

Prenatal exposure to diethylstilbestrol (DES)

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The scientific community now recognizes that exposure to certain environmental chemicals can adversely affect the developing organism, and subsequently result in a lifetime risk of chronic disease (the developmental basis of adult health and disease). Prenatal exposure to diethylstilbestrol (DES) was the first documented example where exposure of the fetus resulted in long-term changes in the offspring that were not apparent until much later in life, usually after the onset of puberty. Diethylstilbestrol was prescribed for pregnant women from the late 1940s to 1970s, with the mistaken belief that it would prevent miscarriage. Worldwide estimates suggest that 2 to 8 million pregnancies may have been treated with DES. Today, we know DES as a “transplacental carcinogen,” because it crossed the mother’s placenta and caused reproductive cancer in her offspring. Although the prevalence of neoplasia is estimated to be very low in the DES-exposed population (0.1%), numerous other abnormalities including subfertility/infertility have a high prevalence (>90%) and occur in both sons and daughters. Together, these reproductive tract abnormalities comprise “the DES syndrome” (1).

For over 3 decades, research from our lab and others using experimental animals have replicated the changes observed in DES-exposed humans. In some cases, experimental animals have predicted changes later found in DES-exposed humans such as oviductal malformations (2), and increased incidence of uterine fibroids (3–5). Molecular studies have shown that many of the DES-associated structural and cellular abnormalities are caused by altered programming of genes such as Hox and Wnt, which play important roles in reproductive tract differentiation (6–8).

Through the years, not only have we gained insights into the mechanisms involved in DES-associated abnormalities, but we have also learned that many problems incurred by DES-exposed men and women may be examples of developmental (prenatal/neonatal/early childhood) exposure to other environmental chemicals with endocrine-disrupting activity. Environmental “hormone mimics,” whether synthetic or naturally occurring, can disrupt developing organ systems and, like DES, cause abnormalities that may not be apparent until much later in life (9). In fact, developmental exposure to endocrine-disrupting chemicals has been proposed to be linked to endometriosis, fibroids, and breast cancer in women, poor

sperm quality and increased incidence of cryptorchidism in men, and subfertility/infertility in men and women. It is interesting to note that abnormalities characterizing the DES syndrome are similar to those described following exposure to other endocrine-disrupting chemicals (1).

Prenatal DES exposure is a continuing story, with indications that vaginal cancer continues to be found in daughters as they age. Further, second-generation effects are surfacing with reports of increased menstrual irregularities (10) and ovarian cancer (11) in DES granddaughters, and increased hypospadias in DES grandsons (12, 13). These trans-generational findings are consistent with changes previously reported in DES-exposed mice (14, 15). This has important implications because it suggests that maternal exposure to an endocrine-disrupting substance like DES, can directly alter the reproductive tract of the person exposed as a fetus, and also affect the health of another generation. Although we do not fully understand the mechanisms involved in the transmission of disease from one generation to another, it likely involves persistent epigenetic changes in some genes such that the fate of tissues or organs are altered. This is an important area of new investigation and critical research direction.

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