NIH Research on the Health Effects of Diethylstilbestrol

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Introduction

The effects of diethylstilbestrol (DES) on the health of women and their offspring have long been a research focus at the National Institutes of Health (NIH). This report is an overview of NIH research related to DES that is primarily conducted or supported by the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS). The Office of Research on Women's Health (ORWH) appreciates the assistance of the NCI and NIEHS in the preparation of this report.

Summaries of DES research funded by NCI and NIEHS for FY2010 are included in this report, which will be posted on the ORWH website at http://orwh.od.nih.gov/.

Background

Diethylstilbestrol, a potent synthetic estrogen first synthesized in 1938, was extensively prescribed world-wide to pregnant women from the 1940s-1970s with the mistaken belief that it could prevent miscarriages and other complications of pregnancy. It was initially given to women with at-risk pregnancies, but ultimately it was also prescribed for normal pregnancies.

In 1971, Herbst[1] reported a strong association between DES use in pregnancy and the occurrence of vaginal clear cell adenocarcinoma (CCA) in a small number (<0.1%) of adolescent daughters of women who took it while pregnant. DES was later associated with frequent non-cancer reproductive problems in DES-exposed daughters; reproductive tract malformations and dysfunction, poor pregnancy outcome, ectopic pregnancies, and premature labor and births have been reported. As DES-daughters age, they may have an increased incidence of uterine fibroids, and may be more susceptible to breast cancer than their unexposed, age-matched counterparts. DES-exposed daughters >40 years of age, exhibit a statistically significant increased risk of developing breast cancer; this risk is even more pronounced in DES-women over 50 years of age, though the small sample size at this age limits statistical significance. DES-exposed mothers also are at increased risk for breast cancer.

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[1] Herbst, AL, Ulfelder H, Poskanzer, DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 284(15):878-81; 1971. [Abstract] (http://www.nejm.org/doi/full/10.1056/NEJM197104222841604)

Prenatally DES-exposed sons have a range of reproductive tract problems including malformations (hypospadias, microphallus, and retained testes) and increased genital/urinary inflammation. Animal models initially developed at NIEHS[2] have demonstrated a range of DES effects in offspring exposed in utero, including reproductive dysfunction, immune system changes, behavioral and sexual abnormalities, and increases in various reproductive and breast cancers. Multigenerational adverse effects have also been observed in prenatally DES exposed animals.

Current NIH research on DES is primarily funded by the NCI and the NIEHS, through both intramural and extramural programs. Specific details about FY 2010 DES research conducted at NIH are available at the following website: http://report.nih.gov/rcdc/categories/ProjectSearch.aspx?FY=2010&ARRA=N&DCat=Diethylstilbestrol (DES). Additional information about NIH-funded projects is available online at http://projectreporter.nih.gov/reporter.cfm.

DES Research at NCI

NCI leads the National Cancer Program and the NIH effort to dramatically reduce the burden of cancer and improve the lives of cancer patients and their families, through research into prevention and cancer biology, the development of new interventions, and the training and mentoring of new researchers.

1. The Division of Cancer Epidemiology and Genetics, part of the NCI Intramural Research Program, conducted "Continuation Of Follow-Up Of Des-Exposed Cohort," in collaboration with five field centers. The project reassembled previously studied cohorts of DES-exposed and unexposed mothers, daughters and sons, and identified subjects with documented exposure status who had not been studied previously, through familial links within the cohorts. Standardized baseline questionnaires were mailed to cohort members to ascertain the risk of cancer and other

[2] Newbold, RR. Lessons learned from perinatal exposure to diethylstilbestrol. Tox. Applied Pharm 199; 142-150; 2004.

disorders. Pathology reports were collected for reported cancers and preneoplastic conditions. Four separate phases of follow-up have been conducted. The purpose of this study is to continue the follow-up through mailed questionnaires and medical record collection, which was begun during the first phase of the study. DES-exposed daughters may be at higher risk of breast, endometrial, and ovarian cancers. DES is a potent estrogen and exposure to high levels of endogenous estrogen in utero is hypothesized to increase the risk of these cancers. Cancer risk in DES-exposed sons will also continue to be assessed, especially for increased risks of prostate cancer. As the offspring who were exposed to DES in utero are currently reaching their late forties, when cancer rates begin to rise, it is important to continue the follow-up of these cohorts to determine if there are long-term increases in cancer risk.

