DES Action VOICE

A FOCUS ON DIETHYLSTILBESTROL

SPRING 2005 #104

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DES Daughters At Increased Risk For Endometriosis

"In utero exposures and the incidence of endometriosis" by Stacy A. Missmer et al, Fertility and Sterility, Vol. 82, No. 6, December 2004.

Reviewed by Sally Keely, M.S.

This prospective cohort study shows a link between in utero diethylstilbestrol (DES) exposure and the incidence of endometriosis. Endometriosis is a painful chronic disease occurring when endometrial tissue is found outside the uterus. This misplaced tissue develops into growths or lesions that respond to the menstrual cycle in the same way that the tissue of the uterine lining does — each month it builds up, breaks down, and sheds. The blood and tissue shed from endometrial growths has no way of leaving the body resulting in internal bleeding and inflammation that can cause pain and infertility.

DES exposed persons have altered estrogen receptors and an increased risk of autoimmune disorders. These factors are associated with endometriosis. It has been suspected therefore that DES Daughters are at increased risk of endometriosis. This study confirms it.

"... the relation between DES exposure and endometriosis may result from a combined effect of increased retrograde menstruation, immune dysfunction, and exogenous estrogen exposure."

Participants in the Nurses' Health Study II (NHSII) which began in 1989 and spanned ten years of follow-up included over 84,000 female nurses aged 25-42 who had (at baseline in 1989) never been diagnosed with endometriosis, infertility, or cancer. Data were collected regarding their in utero environment (including DES exposure) and birth/newborn data.

In utero DES exposed persons have altered estrogen receptors and an increased risk of autoimmune disorders. These factors are associated with endometriosis.

We know that DES Daughters are more likely to present with anatomical complications such as cervical stenosis (narrowing of the cervical canal, sometimes to the point of closure) that may increase the likelihood of retrograde menstruation. In utero

During the study 1226 cases of incidence of laparoscopically confirmed endometriosis were compared according to birth weight, prematurity, multiple gestation, DES exposure and,

continued on page 3

DES Exposure Positively Associated With Paraovarian Cysts

"Risk of Benign Gynecologic Tumors in Relation to Prenatal Diethylstilbestrol Exposure," by Lauren A. Wise, ScD et al, Obstetrics & Gynecology (Green Journal), Vol. 105, No. 1, January 2005.

Reviewed by Kari Christianson

In this study the authors from the National Cancer Institute's DES Follow-Up Study working group report that prenatal DES exposure is associated with an increased risk of paraovarian cysts (noncancerous fluid-filled sacs adjacent to but not part of the ovary). There was no increased risk found for uterine leiomyomata (noncancerous fibroids) or ovarian cysts (noncancerous fluid-filled sacs of the ovaries).

". . . prenatal DES exposure was associated with an increased detection of paraovarian cysts derived from the müllerian or wolffian ducts, but the clinical significance of these cysts is unknown. Our results do not support the hypothesis that prenatal DES exposure increased risk of uterine leiomyomata or ovarian cysts."

Citing research from the DES exposed mouse model from twenty or more years ago in which animal studies suggested an increased inci-

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Join The DES Action Daughters or Sons Listserv

Want to be in touch, via email, with other DES exposed individuals? As a benefit of being a DES Action member you can join either the DES Action Daughters, or DES Action Sons, listserv.

That way you can ask questions and share experiences common only to those of us who are DES exposed.

To join the DES Action Daughters listserv simply send a blank email to:
DESactionDaughters-subscribe@yahoogroups.com

To join the DES Action Sons listserv simply send a blank email to:
DESactionSons-subscribe@yahoodgroups.com

You'll receive an email back from Yahoo! Groups confirming your request to join. It offers two registration options and the easiest is Option 2. Click "Reply" so the note is sent back.

Once we've checked to be sure you are a current DES Action member, you'll receive a welcome to the listserv letter explaining how to send messages. Then you can participate in the email conversations, or just quietly read what is being said and enjoy the learning experience.

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Endometriosis *continued from page 1*

having been breast-fed. The following findings interested me.

(1) The incidence of endometriosis increased linearly as birth weight decreased (under 5.5 pounds).

(2) Women who were born as a multiple were at increased risk even after controlling for birth weight.

