THE DES ACTION VOICE
A FOCUS ON DIETHYLSTILBESTROL
Fall 2004 • #102

Loss of Fertility in Male Rats

By Pat Cody

"ABNORMAL" morphology of the penis in male rats exposed neonatally to diethylstilbestrol is associated with altered profile of estrogen receptor-a protein, but not of androgen receptor protein: A developmental and immunocytochemical study," by H.O. Goyal et al, *Biology of Reproduction* #70, January 2004.

"Exposure of neonatal male rats to estrogen induces abnormal morphology of the penis and loss of fertility," H.O. Goyal et al, *Reproductive Toxicology* 18, 2004.

Dr. Goyal and his colleagues report on how DES affects the structure of the penis, and thus fertility, in rats. They found that the DES rats, compared with a group of untreated rats, had abnormalities that explain their loss of fertility. These changes were a replacement of cavernous spaces and smooth muscle cells needed for erection with fat cells, and, an absence of testosterone. In correspondence with me, Dr. Goyal wrote, "Do DES men, now in their forties and fifties, have higher incidence of erectile dysfunction and/or infertility (or their female partners experience less sexual satisfaction) than other males of their age group?"

We know that some DES sons do have infertility – and perhaps this is an explanation for that condition.

Whether these findings apply to humans is unclear. The one study on fertility in DES sons (Wilcox et al, "Fertility in men exposed prenatally to diethylstilbestrol, *N.E. Journal of Medicine*, May 25, 1995) concludes that, as we wrote in the VOICE for Summer 1995, "Although the DES-exposed men reported urogenital malformations three times as often as the men whose mothers were in the placebo group, there was no significant difference between the exposed and non-exposed men with respect to their ever having impregnated a woman, their age at birth of their first child, average number of children, medical diagnosis of a fertility problem, or length of time to conception in the most recent pregnancy of the female partner."

Dr. Goyal continues his work on this topic. In October he wrote me:

"In recent unpublished data, we found that DES treatment for only postnatal days 1-3 caused abnormal penile morphology, including replacement of cavernous spaces by fat cells. We also found that this treatment suppressed intra-testicular testosterone surge that normally occurs in the first week of life in control rats. This time period (postnatal days 1-7) in DES treatment is very significant because the rat penis at this age is developmentally similar to the human penis in the first trimester of pregnancy, and when there is also a surge in testosterone secretion.

"What causes accumulation of fat cells in the body of the penis is an important question that needs to be answered. Our hypothesis is that neonatal DES treatment, either directly or indirectly via decreased testosterone, reorganizes critical patterns of stromal cell proliferation regression and/or differential in the neonatal period of development, which collectively result in accumulation of fat cells at the expense of cavernous spaces and smooth muscle cells in the body of the penis."

We know that some DES sons do have infertility – and perhaps this is an explanation for that condition. We look forward to hearing more from Dr. Goyal as he continues his intriguing research.

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How to Join the DES Daughters Listserv

DES Daughters should check out DES-L, the DES daughters listserv and online support forum at http://www.surrogacy.com/online_support/des/. To join the listserv, complete the online application and get ready to share support and information with 1,000 other DES daughters! Note: this list is operated independently from DES Action.

DES Action USA 28th anniversary 1978-2004

Yes–I want to get answers about DES. Enclosed is my membership.

All members receive **The DES Action Voice** quarterly. **Those at the $100 level and above receive an annual report on DES Action's work and progress. All contributions are tax deductible.**

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Accountability from Drug Companies?

By Nora Cody

DES Action has often addressed pharmaceutical advertising claims with the question: what about long-term effects? As our readers know, this was our repeated query about hormone treatments including contraceptive pills and hormone replacement therapy (HRT). For years the concerns of DES daughters and mothers about the safety of these products has been dismissed.

Finally, in 2002, the research began to pour out of the Pandora's Box of menopausal drug treatments, and the evidence supported our caution. We have learned about increases in risks for heart disease, stroke and cancer from long-term use of HRT.

Now in the news: a second example of the need for long-term studies – the withdrawal from the market of the arthritis medication Vioxx. Merck Pharmaceuticals took this action after its study showed that patients on Vioxx for longer then 18 months had greater risks for heart attacks.