To date the study has identified excess female breast cancer after age 40 that shows a dose-response effect, as well as increased risk for high-grade lesions of the cervix and vagina. The concern over other hormone-related cancers has not been addressed due to small numbers of cases. In the sons, investigators observed excess risk for urogenital anomalies and infertility, and likely excess of testicular cancer.

To examine the effects in the third generation (offspring of women exposed in utero to DES), investigators assembled a small cohort of granddaughters in 2000. Given their average age, there have been few relevant health outcomes. However, investigators did find an elevated risk for infertility. Though not statistically significant, this outcome was also seen in DES-daughters. In addition, there were three cases of ovarian cancer in the granddaughters, with substantially less than one expected. While both of these observations remain difficult to interpret, they have added some urgency to expand the cohort and continue to follow-up.

A list of Principal Investigators and organizations where the study is being conducted is below:

- Robert Hoover, Divison of Cancer Epidemiology and Genetics, NCI
- Arthur Herbst, University of Chicago
- Julie Palmer, Boston University Medical Campus
- William Strohsnitter, Tufts Medical Center
- Linda Titus-Ernstoff, Dartmouth College

More information on the DES Follow-up Study:

- DES Follow-up Study Homepage: http://www.desfollowupstudy.org/index.asp
- DES Follow-up Study Newsletter: http://www.desfollowupstudy.org/2010_Newsletter.pdf
- DES Follow-up Study: http://www.cancer.gov/clinicaltrials/search/view?cdrid=636988&version=HealthProfessional&protocolsearchid=9378810

2. NCI's Division of Cancer Epidemiology and Genetics also supports another project, "Early Life Exposures and Subsequent Cancer Risk," conducted by principal investigator Robert Hoover. The purpose of this study is to continue the diethylstilbestrol (DES) follow-up, by means of mailed questionnaires and medical record collection. Concern has arisen that DES-exposed daughters may be at higher risk of breast, endometrial and ovarian cancers. Exposure to high levels of endogenous estrogen in utero has been hypothesized to increase the risk of these cancers and DES is a potent estrogen. Cancer risk in the sons will also continue to be assessed, especially for increased risks of prostate cancer. Since the offspring who were exposed to DES in utero are currently reaching their late forties, when cancer rates begin to rise, it is important to continue the follow-up of these cohorts to determine if there are long-term increases in cancer risk. The project is also examining other pregnancy conditions associated with altered hormonal environments to help inform studies of risks associated with DES exposure.

- Maternal and cord blood samples from monochorionic twin, dichorionic twin and singleton pregnancies of similar gestational age will be collected to quantify differences in concentrations of several hormones and other pregnancy products including estriol, estradiol, estrone, testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA-sulfate, progesterone, AFP, prolactin, IGF and IGF-binding protein. Data from medical records and pathology reports will be abstracted to provide information on the mother, baby, pregnancy and placenta.
- In collaboration with NICHD on a study of preeclampsia conducted at Louisiana State University Health Sciences Center, blood samples are being collected from mothers and from umbilical cords with and without preeclampsia. The relationship of pregnancy hormone levels and preeclampsia will be analyzed.
- In this study using data from a cohort study of preeclamptic and uncomplicated pregnancies at the University of Pittsburgh, the investigators are analyzing maternal and

cord blood samples from preeclamptic and normal pregnancies of similar gestational age to quantify differences in levels of various hormones. The investigators will evaluate associations of several maternal, perinatal and pregnancy factors, such as maternal age and birth weight, with hormone levels in normal pregnancies. In addition, the investigators will determine how well maternal levels represent levels in cord blood.

- Umbilical cord blood samples were collected from 75 pregnancies in Boston, MA and 175 in Shanghai, China. Pregnancy hormone concentrations will be determined and correlated with putative breast cancer risk factors.
- The Norwegian birth and cancer registries will be used to investigate the association of several pregnancy and perinatal factors and risk of cancer in adult offspring.

Online Resources from NCI

NCI hosts two Web sites with consumer-oriented information about DES.

First, NCI's factsheet on DES (below) answers 12 frequently asked questions and answers about the drug, including descriptions of the possible health effects of DES, summaries of current research on DES and resources for DES-exposed individuals.

The factsheet is available online at http://www.cancer.gov/cancertopics/factsheet/Risk/DES

NCI's Web page also contains information about behaviors, exposures, and other factors that can influence the risk of cancer, including hormones such as DES. NCI's cancer topics Web page for DES contains several links to pertinent information on DES from resources around NIH and other HHS operating divisions. It is available online at http://www.cancer.gov/cancertopics/causes/des

Scientific Articles from NCI

The NCI's Division of Cancer Epidemiology and Genetics, along with its collaborators, has published DES findings in peer-reviewed journal articles referenced below.

