,” de Jager said. “The reality is that people, especially young children and pregnant women, are still dying from malaria. We cannot afford for people in malaria-endemic regions to refuse spraying of their houses, as it will increase their risk of getting malaria.”

“The scary part is DDT is still there,” said Bailey. “It has this terrible effect. It could have long-lasting effects on human health and development, but then there's the other overall notion that irrespective of DDT, the environment itself affects both women and men.”

Although the study focuses on DDT exposures, Kimmins says it is not a leap to suggest that exposures to more common household endocrine disruptors such as those found in cosmetics and personal care items may act similarly.

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