Easing the regulations for one group, however, is not a license for launching new concoctions for less deadly diseases, and the drug companies are being called to account in a number of ways.

For years the concerns of DES daughters and mothers about the safety of these products has been dismissed. Finally, in 2002, the research began to pour out of the Pandora's Box of menopausal drug treatments, and the evidence supported our caution.

And on October 15, drug maker Pfizer sent a warning to doctors that its painkiller Bextra might also increase the risk of heart attack or stroke in coronary artery bypass surgery patients.

Drug companies, in response to criticism about their rush to market with 'new' or 'improved' products, maintain that taking time for long-term studies would deprive patients of potentially helpful treatments. They get support for this from AIDS patients who face life-threatening illness, and have been willing to take greater risks in order to possibly save their lives.

Easing the regulations for one group, however, is not a license for launching new concoctions for less deadly diseases, and the drug companies are being called to account in a number of ways. We are pleased to see the publication of such books as "The $800 Million Pill: The Truth behind the Cost of New Drugs" by Merrill Goozner, which deals with biotechnology effects on health care, "Overdosed America: The Broken Promise of American Medicine" by Martin Abramson, "The Truth about the Drug Companies: How They Deceive Us and What to Do About It" by Marcia Angell, former editor of the *N.E. Journal of Medicine,* and "Critical Conditions: How Health Care in America Became Big Business – and Bad Medicine" by Donald L. Bartlett and James B. Steele.

(These are all new publications; inquire at your local library or bookstore if you are interested in reading them).

Our lawmakers are also paying attention. Democratic Senators and Representatives have introduced legislation requiring makers of drugs and medical devices to register clinical trials of their products on a web site when the trial begins, and, when it is finished to post the results. We applaud these beginning efforts, but they are not enough. Consumers must demand accountability from our government for the failure of the Food and Drug Administration (FDA) to adequately monitor our drug supply. The FDA should conduct independent testing to verify both the safety and the efficacy of all new drugs. We have a long way to go in preventing repeat performances of the DES debacle. ■

Here is the home page of the CDC binder that many of our readers have received. We are now mailing them to nearly 1,000 libraries throughout the United States. In a few weeks, check that your library got one for their reference department. If they did not, or, if you want another copy of this binder, it's easy – call the CDC at this toll-free number:

1-888-232-6789

CDC

DES UPDATE HOME

For Consumers, Health Care Providers, and DES Update Partners

Diethylstilbestrol (DES) is a drug once prescribed during pregnancy to prevent miscarriages or premature deliveries. In the U.S. an estimated 5 to 10 million persons were exposed to DES from 1938 to 1971, including pregnant women prescribed DES and their children. In 1971, the Food and Drug Administration (FDA) advised physicians to stop prescribing DES because it was linked to a rare vaginal cancer.

After more than 30 years of research, there are confirmed health risks associated with DES exposure. However, not all exposed individuals will experience DES-related health problems. Whether you know for sure or suspect you were exposed to DES, you can use CDC's DES Update to learn more about DES exposure and what you can do about it.

For Consumers

Helpful information on DES research and a guide to help assess whether you might have been exposed to DES, as well as in-depth information for women prescribed DES while pregnant and their DES Daughters and DES Sons.

For Health Care Providers

Resources to help identify and counsel DES-exposed individuals. Material includes essential facts for clinicians and nurses, pharmacology, NCI guidelines, educational tools and resources, and support organizations.

For DES Partners

Tools to help you share information from the DES Update with your organization, including promotional materials, Web site linking kit, fact sheets and newsletter articles.

Tell Your Doctor

This material is not in the CDC binder you received. If you want to let your physician know about this resource, you can copy this page of the VOICE and send to their office, or let them know about the website when you go in for your exam.

CDC

DES UPDATE: HEALTH CARE PROVIDERS

It is estimated that between 5 and 10 million people were exposed to diethylstilbestrol (DES) in the US during 1938-1971. DES was thought to be a safe and effective way to prevent miscarriages or premature deliveries. However, later studies revealed that DES had harmful side effects. Many people are still unaware of their exposure to DES and the potential health effects.

Health Care providers

This section of CDC's DES Update has been specifically designed to help health care providers learn more about DES exposure and its known health effects to facilitate identifying, managing, and counseling DES-exposed patients.