2010

1. Palmer, J.R., Herbst, A.L., Noller, K.L., Boggs, D.A., Troisi, R., Titus-Ernstoff, L., Hatch, E.E., Wise, L.A., Strohsnitter, W.C., Hoover, R.N. Urogenital Abnormalities in Men Exposed to Diethylstilbestrol in Utero. Environ Health 2009;8:37.

2. Hatch, E.E., Troisi, R., Wise, L.A., Titus-Ernstoff, L., Hyer, M., Palmer, J.R., Strohsnitter, W.C., Robboy, S.J., Anderson, D., Kaufman, R., Adam, E., Hoover, R.N. Preterm Birth, fetal growth, and Age at Menarche among women exposed prenatally to diethylstilbestrol (DES). Reprod Toxicol 2010;31:151-7.

3. Strohsnitter, W.C., Noller, K.L., Troisi, R., Robboy, S.J., Hatch, E.E., Titus-Ernstoff, L., Kaufman, R.H., Palmer, J.R., Anderson, D., Hoover, R.N. Autoimmune disease incidence among women prenatally exposed to diethylstilbestrol. J Rheumatol. 2010;37:2167-73.

4. Titus-Ernstoff, L., Troisi, R., Hatch, E.E., Palmer, J.R., Hyer, M., Kaufman, R., Adam, E., Noller, K., Hoover, R.N. Birth defects in the sons and daughters of women who were exposed in utero to diethylstilbestrol (DES). Int J Androl. 2010;33:377-84.

2008

1. Camp EA, Coker AL, Troisi R, Robboy SJ, Noller KL, Goodman K, Titus-Ernstoff L, Hatch EE, Herbst AL, Kaufman RH, Adam E. Cervical Screening and General Physical Exam Behaviors of Women Exposed In-utero to Diethylstilbestrol. Journal of Lower Genital Tract Disease 2008;12:111-7.

2. Strohsnitter WC, Hatch EE, Hyer M, Troisi R, Kaufman RH, Robboy SJ, Palmer JR, Titus-Ernstoff L, Anderson D, Hoover RN, Noller KL. The association between in utero cigarette smoke exposure and age at menopause. Epidemiology 2008;167:727-733.

3. Titus-Ernstoff L, Troisi R, Hatch EE, Palmer J, Hyer M, Wise L, Kaufman R, Adam E, Strohsnitter W, Noller K, Herbst AL, Cole B, Gibson-Chambers J, Hartge P, Hoover RN. Cancer Occurrence in Offspring of Women Exposed *in utero* to Diethylstilbestrol (DES). Epidemiology 2008;19:251-257.

2009

1. Camp EA, Coker AL, Robboy SJ, Noller KL, Goodman KJ, Titus-Ernstoff L, Hatch EE, Herbst AL, Troisi R, Kaufman RH, Adam E. Breast cancer screening in women exposed in-utero to diethylstilbestrol. Breast Cancer Screening in Women Exposed *In Utero* to Diethylstilbestrol. Journal of Women's Health 2009;18:547-552.

2007

1. Troisi R, Hatch EE, Titus-Ernstoff L, Hyer M, Palmer J, Robboy S, Strohsnitter WC, Kaufman R, Herbst A, Hoover RN. Cancer Risk in Women Prenatally Exposed to Diethylstilbestrol. Int J Cancer 2007;121:356-60.

2. Wise L, Titus-Ernstoff L, Palmer JR, Hatch EE, Perez KM, Strohsnitter W, Kaufman R, Anderson D, Hoover RN, Troisi R. Time to pregnancy, offspring sex ratio, and other fertility outcomes in men exposed prenatally to Diethylstilbestrol (DES) Am J Epidemiol 2007;166:765-74.
3. Troisi R, Titus-Ernstoff L, Hyer M, Hatch E, Robboy S, Strohsnitter W, Palmer J, Øglænd B, Adam E, Kaufman R, Herbst AL, Hoover RN. Preeclampsia Risk in Women Exposed Prenatally to Diethylstilbestrol (DES). Obstet Gynecol 2007;110:113-20.

4. Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. Environ Health Perspect. 2007;115:1314-9.