And most importantly to us,

(3) The rate of endometriosis was **80% greater** among women exposed to DES in utero.

That is close to double the incidence of endometriosis among DES Daughters and it was even greater among Daughters with concurrent infertility.

Further analysis of the affected DES exposed cases showed, "the trimester of initial DES exposure did not affect the rate of endometriosis, but that any DES exposure of five or more weeks nearly tripled the rate compared to those exposed for less than five weeks."

As a mathematician I find this study to be very well conducted. The researchers were exclusive rather than inclusive. So although the number of confirmed DES exposed participants with endometriosis was small (21 cases), this study shows a significant link between in utero DES exposure and endometriosis. The results are statistically sound, and for DES Daughters extremely important!

I look forward to discussing this study with you online in the new DES Action DES-Daughters listserv! For more information about endometriosis, please visit the Endometriosis Association at www.endometriosisassn.org.

Paraovarian Cysts *continued from page 1*

dence of epithelial tumors in the reproductive tract as background information for this study, NCI researchers investigated the association of prenatal DES exposure and the risk of benign gynecologic tumors in the daughters of women who were given the drug while pregnant.

"Our findings for paraovarian cysts are consistent with animal studies showing that developing reproductive organs are a potential in utero target for the long-term toxic effects of DES."

Two of the cohorts from the collaborative follow-up study of DES exposed and unexposed women (DESAD and Dieckmann) were used. NCI researchers investigated self-reported paraovarian cysts, ovarian cysts and uterine leiomyomata, as reported in the 1994 and 1997 questionnaires to these groups. Three gynecologists, not made aware of the exposure status of the participants, reviewed all medical, surgical and pathology reports related to the responses.

"In the present study, we included all cysts that could be classified into the following histologic types of cysts: functional cyst (including follicular and corpus luteum cysts), cystadenoma (serious and mucinous) or simple cyst; endometrioma (chocolate cyst); benign cystic tertoma (dermoid cyst); or paraovarian cysts, defined to include hydatid, paratubal, or any type of cyst believed to originate from remnants of the most cephatic portion of the müllerian or wolffian ducts."

Only lesions 2 cm or larger were included to minimize the influence of detection bias by health care providers aware of the woman's DES exposure status. This study did not include women with polycystic ovarian disease (numerous cysts on the ovaries).

Additionally, a separate analysis was undertaken to investigate uterine leiomyomata and no association to prenatal DES exposure was found. A detailed description of all methods and analyses is included in the article, including the limitation of the design study to only benign tumors requiring surgery.

"Our findings for paraovarian cysts are consistent with animal studies showing that developing reproductive organs are a potential in utero target for the long-term toxic effects of DES."

In acknowledging the limitations and potential bias of a self-reported study, no matter how thoroughly investigated or reviewed, the authors express concern that the results may be due to detection bias, in part because of greater surveillance of the DES exposed women. Nonetheless, this article offers important new information for DES Daughters and their health care providers.

As the authors point out, benign gynecologic tumors among all women are common in the US. The treatment for the type and size cysts discussed in this article is surgery, depending on symptoms of discomfort and pain the women have experienced, whether the women are DES exposed or not. A large portion of women with cysts may have no symptoms and need no treatment unless these tumors interfere with fertility.

DES Action Calls on Congress for More DES Research Money

by Kari Christianson

DES Action is actively requesting increased federal spending on DES research. Along with other member groups in the "Friends of NIEHS" coalition, DES Action submitted testimony to Congress asking for additional funds for the National Institute of Environmental Health Sciences (NIEHS) - where many DES studies are done. NIEHS is part of the National Institutes of Health (NIH). The request calls for an increase in NIEHS funding by $35 million for fiscal year 2006. Here is a portion of testimony that spells out the urgent need for more research funding for NIEHS research in general, and for additional DES studies in particular.

Written Testimony of the Friends of the National Institute of Environmental Health Sciences (NIEHS) for the Subcommittee on Labor, Health and Human Services, Education and Related Agencies, Senate Committee on Appropriations. Submitted by: David J. Whitcomb, Friends of NIEHS Co-Chair; Asua Ofosu, Friends of NIEHS Co-Chair

The Friends of the National Institute of Environmental Health Sciences (NIEHS) group appreciates the opportunity to comment on the Fiscal Year (FY) 2006 appropriation for the institute. The Friends of NIEHS is a

coalition committed to expanding the National Institutes of Health's (NIH) environmental health research portfolio through increased appropriations for NIEHS. Comprised of over fifty patient, health care provider, children's health, and industry groups, the Friends of NIEHS represents an enormously broad constituency dedicated to improving the nation's knowledge about our health and our environment.

