An organicist view of development and carcinogenesis: Endocrine Disruptors

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A massive introduction of man-made chemicals into the environment has taken place during the last 60 years. These chemicals were found to have hormonal activity a long time after their release into the environment. Later on, reproductive and endocrine effects were observed in wildlife species, suggesting a cause-effect relationship.

In 1991 the Wingspread Conference was held in Wisconsin to address these findings. The participants proposed that the developmental alterations observed in a diversity of wildlife species was due to exposure to multiple chemicals that, through different modes of action, disrupted the endocrine system of the developing organisms. They noticed that some of the effects observed in the genital tract of wildlife were comparable to those seen in the daughters and sons of women who had been exposed during pregnancy to the synthetic estrogen diethylstilbestrol (DES).

Contrary to the perception dominant among laboratory researchers of a rigid, genocentric "developmental program", field scientists were aware of the important role of the environment in embryogenesis. To the Wingspeard participants, the DES syndrome revealed the plasticity of the fetus. They also observed that, in addition to banned chemicals such as DDT and PCBs, other sources of endocrine disruptors were being introduced into the environment and human food. The anti-oxidant nonylphenol, which had just been shown to leach from laboratory plastic ware, was one such example and headed a growing list of chemicals that were identified subsequently as being endocrine disruptors. Plasticizers, disinfectants, sunscreens and newly introduced pesticides were added to the list. The participants of the Wingspread Conference concluded that the developmental abnormalities observed predominantly in birds might indicate what was happening in mammals, including humans.

One year later, a meta-analysis concluded that the quantity and quality of human sperm had decreased during the last half-century, coincidental with the introduction of chemicals into the environment. Further, a variety of reports were attesting to the increased incidence of male genital tract defects, such as cryptorchidism, hypospadias and testicular cancer. It was postulated that these diverse outcomes might be the result of extemporaneous exposure to man-made estrogens during fetal development.

The DES syndrome was described at a time when the *Zeitgeist* was that the development of the genital tract in mammals is genetically determined, albeit indirectly, through the differentiation of the primitive gonad into ovaries or testes. It was believed that systemic estrogens were irrelevant because they are bound by plasma α-fetoprotein, thus limiting their influence on the developing fetus. The realization that estrogen levels within a physiological range affect development materialized from a series of experiments dealing with hormonal influences on behavior. It was found that the adult behavior of rodents was influenced by the position of the fetus in the mother's uterus. These effects were related to the differences in free estrogen levels

in the fetus, which were higher in animals placed between two females and lower in animals placed between two males.

Most of the work done to explore whether environmental endocrine disruptors were the causal agents of the increase of genital tract malformations and hormone-related cancers used bisphenol-A (BPA) as a model agent. BPA is a monomer used in the manufacture of polycarbonate plastics and epoxy resins from which food and beverage containers and dental materials are made. BPA has been shown to leach from these materials under normal conditions of use.
Exposure to environmentally relevant doses of BPA during fetal life results in morphological and functional alterations of the male and female genital tract and mammary glands in fetuses. In male mice, BPA exposure results in increased body weight, decreased sperm production, and an enlarged prostate associated with alterations in histoarchitecture and increased expression of stromal androgen receptor. In female mice, BPA exposure results in increased body weight, advanced puberty, altered estrous cyclicity, and early reproductive aging. The mammary glands of these mice are also affected as evidenced by alterations in DNA synthesis within their epithelium and stroma, the migration pattern of the ductal tree into the stroma at puberty, and an increased presence of the epithelial structures where cancer arises. In addition, perinatal exposure to BPA increases the sensitivity of the mammary gland to estrogens. This is particularly worrisome, since exposure to ovarian estrogens is considered the main risk factor for breast cancer. These effects of *in utero* exposure to BPA on the development of the male and female genital tract and mammary glands in adulthood are consistent with the notion that prenatal exposure to estrogens may predispose the tissue to earlier onset of disease, reduced fertility and mammary and prostate cancer.

In summary, exposure to environmentally-relevant doses of the xenoestrogen BPA during morphogenesis of estrogen-target tissues and organs results in changes that become fully manifested during adult life. The observed organizational and functional changes provide important pieces of evidence to the understanding of how exposure to endocrine disruptors affects male and female reproduction in mammals. This ongoing research has both practical and theoretical implications. The former is the realization that wildlife and humans are affected by environmental exposure to endocrine disruptors at levels previously considered to be irrelevant. The latter is that the prevalent view that development is the unfolding of a genetically determined program is incorrect. Developmental biology now has the tools to successfully revisit the old tradition of ecological regulation of development. The emerging field of endocrine disruptors promises to provide new insights into the mechanisms underlying the development of hormone-target organs.