2006

1. Hatch EE, Troisi R, Wise LA, Hyer M, Palmer JR, Titus-Ernstoff L, Strohsnitter W, Kaufman R, Adam E, Noller KL, Herbst AL, Robboy S, Hartge P, Hoover RN. Age at Natural Menopause in Women Exposed to Diethylstilbestrol in Utero. Am J Epidemiol 2006;164:682-688.

2. Troisi R, Hatch EE, Titus-Ernstoff L, Palmer JR, Hyer M, Strohsnitter W, Robboy SJ, Kaufman RH, Herbst AL, Adam E, Hoover RN. Birth Weight and Breast Cancer Risk in Women Exposed and Unexposed to DES *In Utero*. Br J Cancer 2006;94:1734-7.

3. Palmer JR, Wise LA, Hatch EE, Troisi R, Titus-Ernstoff L, Strohsnitter W, Kaufman R, Herbst AL, Noller KL, Hyer M, Hoover RN. Prenatal diethylstilbestrol exposure and risk of breast cancer. Cancer Epidemiol Biomarker Prev 2006;15:1509-14.

4. Titus-Ernstoff L, Troisi R, Hatch EE, Wise L, Palmer J, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Herbst AL, Gibson-Chambers J, Hartge P, Hoover RN. Menstrual and Reproductive Characteristics of Women whose Mothers were Exposed to DES *in utero*. Int J Epidemiol 2006;35:862-8.

5. Titus-Ernstoff L, Troisi R, Hatch EE, Palmer JR, Wise LA, Ricker W, Hyer M, Kaufman R, Noller K, Herbst AL, Hartge P, Hoover RN. Mortality in Women given Diethylstilbestrol (DES) During Pregnancy. Br J Cancer 2006;95:107-111.

6. Larson PS,Ungarelli RA, de Las Morenas A, Cupples LA, Rowlings K, Palmer JR, Rosenberg CL. In utero exposure to diethylstilbestrol (DES) does not increase genomic instability in normal or neoplastic breast epithelium. Cancer. 2006;107:2122-6.

2005

1. Wise LA, Palmer JR, Rowlings K, Kaufman RH, Herbst AL, Noller KL, Titus-Ernstoff L, Troisi R, Hatch EE, Robboy SJ. Risk of benign gynecologic tumors in relation to prenatal diethylstilbestrol exposure. Obstet Gynecol 2005;105:167-73.

2. Strohsnitter WC, Noller KL, Titus-Ernstoff L, Troisi R, Hatch EE, Poole C, Glynn R, Hsieh C-C. Breast cancer incidence in women prenatally exposed to maternal cigarette smoke. Epidemiology 2005;16:342-45.

3. Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. Fertil Steril 2005;84:1649-56.

4. Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. Epidemiology 2005;16:583-6.

2003

1. Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett K, Hoover R. Psychosexual characteristics of men and women exposed prenatally to Diethylstilbestrol. Epidemiology 2003; 14:155-60.

2002

1. Kaufman RH and Adam E. Findings in female offspring of women exposed in-utero to diethylstilbestrol. Obstet Gynecol 2002;99:197-200.

2. Palmer JR, Hatch EE, Rosenberg CL, Hartge P, Kaufman RH, Titus-Ernstoff L, Noller KL, Herbst AL, Rao RS, Troisi R, Colton T, Hoover RN. Risk of breast cancer in women exposed to diethylstilbestrol in utero: preliminary results (United States). Cancer Causes Control 2002;13:753-8.

2001

1. Palmer JR, Hatch EE, Rao RS, Kaufman RH, Herbst AL, Noller KL, Titus-Ernstoff L, Hoover RN. Infertility among Women Exposed Prenatally to Diethylstilbestrol. Am J Epidemiol 2001;154(4):316-321.

2. Strohsnitter WC, Noller KL, Hoover RN, Robboy SJ, Palmer JR, Titus-Ernstoff L, Kaufman RH, Adam E, Herbst AL, Hatch EE. Cancer risk in men exposed in utero to diethylstilbestrol. J Natl Cancer Inst 2001;93(7):545-51.

3. Titus-Ernstoff L, Hatch EE, Hoover RN, Palmer J, Greenberg ER, Ricker W, Kaufman R, Noller K, Herbst AL, Colton T, Hartge P. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. Brit J Cancer 2001;84(1):126-133.

4. Hatch EE, Herbst AL, Hoover RN, Noller KL, Adam E, Kaufman RH, Palmer JR, Titus-Ernstoff L, Hyer M, Hartge P, Robboy SJ. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States). Cancer Causes Control 2001;12:837-45.

