DES Action® VOICE

Inside

A Focus On Diethylstilbestrol

FALL 2015 #146

Alarming 'Very Late Recurrence' of DES-Related Cancer Reported

By Virginia Pelley

The clear cell adenocarcinoma (CCA)-DES link is a crucial piece of DES history: It provided evidence of the drug's great potential to harm the health of those exposed to it and alerted those exposed that they need to be extra-vigilant in monitoring their reproductive health. And now, the discovery of a recurrence of that cancer in one woman serves as a reminder that the vigilance of the DES exposed needs to remain robust throughout their lives.

CCA is thought to affect 1 per 1,000 DES-exposed women, researchers noted in their case study published in *Gynecologic Oncology Research and Practice* in July. Although clear cell adenocarcinomas of the lower genital tract are rare, they have a greater tendency to recur late and develop in other parts of the body much more than very common types of cancer, such as squamous cell carcinomas, a common type of skin cancer.

"Most recurrences of clear cell adenocarcinoma of the vagina and cervix are diagnosed within the 3 years after primary tumor treatment, but late recurrences have been reported with few cases 8 years after initial diagnosis," the researchers wrote. "To date the latest recurrence reported in DES-exposed patients is 19 years after initial therapy. Here, we present the case of a woman with intrauterine DES exposure who developed recurrence as distant metastases [cancer cells reappearing in other parts of the body, in this case, in the woman's liver] without local relapse, 24 years after initial curative treatment."

The woman in the case study was originally diagnosed with clear cell adenocarcinoma of the cervix in 1990, when she was 20 years old. Her health history was unremarkable other than her in utero exposure to DES. Although researchers deemed the treatment that rid her of the malignancy "conservative," she was infertile afterward. She followed up frequently and remained cancer-free until 2014, when doctors found a tumor in her liver that had a "tubular" shape, which led them to believe it had metastasized from her earlier CCA because tubular-shaped tumors are the most frequently seen in DES-related CCA cases.

"In our patient, the absence of local relapse suggests the possibility

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Fertility Researchers Can Learn from DES Tragedy, Pioneers Warn

By Virginia Pelley

The lessons learned from the saga of DES should serve as a warning to medical professionals about the dangers of approving drugs for patient use without adequate study of their long-term effects, longtime DES researchers Arthur L. Herbst, MD, and Diane Anderson wrote in their important "history of medicine" article "Diethylstilbestrol (DES) Pregnancy Treatment: A Promising Widely Used Therapy with Unintended Adverse Consequences," published in the September issue of *The American Medical Association Journal of Ethics*.

Recurring miscarriages in the late 1930s, when diethylstilbestrol was developed, were thought to be "due to a faulty hormonal environment of the fetal-placental unit, rather than primarily to genetic causes, as we have subsequently learned," they wrote. "There were studies at that time indicating that compromised pregnancies had a deficient output of the hormone progesterone, and further studies conducted in the late 1940s in Boston using very crude measuring techniques suggested that this deficiency could

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JOIN THE CONVERSATION

New Member Benefits!

Part of our upgrade to the DES Action USA website includes a new members-only area. As a member, you'll be able to log in to the Members Area for access to:

- **Rate Your Doc**—we've always offered lists of doctors that were recommended by other DES-exposed members. Now you can share your knowledge, and maybe spare some fellow members some pain, about the doctors in your area. Rate your doctor by entering his or her name, location and specialty, then add your comments: Is he or she knowledgeable about DES? Open to discussing options or fears? Tell your fellow members.
- **VOICE Newsletter**—current and historical. The VOICE is the most popular member benefit of DES Action. Now access all 36 years of newsletters and search for any topics or articles you need. The VOICE documents the history, the science and the personal stories of DES and all of us who were exposed.
- **Attorney List**—If you're interested in getting involved in possible future DES-related litigation, we offer a list of knowledgeable attorneys DES Action members have shared with us who might be able to help.
- **Exclusive Content**—an expanding collection of articles and videos accessible only to current DES members.

And more! Update your mailing address, pay your membership dues or make a donation online.

DES Action USA on Facebook

Like DES Action USA on Facebook and follow us on Twitter to stay up-to-date on medical and environmental health news that affects you, your loved ones and the planet. Share your thoughts with an engaged and active community. There's a ton of information swirling online 24/7 that affects the DES population—don't let it pass you by!

Online Support Group for DES Daughters

Here is a safe place for discussing very personal issues that arise for DES Daughters. We live in the farthest reaches of the country but have developed a sense of community together, via our email listserv.

What we talk about is private—just between us—so we can feel free to raise questions on topics we aren't comfortable bringing up with others. What is amazing is the depth of knowledge in the responses.