Over the last several years Congress has shown a strong commitment to health research sponsored by NIH. This financial commitment has allowed the nation to dedicate resources to emerging scientific opportunities that will lead to beneficial health outcomes for Americans. We thank Congress for fulfilling its commitment to double the NIH overall budget. However, we remain concerned about how we will fund these opportunities in the upcoming years.

This dilemma is particularly true for the NIEHS. This institute plays a critical role in what we know about the relationship between our environmental exposures and disease onset. Through the research sponsored by this Institute, we know that Parkinson's disease, breast cancer, birth defects, miscarriage, delayed or diminished cognitive function, infertility, asthma and many other diseases and ailments have confirmed environmental triggers. Specifically, NIEHS has played an important role in discovering the mechanisms by which DES (diethylstilbestrol) causes damage, through its historical and ongoing work on DES in the animal model. Continuing research of these mechanisms is vital to help determine future health events related to DES, such as the possibility of third generation effects in the grandchildren of women who took DES during pregnancy. Our expanded knowledge, as a result, allows both policy makers and the general public to make important decisions about how to reduce toxin exposure and reduce the risk of disease and other negative health outcomes.

While there are many competing interests that must be considered in the FY 2006 budget, a top priority for Americans is medical research that explores the relationship between disease and the environment. The members of the Friends of NIEHS respectfully request a total of $680 million for FY 2006 for the National Institute of Environmental Health Sciences.

Our Day in Court Affirmed

by Pat Cody

DES Daughter Susan Hansch, filing a lawsuit against Eli Lilly because of infertility, won her right to a day in court. Federal Judge Claudia Wilken (U.S. District Court, San Francisco) ruled in mid January that *even though Hansch knew about her exposure years ago, the statute of limitations on when she should file should be decided by a jury* (Lilly had tried to have her suit dismissed). Similar decisions in support of DES Daughters were made in March, one in Seattle and one in D.C.

In a comment on the January decision for his client, Hansch's attorney Aaron Levine pointed out:

Most personal injury cases involve trauma — car accidents, slip and fall, train wrecks, etc., together with broken bones or torn muscles. It is easy to place the blame and the injury together. The fact of the injury and the wrongful act is apparent and simultaneous. DES injuries do not have the clarity of a defining moment. In DES cases (1) the exposure occurred three decades before the DES Daughter tests the system; (2) the victim didn't even take the drug; (3) the primary fear of the DES Daughter is cancer, not fertility; and (4) the infertility doctors always keep up hope and never let them believe the DES changes are a significant obstacle. These DES Daughters can't see the injury, they can't feel it, nor do they know what the exact cause of their infertility is....

"In no other product are the victims lulled into inaction as the DES Daughters. The manufacturers have required confidentiality in every one of the thousands of suits, as a condition to settlement, thus denying the public of the news, then they claim that the DES Daughters should have known. In no other class of victims is the statute of limitations so pernicious and unfair. The DES manufacturer built a time bomb with a long fuse that takes over thirty years to manifest its damage. Now they are attempting to benefit from the defect. Nonetheless, thousands of DES cases have been settled for the last twenty five years and will continue in the future."

> *"The DES manufacturer built a time bomb with a long fuse that takes over thirty years to manifest its damage. Now they are attempting to benefit from the defect."*

Research on Uterine Development — Perhaps an Answer to Infertility

by Pat Cody

"Developmental diethylstilbestrol exposure alters genetic pathways of uterine cytodifferentiation," by Wei-Wei Huang et al, in *Molecular Endocrinology*, 2005.

Successful implantation of an embryo requires a simple columnar tissue lining the uterus. Any disturbance in the development of this tissue, by a chemical like DES, results in changes that contribute to infertility.

Researchers at Tulane University in New Orleans, working with mice under the guidance of noted DES scientist John McLachlan, made this report. They discovered that abnormal changes occurred when the neonatal female mice (a development stage similar to in-utero life in humans) were treated with DES.