2000

1. Hatch EE, Herbst AL, Hoover RN, Noller KL, Adam E, Kaufman RH, Palmer JR, Titus-Ernstoff L, Hyer M, Hartge P, Robboy SJ. Incidence of squamous neoplasia of the cervix and vagina in DES-exposed daughters. Ann Epidemiol 2000;10(7):467.

2. Kaufman RH, Adam E, Hatch EE, Noller K, Herbst AL, Palmer JR, Hoover RN. Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. Obstet Gynecol 2000;96(4):483-9.

1998

1. Hatch EE, Palmer JR, Titus-Ernstoff, Noller KL, Kaufman RH, Mittendorf R, Robboy SJ, Hyer M, Cowan CM, Adam E, Colton T, Hartge P, Hoover RN. Cancer risk in women exposed to diethylstilbestrol in utero. JAMA 1998;280(7):630-4.

DES Research at NIEHS

The NIEHS supports research to understand the effects of the environment on human health. The mission of NIEHS is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease. The NIEHS conducts DES research through its Intramural Division, and the Institute supports and funds meritorious DES research through its Division of Extramural Research and Training.

1. DES research through the NIEHS Intramural Division

DES has been the focus of experimental animal studies at NIEHS for more than 30 years. NIEHS researchers developed a rodent model of prenatal DES-exposure that proved useful in replicating and predicting adverse health effects in prenatally exposed men and women. This experimental model has been used world-wide to study mechanisms involved in DES-toxicities, and adverse effects of less potent environmental estrogens.

In addition, NIEHS Epidemiology Branch led the DES Study; a follow-up of the Dieckmann[3] randomized clinical trial of DES conducted in the early 1950s at the University of Chicago. A total of 848 boys and 805 girls were born to women in the Dieckmann study, half of whom were exposed to high levels of DES during pregnancy and the other half of whom received placebo.

When DES was identified in 1971 as a transplacental carcinogen (Herbst 1971), the University of Chicago attempted to trace the women who participated in the clinical trial, and also their offspring. The daughters and sons were studied for risk of cancer and abnormalities of the reproductive tract. While the daughters continued to be followed, no further contact with the sons was made until 1991, when the NIEHS follow-up study was initiated.

The NIEHS DES study was conducted to pursue hypotheses about possible non-cancer health effects of prenatal estrogen exposure in adults as suggested by laboratory animal studies or clinical reports. Such possible health effects include allergy, infection and autoimmune diseases, cognitive function, male fertility, menstrual cycle function, onset of menopause and age of menarche in the daughters of prenatally-exposed women. Given the estrogen-like activity of several classes of environmental contaminants, the identification of risk in this highly-exposed DES group could suggest more specific hypotheses for the study of the presumably-weaker effects of environmental estrogens. Allen Wilcox, the principal

[3] Dieckmann WJ, Davis ME, Rynkiewicz LM, Pottinger RE. Does the administration of diethylstilbestrol during pregnancy have therapeutic value? Am J Obstet Gynecol 1953;66:1062-81.

investigator for the study, and his group were able to trace and study 494 sons (253 exposed and 241 unexposed) and 542 daughters (296 exposed and 246 unexposed).

For more information on the NIEHS DES study, visit: http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/des/index.cfm.

1. The NIEHS Division of Extramural Research and Training supports and funds DES research projects at several institutions:

- The project "Nongenomic Signaling Mechanisms of Environmental Estrogens," is conducted by principal investigator Cheryl Watson at the University of Texas Medical Branch Galveston. In this study the investigators will address (1) the structural requirements for activating mERa to generate signals and their linked functions, by comparing the effects of alkylphenol xenoestrogens having varying carbon- chain lengths and structures, and prominent physiological estrogens (E2, estriol, and estrone); (2) active alkylphenols' ability of to act in combination with physiological estrogens via additive, synergistic, and antagonistic mechanisms; and (3) the G protein coupling of these responses. G proteins likely lie upstream of the signaling responses shown by previous work. The investigators seek direct evidence for G protein subtype interactions with mERa via co-immunoprecipitation, use of specific inhibitors, and dominant-negative G protein subtype and decoy interaction peptide approaches. Changes in G protein coupling in response to both physiological estrogens and alkylphenol xenoestrogens will be examined. The investigators' long-term objective is to use the established model system to answer a variety of detailed mechanistic questions about how specific structural features of different physiological estrogens and xenoestrogen subclasses affect actions through the nongenomic pathway and the mERa, and thereby disrupt endocrine processes. The significance of the proposal is to assist in knowing how environmental estrogens disrupt normal signaling and reproductive functions will enable design of new prevention and treatment strategies to deal with their toxicity. Demonstrating their low-dose effects will also guide re-evaluation of Federal regulations setting legal contamination limits for environmental estrogens. The extent and mechanisms by which

environmental estrogens contribute to diseases of estrogen overexposure (e.g., breast and pituitary cancers, infertility) must be understood so that exposures can be limited to safe levels.