GENERAL DES INFORMATION

Pharmacology

An overview of the pharmacology of DES, data indicating lack of efficacy for DES use as prevention of miscarriage, and clinical indications and current uses for DES.

DES Brand Names

A list of the most commonly used names and spellings for DES and similar drugs.

Resources and Educational Tools

A series of educational tools and resources for clinicians and nurses, DES lecture presentation, case studies, self-study module, a listing of DES support organizations, and a DES research bibliography.

IN-DEPTH INFORMATION TO IDENTIFY AND MANAGE DES EXPOSED PATIENTS

Information To Identify and Manage DES Patients

Research has revealed health effects for women prescribed DES during pregnancy and the offspring (DES Sons and Daughters) born of those pregnancies. In addition, research is underway to determine if the offspring of DES Sons and Daughters might have health effects related to DES exposure. These grandchildren of women prescribed DES during pregnancy are sometimes called the "Third Generation."

Supplemental DES Materials for Nurses

Nurses have an important role in identifying persons who might have been exposed to DES during intake interviews, as well as in counseling patients and assisting in appropriate referrals for further information and treatment. Information in this section will help you facilitate this role.

Infertility and Ovariam Cancer Risk

By Pat Cody

"OVARIAN cancer risk associated with varying causes of infertility," by Louise A. Brinton et al,"*Fertility and Sterility* August 2004.

This study found that infertility patients had nearly twice the rate of ovarian cancer than did the general female population.

First, some definitions. Infertility is usually diagnosed when a woman has had 12 months of sexual activity without pregnancy, and in the absence of contraception. "Primary" infertility is the term for women who have never had a pregnancy, and "secondary" for women who have had a previous pregnancy.

The research covered 12,193 women evaluated for infertility between 1965 and 1985, and ovarian cancer reported from this group up through 1999. These researchers found 45 cases among this large group. A group of similar size, who were not infertile, would have about half the number of cases. The ovarian cancer risk was higher for patients with primary infertility, and particularly high for patients who never subsequently conceived. Women with endometriosis had the highest risk, with a further elevated risk among those with primary infertility as well. Comparisons among the infertile women also showed links with endometriosis. The authors note that other factors associated with ovarian cancer risk, such as ovulation-stimulating drugs, had a minimal impact on this risk estimate.

This study found that infertility patients had nearly twice the rate of ovarian cancer than did the general female population.

In an interview with Reuters Health Information, lead author Dr. Brinton said:

"I think it's important to stress that the association of infertility to subsequent ovarian cancer appears primarily to derive from the inability to bear children, rather than to specific causes of infertility. The exception is endometriosis, and possibly tubal factor, which also appears to somewhat increase the risk of subsequent ovarian cancer. We are currently conducting a large study in Denmark aimed at further clarifying whether endometriosis is more strongly linked with specific types of ovarian cancer. We hope eventually to explore molecular markers that might link endometriosis to ovarian cancer."

The conclusion of this research is that determination of ovarian cancer risk should take into account the type of infertility and underlying causes. Many DES daughters are infertile, and some of them have endometriosis. What about early detection, or screening for ovarian cancer? Arthur Haney M.D., in reply to our question about this, writes:

"Unfortunately, there are no effective screening tools for ovarian cancer, despite a substantial amount of effort put forth to find them. The disease is silent in the early stages and is typically detected only after symptoms indicative of an advanced stage are present. This is one of the most serious problems in gynecology as this is a relatively high case-fatality rate cancer. The average of women who have ovarian cancer detected is above 60." ■

The ovarian cancer risk was higher for patients with primary infertility, and particularly high for patients who never subsequently conceived. Women with endometriosis had the highest risk, with a further elevated risk among those with primary infertility as well.

We always need the names of physicians who are informed about DES and sensitive to the needs of their patients. If you have such a referral, let us know!

Questions About Prpogesterone Cream

By Nora Cody

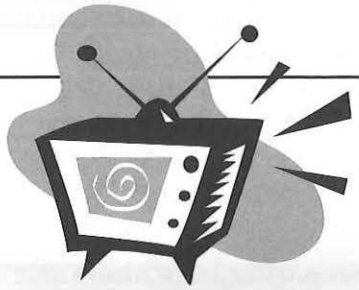
"BIOEQUIVALENCE of over-the-counter (OTC) progesterone cream (PC)" by Anne C. Hermann et al, reported at a conference of the American Society for Clinical Pharmacology and Therapeutics (ASCPT).

