Research Summary

Developmental Exposure to the Soy Phytoestrogen, Genistein

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Developmental abnormalities and reproductive tract dysfunction and disease are significant public health concerns, especially with incidences of birth defects, early fetal loss, precocious puberty, early reproductive senescence, subfertility/infertility, and cancers reported to be on the increase. Taken together, these trends have a serious economic and emotional impact on our society. The causes of many of these varied clinical problems are unknown, however, they may have a common basis originating early in development. In fact, the idea of "the fetal basis of adult disease" is quickly gaining scientific attention.

The long-standing research focus of our lab has been to study mechanisms involved in normal and abnormal reproductive tract differentiation and development. The contribution of environmental factors in abnormal developmental and long-term consequences has been of particular interest. A growing area of scientific knowledge suggests that a broad range of chemicals in our environment, including synthetic and naturally occurring substances, may be producing a wide range of adverse effects across species including humans, by disrupting the normal function of the endocrine system (1-5). Initial concern focused only on chemicals with estrogenic activity, but attention broadened to include all chemicals that exert their effects by mimicking or interfering with the normal actions of any endocrine hormone; these chemicals are collectively referred to as "endocrine disrupters". With over 80,000 chemicals reported by the National Toxicology Program (NTP) to be in commercial use today, and few tested for endocrine disrupting activity, much interest has been generated in determining potential adverse effects that may be associated with their exposure. Since many of these chemicals, which are known to bio-accumulate, are used in a variety of industrial and consumer products, widespread environmental contamination is indeed a possibility. Although it is often assumed that few of these chemicals are likely to pose a significant health risk at the exposure levels that exist, in reality, the full extent of the health consequences of most of these chemicals is unknown. For this reason, it is imperative to identify chemicals with potential endocrine disrupting activity, and further, determine if exposure at environmentally relevant levels constitutes a human or ecological health risk. Our studies specifically focus on effects of estrogenic chemicals and are designed to help address these public health concerns. Further, our studies and research approach are aimed at providing an increased basic understanding of the role of estrogens in normal and abnormal reproductive tract development and differentiation.

While the extent of risks from endocrine disrupter exposure continues to be debated, ample evidence exists in multiple species, including mice and humans, to link developmental exposure to the synthetic estrogen diethylstilbestrol (DES) to numerous detrimental effects. For example, poor reproductive outcomes, developmental abnormalities, and development of tumors later in

life have been reported in both males and females following exposure to DES during critical windows of differentiation [for review, (6)]. Using the DES-exposed mouse model that was developed and characterized in our laboratory, observations have been made (7-12) that when coupled with similar findings in DES-exposed humans (6) add to the substantial literature base documenting the potential adverse consequences of developmental exposure to environmental chemicals with estrogenic and/or endocrine disrupting activity. We continue to use DES as a prototype estrogen, because of its well-documented adverse effects, to study lesions that occur at low frequency and that may have an environmental estrogen component. Although DES is a potent estrogen, effects observed at low doses are guiding our investigation of potential adverse effects of weaker environmental estrogens. In support of NIEHS/NTP goals to provide toxicological evaluations on chemicals of public health interest, our studies are designed to identify early markers of estrogenic exposure that can be used to predict subsequent adverse effects. Comparison of a number of chemicals, over a wide dose range, using multiple early markers will provide mechanistic data essential in evaluating risks to endocrine disrupting substances. The effects reported in our experimental animal model may have widespread biological implications since many of the same hormonal mechanisms are present across species.

Recognizing that the developing organism is exquisitely sensitive to perturbation by chemicals with "hormone-like" activity, research in our lab is based on the central premise that exposure to endocrine disrupting chemicals at inappropriate times or amounts, during critical stages of genital tract differentiation, will permanently alter the developmental program of these tissues so that they respond atypically to further stimuli or cues. These developmental alterations may manifest later in life as structural, functional, or long-term pathological changes including neoplasia in both males and females.

Using our experimental animal model, we have investigated the potential adverse effects of the phytoestrogen genistein on development and differentiation. Our objectives are to study mechanisms involved in these effects, and to couple these data with early predictive markers so that genistein and other endocrine disrupting chemicals can be more accurately assessed for human health risks. Thus far, we have shown that developmental exposure to genistein causes abnormalities in differentiating tissues including ovaries, genital tract tissues and mammary glands; some of these alterations include neoplasia later in life. These data point to the adverse consequences of altering the hormonal milieu during development.

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