- The project "DES and the Regulation of the Uterine Cytodifferentiation," is conducted by principal investigator Liang Ma at Washington University. The molecular mechanism by which DES affects reproductive tract development is unknown. To address this mechanism is important because many synthetic and naturally occurring chemicals mimic estrogen and could affect the health of the next generation in a similar fashion as DES did. This proposal will dissect the genetic pathways affected by DES during female reproductive tract (FRT) development. Preliminary studies show that several developmental control genes are regulated by DES during critical period of uterine cytodifferentiation. In particular, homeodomain protein Msx2 appears crucial in counteracting the effect of DES on the developing FRT as DES induces very dramatic reproductive patterning defects in Msx2 mutants, resulted from altered molecular changes in these mutants. The present grant will continue to test the hypothesis that DES can change uterine epithelial cell fate by affecting genetic pathways governing uterine cytodifferentiation. In aim 1, the role of Msx2 in uterine and vaginal development and DES-induced FRT malformations will be rigorously examined. In aim II, the investigators will use gain and loss of function approaches in vivo to examine whether Klf4 is both necessary and sufficient for DES-induced uterine metaplasia. Finally in aim III, the investigators will test the hypothesis that DES affects luminal epithelial architecture through modulation of the Wnt pathway. By completing these studies, they should be able to build genetic pathways controlling uterine development and address how DES can cause abnormal FRT patterning through modulation of these pathways. Their long term goal is to use mouse as a model to study reproductive tract development and how exogenous factors can influence this process.
- The project "Estrogen T-Cell Interactions," is conducted by principal investigator Prakash Nagarkatti at the University of South Carolina at Columbia. In the current study, the investigators will test the central hypothesis that prenatal exposure to DES alters the positive and/or negative selection of T cells in the thymus leading to generation of

skewed T cell repertoire with enhanced reactivity towards self antigens and decreased response against non-self antigens. In aim# 1, they will investigate whether the regulation of Fas and Fas ligand genes involves estrogen responsive elements (ERE) and other transcription factors. Aim# 2 will test if prenatal exposure to DES alters positive and negative selection of T cells in the thymus and thereby skewing the immune responsiveness of mature T cells to self rather than non-self antigens. Aim# 3 will investigate the role of ERa in DES induced apoptosis and development of autoimmunity. Also, the role of T cell-stromal cell interactions in DES-induced thymocyte apoptosis will be studied. In Aim# 4, the mechanism by which prenatal DES exposure leads to increased susceptibility to autoimmune disease postnatally will be tested. Together, the studies proposed should provide novel information on the mechanism by which prenatal exposure to DES leads postnatally to increased susceptibility to autoimmunity and cancer and to development of potential approaches to prevent such immunotoxicity. Thus, studies are aimed at providing insights into the mechanism by which estrogens mediate their toxic effects on the immune system, thereby leading to the development of strategies for their prevention and treatment.

- The project "Alteration of Hox Gene Expression by Endocrine Disrupting Chemicals," is conducted by principal investigator Hugh Taylor at Yale University. The objective of this proposal is to test the hypothesis that the mechanism by which endocrine disrupters affect the development of the reproductive tract is by altering the epigenetic regulation of HOX gene expression. While the initial regulation is mediated through the estrogen receptor (ER a or (b), persistent defects in HOX gene expression after exposure to endocrine disrupters suggests epigenetic alteration of HOX expression. In this application the investigators will determine the molecular mechanisms that regulate HOXA10 and HOXA11 as well as identify epigenetic modifications that regulate HOX genes in both mice and humans. First the investigators will characterize the 5' and intronic regulatory regions of HOXA10 and HOXA11 and identify transcription factor binding sites. Based on preliminary data, the investigators hypothesize that these regulatory regions are methylated in response to xenoestrogen exposure. The investigators will identify the potential impact of DES induced methylation on transcriptional regulation of these genes.