It's a terrific resource for information and support from DES Daughters who wrestle with the effects of menopause, family relationships and medical diagnosis issues specific to DES exposure. To join the support group, send an email to: DESactionDaughters-subscribe@yahoogroups.com.

How to Log In

To log into the members area, go to http://members.desaction.org and click on Members in the navigation bar. Enter the email address we have on file and the default password: desUSA2015. Once you are logged in, you can go to Your Account and change your password and update other information.

If you have any problems, email us at members@desaction.org or call us at 800-337-9288.

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MISSION STATEMENT

The mission of DES Action USA is to identify, educate, empower and advocate for DES-exposed individuals.

Contacts

Sister Organizations

Australia

DES Action Australia, Inc.
PO Box 282
Camberwell 3124 Vic. Australia
info@desaction.org.au
www.desaction.org.au

DES Action NSW
14 Edmundson Close
Thornleigh NSW, 2120, Australia
C_devine@bigpond.net.au
www.desnsw.blogspot.com

France

Reseau DES France
1052 rue de la Ferme de Carboue
40000 Mont de Marsan, France
reseaudesfrance@wanadoo.fr
www.des-france.org/accueil/index.php

The Netherlands

DES Centrum
Wilhilminapark 25
Postbox 1173
3860 BD Nijkerk
voorlichting@descentrum.nl
www.descentrum.nl

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(800) DES-9288 (800) 337-9288
Email: info@desaction.org
www.desaction.org

Editorial Director and Social Media Manager.....Virginia Pelley
Membership and Operations Manager.....Kimberly Bliss
Communications Director.....Julie Livingston
Financial Manager.....Aundra Goodrum

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Alarming 'Late Reccurence'

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that quiescent [dormant] tumor cell may have been initially present in the liver and peritoneum and became activated after a prolonged interval and/or evolved slowly and finally became symptomatic," the researchers wrote.

Earlier cases of recurrence have involved cancer of the lungs, pelvis and lymph nodes but this is the first known case of liver cancer traced back to DES-related CCA.

"This case represents the longest reported disease-free interval till recurrence," wrote the authors. "[and] it re-emphasizes the necessity of long-term surveillance of DES-exposed women and confirms previous reports recommending the importance of frequent follow-up examination not only of the pelvis but also of all distant potential sites of metastasis."

It might be a good idea to mention this case report to your doctor; you can read it online at http://bit.ly/1L8JaUA for more information. DES VOICE

Learn from DES Tragedy

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be corrected by administering DES to the mother, which would then lead to a healthy pregnancy."

No immediate abnormalities in newborns exposed in utero to DES were observed in early studies, they go on to say, yet as we know, doctors continue to draw links between health problems and past DES exposure to this day.

"This is a tragic example of a therapy that looked promising and was based on the best (but faulty) scientific evidence available at the time," they wrote. "However, due to the sensitivity of the developing fetus to an externally administered artificial hormone, unanticipated and severely adverse consequences developed. … There is still a risk of prescribing treatments that anecdotally appear promising but are not scientifically proven."

These risks, in particular, affect the vulnerable population of women seeking treatments for infertility, Herbst and Anderson point out.

This is because—despite a statistical drop in infertility—it's big business and growing fast. *The Wall Street Journal* reported in May that the US infertility treatment market now totals $3.5 billion annually, up from $2.25 billion in 2000. When billions of dollars are at stake, drug companies are not known to err on the side of caution when it comes to seeking approval from the Food and Drug Administration, which could have terrible consequences for countless women and children.

DES sons and grandchildren: the research

Herbst and Anderson also describe the ongoing research regarding the health effects of DES on sons and grandchildren in addition to study of the drug's effects on DES daughters.

"For DES-exposed sons, an increased risk of cancer has not been demonstrated, but they do have increased prevalence of maldescent [improper or incomplete descent] of the testes, epididymal [a tube that stores and transports sperm from the testes] cysts, hypotrophic [decreased size of] testes, and varicoceles [enlargement of the veins, a common cause of low sperm count and infertility]," they wrote.

"This unique population continues to be studied long-term in a multi-institutional study by the National Cancer Institute, both to monitor the possible adverse health effects of DES in this population and to clarify which potential adverse effects are statistically significant and therefore of increased medical concern."

In addition to the possibility of increased rates of cancer, researchers are also investigating whether DES sons are at increased risk for autoimmune diseases and cardiac problems, Herbst and Anderson wrote.

DES granddaughters tend to get their first periods at later ages and experience more irregular menses than their unexposed peers, they continue, but other health effects haven't been studied enough for researchers to draw definitive conclusions yet.