They concluded that, "developmental exposure to DES can perturb normal uterine development by affecting genetic pathways governing uterine differentiation."

If this change holds true for humans, it may provide an explanation for the infertility experienced by some DES daughters.

Behavioral and Sexual Effects?

by Pat Cody

Over the years one of the most perplexing concerns expressed in the DES community has been whether DES exposure affected the neurological system and sexual differentiation. Our readers are aware of physical changes, such as the T-shaped uterus, the higher risk for breast cancer in Mothers and Daughters, and the risk for clear cell cancer in Daughters. Experiments with mice show effects on the reproductive system that also appear in DES Daughters. However, reports on possible neurological effects on humans have not come from experiments but involve analyses of existing factors.

Here, some of the difficulties in getting a valid study are caused by a wide spread in the DES dosages Mothers got, in the time in pregnancy when they got it, and for how long they took it. Some Mothers began in the classic Smith & Smith regimen of four pills a day, increasing every two weeks until at the end — the 37th week — they were taking 125 mg. per day. This meant the DES-exposed daughter or Son had DES during the critical developmental stages of his or her fetus. Other Mothers had DES only in the last months, after most development had occurred and fetal life was concentrated on growth.

One 1983 research paper by Vessey, et al stated that, "sex hormones are, however, known to have effects on the organization of the brain in experimental animals with consequential behavioural effects." Another, often cited, 1982 study by Melissa Hines, et al reported that female rats exposed to DES had altered features of childhood social play and "increased masculine mounting behavior," while other researchers (Monroe and Silva) noted that same year a decrease in mounting behavior in adult male rats who had been exposed to DES.

Thus, it is apparent that DES did reach the fetal brain in these animals. In an ordinary human pregnancy, the Mother's estrogen does not reach the fetal brain. We do not know if DES did reach the brain and, if it did, whether it could influence brain development. There may be protective factors in humans so that DES would not have the same effects as it has shown in lower mammals.

We have seen reports on animal models that similar environmental estrogens can significantly alter the normal biological process of sex and gender differentiation in the brain. Perhaps DES also has had these effects in humans.

We have seen reports on animal models that similar environmental estrogens can significantly alter the normal biological process of sex and gender differentiation in the brain.

Yet Theo Colborn and her collaborators, in *Our Stolen Future,* write that, "Reports linking wildlife contamination with such unexpected behaviors as females sharing nests and feminized males inevitably raise questions about human parenting and sexual choice. Could hormone disruption alter these human attributes? The science on this is slender indeed. While emerging evidence suggests that variations in sexual preference may stem from differences in biology, scientists have only a dim understanding of the factors involved..."

Our readers may recall in our Spring 2003 issue #96 we summarized an article from the *Journal of Epidemiology* on psychosexual characteristics of DES Daughters and Sons. The data came from the survey of the ongoing study group followed now at the National Cancer Institute for nearly 30 years. Questionnaires were analyzed from 3,946 DES Daughters and 1,761 unexposed women and from 1,343 Sons and 1,356 unexposed men. Results showed that 95% of the subjects, male and female, whether exposed or not, reported exclusively heterosexual partners. One percent of all respondents, exposed or not, reported "mostly same sex." On possible psychological effects, where questions were only asked of the women, 16% of the DES Daughters and 17% of non-exposed women reported diagnosis and treatment for mental illness – with depression accounting for 78% of the illnesses.

Without a doubt, more research is needed. We invite comments from our readers (158 S. Stanwood Rd., Columbus, OH 43209 or desaction@columbus.rr.com) and conclude with what a scientist once wrote, "Absence of evidence is not evidence of absence."

BOOK Notes

Understanding Menopause

by Pat Cody

A twelve-member panel chaired by Carol Mangione, M.D., from UCLA has studied menopause treatment, as requested by the National Institutes of Health.

The consensus statement, released in late March, concluded that, "for women who don't have very serious symptoms, waiting it out may be the best strategy."

This is in line with the thinking of Janine O'Leary Cobb, whose revised edition of *Understanding Menopause* has just been published in Canada by Key Porter Press (available at $17.47 in Canadian dollars from amazon.ca).