This research was designed to compare the effects of over-the-counter progesterone cream (OTC-PC) with the FDA-approved progesterone pill (also used in gels, injections and an intra-uterine device). The study was small – 12 postmenopausal women.

What were the results? They found that the progesterone cream in a dosage of 40 mg used twice a day provided equal exposure to that given with FDA-approved pills at a dose of 200 mg a day.

Why the concern? "This raises the question of whether OTC PC should be regulated since it may provide significant exposure compared to FDA approved products," the authors wrote. In a press release on this study, the ASCPT points out that "The cream is advertised as a substitute for other forms of prescription progestogens as well as for treatment of a wide array of syndromes for which there is minimal scientific evidence of efficacy. Symptoms that progesterone cream purportedly treats include premenopausal syndrome, postmenopausal symptoms (e.g. fatigue, hot flashes, allergies, breast tenderness, memory loss), osteoporosis, thyroid dysfunction, weight gain, autoimmune disorders, irritability and depression. These claims, in conjunction with marketing progesterone USP as "natural", have led to widespread popularity of the cream."

But – the press release concludes: "The use of topical progesterone without medical supervision is concerning because of the possibility of increased risk of coronary artery disease, stroke, thrombosis and breast cancer.... Over-the-counter progesterone cream yields the same exposure to progesterone as the prescription oral micronized capsules. Women who use the non-prescription form of this drug do not have the benefits of physician counseling, screening and supervision." ■



DES-RELATED DOCUMENTARY ON PBS

The story of cancer daughter Judith Helfand in a film she made, "A Healthy Baby Girl", may come to your PBS station soon. Originally shown as one of the PBS series "Point of View" (POV), PBS is now re-issuing a series of these programs under the heading "True Lives." Judith's documentary is one in this series, so if you missed it before you can see it sometime over the next months. Tell your friends and family and check your local TV listings.

DES ACTION TRIBUTE PROGRAM

We'd like to offer a great idea for that person who has everything: the DES Action Tribute Program. Our Tribute Program is a way for you to make your contribution in someone's honor or memory. Holiday gifts, birthdays, anniversaries, or memorial remembrances—all are appropriate occasions for a Tribute gift.

When you send your Tribute gift to DES Action, simply enclose a note indicating in whose honor and for what occasion the gift is given. Make sure to include the honoree's name and address as well as your own. We send an acknowledgment letter to you and to the honoree. The amount of the gift is not mentioned.

Caution on Soy Supplements

By Pat Cody

"ENDOMETRIAL effect of long-term treatment with phytoestrogens," Unfer et al, *Fertility and Sterility* July 2004.

This is the longest clinical trial yet on the effects of phytoestrogens – soy isoflavones — on the lining of the uterus (endometrium).

Phyto or plant estrogens have effects similar to estrogens and many women believe that as they are 'natural' they may be safer than the estrogen compounds in hormone replacement therapy (HRT).

Doctors at the University of Perugia in Italy followed 298 post-menopausal women for five years. These women had an average age of 50 and were post-menopausal. Researchers divided them into two groups. One group took 150 mg of soy isoflavones a day and the other a placebo (usually most isoflavone supplements are given at a dosage of no more than 80 mg a day).

At the end of five years, they found six cases of endometrial hyperplasia in the soy group and none in the placebo group. Why is this important? Endometrial hyperplasia is excessive growth of the endometrium and some types of this hyperplasia will progress to cancer. Whether the smaller and more usual dosage of 80 mg daily would have a similar effect is not known. However, in a press release about this article, Marian Diamond M.D., President of the American Society for Reproductive Medicine, warns:

"Phytoestrogens, like soy isoflavones, are drugs whose physiologic effects have not been completely mapped out. Patients need to recognize that even though these compounds are often sold over-the-counter as nutritional supplements, they are potent drugs. It is a good idea to consult your physician before starting self-treatment with isoflavones." ■

DES Action USA 25th anniversary 1978-2004

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