

## New insight into how neonatal exposure to DES affects uterus function in mice

By Robin Mackar

NIEHS in-house researchers are well known for their work on diethylstilbestrol (DES). Continuing in that tradition, a new [study](http://www.ncbi.nlm.nih.gov/pubmed/24002655) (<http://www.ncbi.nlm.nih.gov/pubmed/24002655>) finds that mice exposed briefly to DES, a synthetic form of the female hormone estrogen, immediately after birth, had abnormal expression of the sine oculis homeobox 1 (Six1) gene in the uterus when they became adults.

The study, published in the October issue of *Molecular Endocrinology*, is the result of collaborative work between the Laboratory of Reproductive and Developmental Toxicology (LRDT) and the Laboratory of Molecular Carcinogenesis (LMC).

"DES exposure, just after birth, caused changes in specific epigenetic marks that regulate how genes are expressed in the uterus," said Carmen Williams, M.D., Ph.D., head of the LRDT [Reproductive Medicine Group](#) and lead researcher on the study. "Some of these epigenetic changes persisted long after exposure," Williams noted.

### Epigenetic changes

Epigenetic changes mean that the underlying DNA sequence remains normal, but gene expression has been modified. In this case, the epigenetic changes were observed in a gene called Six1. Very little is known about how Six1 is regulated. "In humans the Six1 gene is associated with several types of cancers, including breast and cervix cancers," said Wendy Jefferson, Ph.D., a biologist in the Reproductive Medicine Group and first author on the paper.

DES was found to change the specific histone modifications that are associated with Six1 gene-regulatory regions functioning in the adult uterus. The particular histone modification changes found are typical of genes that are actively generating proteins. Persistence of the epigenetic changes probably explains why the Six1 protein is abnormally expressed in the uterus of older adult mice, when it normally is not there.

"These findings suggest that epigenetic changes, induced by early life exposures to estrogenic compounds, may explain the long-term effects of this exposure on fertility and the later development of cancer," Williams said.

As a follow up to these animal studies, the researchers are collaborating with [Victoria Bae-Jump, M.D., Ph.D.](#), (<http://www.nccancerhospital.org/members/victoria-l.-bae-jump>) and her colleagues at the University of North Carolina at Chapel Hill Lineberger Comprehensive Cancer Center, to determine if Six1 expression is abnormal in the uterus of women with endometrial cancer.

DES was prescribed to millions of pregnant women between 1940 and 1971 to prevent miscarriage, premature deliveries, and other complications. Clinical studies found DES to be ineffective for these purposes and it is no longer prescribed. However, ongoing research by NIH and others continues to investigate the long-term health consequences associated with exposure to DES.

Citation: [Jefferson WN, Chevalier DM, Phelps JY, Cantor AM, Padilla-Banks E, Newbold RR, Archer TK, Kinyamu HK, Williams CJ.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24002655>)

2013. Persistently altered epigenetic marks in the mouse uterus after neonatal estrogen exposure. *Mol Endocrinol* 27(10):1666-1677.

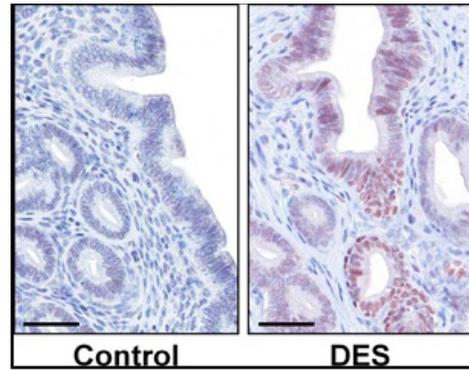
(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)



*Jefferson has been working with Retha Newbold, formerly with NIEHS, and others, to understand the effects of DES. She has authored many papers on the topic. (Photo courtesy of Steve McCaw)*



*Williams, who heads the Reproductive Medicine Group, uses her skill set as a physician-scientist to better understand the link between environmental exposures and reproductive health problems. Members of her group collaborated with scientists in the LMC Chromatin, Epigenetics, and Expression Group headed by lead researcher and LMC Chief Trevor Archer, Ph.D. (Photo courtesy of Steve McCaw)*



*This image from the journal clearly shows the expression of *Six1* (brown staining) in the uterine epithelial cells of adult mice that were treated for 5 days, after birth, with DES.*

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