Second, they will define the epigenetic changes that lead to persistent Hox gene alteration in the absence of continued exposure in mice. Finally, the investigators will determine if the molecular mechanism by which endocrine disrupters alter HOX gene expression in mice is conserved in humans. The investigators will examine uterine tissue from women with known in utero DES exposure. They have previously shown that Hox genes are necessary for reproductive tract development and that altered Hox expression leads to developmental or functional alterations. Here the investigators expect to demonstrate that endocrine disrupters alter HOX gene expression and will determine the molecular mechanisms that mediate this regulation. No good model exists to explain the mechanism of both the acute and long term diminished HOX gene expression following endocrine disrupter exposure in utero. The investigators hypothesize that the effects are maintained long after exposure through epigenetic mechanisms such as methylation of HOX genes.

- The project "Effects of Environmental Estrogen Exposure on the Heart," is conducted by principal investigator Hong-Sheng Wang at the University of Cincinnati. The goal of the investigators' proposed study is to elucidate the toxicological effects of exposure to estrogenic xenobiotics on the cardiac system, and to define the underlying pharmacological mechanisms of actions of these agents. They will also investigate the molecular basis for the sex-specific susceptibility to estrogenic xenobiotics-induced cardio-toxic effect. The investigators' central hypothesis is that E2 and estrogenic EDCs, via activation of membrane associated ER mechanisms, alter cardiac Ca2+ handling in a sex-specific manner, and that the actions of at least some estrogenic agents contribute to arrhythmogenesis in female hearts. The investigators propose three Specific Aims to address this hypothesis: Aim 1 is to determine the cellular mechanism(s) underlying the pro- arrythmogenic effects of EDCs and E2 in rat ventricular myocytes; Aim 2 is to define the molecular basis for the sex-specificity of susceptibility to rapid E2/EDC effects on contractile function and arrhythmogenesis of ventricular myocytes; and Aim 3 is to determine the effects of E2/EDCs on cardiac arrhythmias at the whole organ level, especially during pathologic stress, including catecholamine stimulation and ischemia, and explore potential preventive/therapeutic strategies for protection against such arrhythmias. The proposed study investigates the toxicological effects and underlying

mechanism of exposure to estrogenic xenobiotics and other environmental estrogenic compounds on the cardiac system, particularly in women. These studies have high clinical relevance, particularly with respect to arrhythmias in women in the at risk population. The results will provide critical knowledge for the development of protective measures against environmental estrogenic cardiac risk factors, and the development of novel preventive or therapeutic strategies for cardiac diseases related to these risk factors.

- The project "Environmental Epigenetics and Stem/Progenitor Cell Injury," is conducted by principal investigator Tim Huang at Ohio State University. The investigators propose that immature cells located in the stem/progenitor compartment of the human breast are prime targets of this environmental insult. In Specific Aim 1, primary breast stem/progenitor cells will be exposed to xenoestrogens - diethylstilbestrol, bisphenol A, or 17β-estradiol in an in vitro system. 'Global analysis is expected to identify altered methylation status in 1-2% of ~29,000 CpG islands analyzed. These epigenetic events can be the direct results of exposing stem/progenitor cells to xenoestrogens. The epigenetic memory of this injury is then transmitted to differentiated epithelial cells and in turn leads to breast tumorigenesis in a xenograft model. In Specific Aim 2, the investigators will functionally determine whether the prolonged exposure of these endocrine chemicals to stem/progenitor cells disrupt the homeostasis of estrogen signaling and triggers an epigenetic cascade in its downstream targets. Polycomb repressors can be recruited to promoter CpG islands followed by the addition of DNA methyltransferases at these promoters. Acquired DMA methylation, as a result of increased local methyltransferase activities, marks the heritable gene silencing. In Specific Aim 3, the investigators will demonstrate that CpG island hypermethylation induced by xenoestrogen exposure is also observed in clinical samples. The presence of these molecular alterations in primary breast tumors may constitute a xenoestrogen epigenotype(s). In this regard, patients exhibiting this epigenotype are likely exposed to xenoestrogens in their early lives. In addition, low levels of these methylation changes may exist in normal looking mammary epithelial, leaving a field of cancerization in the human breast. This type of CpG island hypermethylation can be tracked as molecular relics using a mathematical modeling approach developed in our laboratory. The

investigators will develop the model further to recreate the history of xenoestrogen-induced breast tumorigenesis, from pre-neoplastic lesions to hyperplasia to carcinoma in situ to invasive carcinoma. Clinical sensitivity and specificity of potential CpG island loci pinpointing the xenoestrogen epigenotype will be provided as a quantitative milestone for this U01 project. These loci are future biomarkers for early breast cancer detection and are putative biosensors to environmental estrogens.