Ms Cobb was the founder of the bi-monthly newsletter about menopause, "A Friend Indeed" (available from 231 North 3rd St., Pembina, ND 58271-0260) which prints an excerpt about hormones from her book in its latest issue.

Remembering a Friend

by Kari Christianson

*The DES-exposed population is identified by our place in the family: we are DES Mothers, DES Daughters, DES Sons, and Third Generation DES Granddaughters and DES Grandsons. Nowhere do we use the term "**DES Fathers**." Yet many of us know or experience fathers who share concerns about the health of their DES-exposed family members and are involved in advocating for more DES education and research with us. DES Action Board of Directors Vice-President Michael Freilick has written about a DES Father who was a friend to many of us in this organization. So, on behalf of all our special DES Fathers, here is a tribute in memory of one special DES Father.*

Morty Saks, the husband of Libby Saks, passed away in early March. Libby has been a big part of our DES group for years.

I think of many things when I remember Morty. I remember our DES Action board meetings on Long Island, where he was always there to help us out. He would drive us to our dinners and always have a happy and caring attitude about everything.

I think about my own medical problems as I think about what Morty went through in the last couple of years. As I understand it, he was given new medicine to try to help him fight his battle against cancer. I, too, have been given new medicines over the years to prolong my life. Perhaps with Morty going through his illness, other patients in the future may benefit from the knowledge doctors get from this.

There was a newscaster in the Philadelphia area who once said that we are measured here on Earth by the number of lives we touch. This newscaster was killed in a tragic accident a number of years ago. The memories about him are still alive with the people who remember him. The love and caring and happiness that Morty had will never go away. He will be remembered in that way.

— Mike Freilick

Prostate Changes *continued from back page*

storage items — we just don't."

California lawmakers are considering a bisphenol A ban in all products used by children ages 3 and younger. That would include baby bottles and plastic toys.

Bisphenol A is generally "in clear, hard plastic, not the softer, non-clear containers," explains vom Saal who joins Timms in urging consumers to use alternatives, especially in the kitchen and nursery.

DES Action's Pat Cody concurs. She says avoiding plastic containers which have been shown to leach chemicals into food and beverages is something those of us who are DES exposed can easily do. "We've already had enough synthetic estrogens in our lives!" she adds.

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Compound Similar to DES Implicated in Prostate Changes

by Fran Howell

When you hear of bisphenol A, pay close attention. It's a chemical used in plastics and tin cans. Interestingly, bisphenol A was created as a synthetic estrogen – and is quite similar to DES!

Here's the headline of an interesting article by reporter E.J. Mundell in HealthDay News on May 2, 2005: Plastics Compound May Cause Prostate Abnormalities: Mouse study implicates bisphenol A, found in food-storage containers.

According to the article, biology professor Fred von Saal, from the University of Missouri, and biomedical sciences professor Barry Timms, at the University of South Dakota School of Medicine teamed up to take a closer look at bisphenol A. Their study was published in the online edition of the Proceedings of the National Academy of Sciences.

Timms told reporter Mundell that he and von Saal looked at bisphenol A because of the medical problems caused by DES, and "because they realized "that very small physiologic levels of these synthetic estrogens had an impact on prostate development."

The researchers gave pregnant mice low doses of bisphenol A and found an increased risk for prostate abnormalities. Their study showed that male mouse fetuses exposed to bisphenol A had significant malformations of the urethra, and abnormally large prostate ducts. Timms thinks the compound may overstimulate some prostate cells, which increases cell growth. It may mean that exposed mice will end up with larger prostates than unexposed mice as they mature.

Having an enlarged prostate is not cause for great alarm, but getting prostate cancer is a significant health issue. Professor vom Saal is quoted as saying "female sex hormones - elevate receptors, priming the response system to male hormones in the prostate. So what you have is an organ that's hypersensitive to male sex hormones, and that's a risk factor for prostate cancer."

A plastics industry spokesman dismisses the study claiming the bisphenol A dose given the mice was high. But the researchers defend their work saying the amount was "much lower than the 'safe' level determined for humans by the Environmental Protection Agency."

What vom Saal wants is a ban on the use of bisphenol A in food packaging. He's quoted in the article as saying, "I don't mind it being used in airplane wings and computers, things like that. But the idea that we need this in food

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