3 Additionally, the NIEHS Division of Extramural Research and Training supported DES research grants utilizing ARRA funds:

- The project "Prenatal Developmental Immunotoxicity of Diethylstilbestrol and Methoxychlor," is conducted by principal investigator Christine Ann Broussard at the University of La Verne. The investigators hypothesize that diethylstilbestrol and methoxychlor (two established EDCs) alter T cell differentiation when present during prenatal immune system development, ultimately leading to inappropriate immune suppression or activation. Using an in vitro prenatal T cell differentiation assay, the experiments in this proposal will determine whether DES and MXC 1) are capable of altering the immune system during embryological development at low doses, 2) are mediating their effects through inhibition of development, or 3) are mediating their effects through induction of apoptosis. This stage-specific analysis of DES and MXC will enhance our understanding of how and when these endocrine disruptors affect the immune system, and will form the basis for assessment of prenatal immunotoxicity of other EDCs and for strategies to prevent immune disease induced by gestational EDC exposure. Endocrine-disrupting chemicals (EDCs) are present throughout the environment, from wastewater releases (e.g. personal care products and pharmaceuticals) to additives in plastic (e.g. bisphenol A) to pesticides used on food crops (e.g. atrazine). Growing evidence suggests that EDCs negatively influence the immune system, potentially leading to immune diseases like asthma, allergies, autoimmune disease, repeated ear infections, and poor vaccine responses, particularly in children. The proposed research will enhance our understanding of how and when EDCs affect the

immune system, and will form the basis for assessment of prenatal immune impacts of EDCs and for strategies to prevent immune disease caused by prenatal EDC exposure.

- The project "Epigenetic Marks of Xenoestrogen Exposure," is conducted by principal investigator David Waxman at Boston University. This application addresses broad Challenge Area (08) Genomics and specific Challenge Topic 08-ES-104, Identification of Alterations in Epigenetic Marks Related to Environmental Exposures. Environmental exposure to foreign chemicals with estrogenic activities is widespread and is proposed to impact adversely on human health. The overall goal of this project is to investigate the hypothesis that perinatal exposure to xenoestrogens induces epigenetic marks associated with permanent changes in expression of key genes controlling female reproductive tract development, which are, in turn, linked to the observed reproductive tract abnormalities and increased incidence of uterine cancer. It is proposed that each xenoestrogen has a unique epigenetic signature as a result of its unique activity as a selective estrogen receptor modulator. These hypotheses will be tested using in utero mouse models of exposure to the xenoestrogens diethylstilbestrol and bisphenol-A. Diethylstilbestrol is a potent xenoestrogen linked to major reproductive tract developmental abnormalities in mouse models and in exposed humans, while bisphenol-A is a weak xenoestrogen that induces more modest reproductive toxicities in the mouse; the consequences of human exposure to the latter chemical are not definitively established. Discovery of the epigenetic signatures that are common, as well as those that are unique, to each xenoestrogen will help elucidate the reproductive toxicology associated with each chemical. These studies will provide important new insight into the mechanisms through which endocrine-active environmental chemicals induce reproductive toxicities, and may, ultimately, lead to new strategies for detection and prevention of adverse effects in exposed individuals. The significance of the studies proposed is major, both in terms of the new scientific knowledge that is expected to result, and for the potential impact on the large number of individuals that are exposed to environmental xenoestrogens. This project investigates the actions of environmental chemicals that exert reproductive toxicities, with special emphasis on environmental estrogens that induce female reproductive tract toxicities in humans and other exposed mammals. The studies that are

proposed will provide important new insight into the mechanisms through which endocrine-active environmental chemicals induce reproductive toxicities, and may, ultimately, lead to new strategies for detection and prevention of adverse effects in exposed individuals. In addition, the economic stimulatory impact is also expected to be major, advancing Recovery Act goals through the direct hiring of research staff to support the needs of this project and via the positive economic stimulus that will result from the expenditure of laboratory research supplies funds.

Scientific Articles from NIEHS

The NIEHS Division of Intramural Research investigators and their collaborators have published DES research findings in peer-reviewed journal articles. To find out more about these studies, please reference the following journal articles.

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Grantees funded through the NIEHS Division of Extramural Research and Training have published research findings in peer-reviewed journal articles. To find out more about these studies, please reference the following journal articles.

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