The same is true for grandsons who have been exposed to DES; some studies have suggested that they're at an increased risk for hypospadias, a condition in which the opening of the urethra is on the underside of the penis instead of on the tip. (Left untreated, hypospadias can hinder a boy's ability to use a toilet and as an adult, he might have trouble getting erections, according to MayoClinic.org.)

In addition, 700 cases of clear cell adenocarcinoma (CCA, a rare cancer strongly associated with DES exposure) of the vagina and cervix diagnosed since 1948—of which two-thirds of the cases have a history of DES exposure—are still undergoing evaluation with the Registry for Research on Hormonal Transplacental Carcinogenesis, established in Boston but now at the University of Chicago. Researchers have also keeping track of cases of CCA of the fallopian tubes as well.

The publication of this paper will remind researchers of the significance of DES in our medical history and also of the opportunity for the study of long-term exposure to endocrine disruptors that DES has tragically afforded us. It should also help keep DES on researchers' radar so that they continue to add to our body of knowledge about its negative health effects. DES VOICE

Smith College Hosts DES Historical Collection

By Virginia Pelley

Thanks to former DES Action Program Director Kari Christianson's efforts, a collection of DES Action USA materials including audio, video and photos will be preserved in the Sophia Smith Collection, the internationally recognized repository of material documenting women's history at Smith College in Northhampton, Massachusetts.

"I could not be more pleased that our records are in a collection that puts a premium on preserving women's history for future generations," Christianson says. "So we can continue learning about and from all of our experiences."

Director of special collections for the Smith College libraries, Elizabeth Myers says the library has received more than seven boxes of materials from DES Action. The collection will help visitors understand that "Women's health history of DES exposure is about the health history of some men, too It's also part of a broader context of adverse health harm caused by prenatal and early life exposure to endocrine disruptors such as

Elizabeth Myers

DES, the first identified endocrine disruptor shown to cause human health and reproductive harm," Christianson says.

Myers was gracious enough to answer some of our questions about the new collection:

DES Action: About how big is this collection and what, generally, does it contain (e.g., print, newspaper clippings, audio interviews, photos)?

Elizabeth Myers: The DES Action Records are 6 linear feet, dating from 1952 to 2014. The collection includes meeting minutes, agendas, slideshows, educational documents, newspaper clippings, press releases, correspondence, journal articles, campaign materials, VHS tapes, surveys, reports, awareness week materials, book proposals, essays, medical research, memos, advertisements, brochures, fact sheets, symposium documents/ materials, information packets, grant requests, congressional resolutions, legal briefs, federal documents on DES, organizing materials, articles of incorporation, biographical information on DES Action co-founder Pat Cody and former executive director Nora Cody, former DES Action program director Kari Christianson, and former executive director Fran Howell, study forms, bylaws, photographs, notes and notebooks, ephemera and posters.

Can you describe some of the highlights of the collection? What are a couple of your favorite items?

The DES Action records are not processed yet, just inventoried, so I don't want to claim a favorite item just yet. I think there are many, many items in the collection that researchers will find to be historically important, especially the correspondence, campaign materials and photos.

Did you learn anything new about DES activism or DES generally from the collection?

Housing the DES Action records in the archives places it in a larger body (or constellation) of women's health initiatives, especially related to reproductive health. I think the records tell an important story of an initially small organization that grew to national prominence and which has celebrated successful campaigns for the health of women, men and children.

What are some of your favorite collections or pieces in the library overall?

Picking favorite collections is kind of like picking a favorite child. There are so many in the Sophia Smith Collection (over 700 individual collections), that it's impossible to list all of them. What constantly impresses me about the collection is its depth—we have the papers of Clara Barton to Margaret Sanger to Gloria Steinem. There are many, many more women who are less famous but no less distinguished in their work for women's rights, equality, reproductive health and well-being. This includes women of color, women founding grassroots organizations, women of diverse sexualities and gender identity, all in the name of social justice and feminist activism.

Kari also mentioned that the library is moving and some (all?) collections will be digitized and possibly available online. Can you tell me about that, when the project is slated for completion, a bit about what it will entail and whether any materials might be available online to students or to the general public?

Smith College is currently engaged in a library renovation project. We are in the planning phase, with design to follow in early 2016. In 2017, the archives will leave our current location in the Alumnae Gym and head to temporary swing space on campus for two years. We are planning on moving into the new Neilson Library in 2020. The materials will continue to remain open for researchers to use during our move out and back in.

We do digitize materials in the collections, but rarely an entire collection. This is because not everything can go on the open Web (copyright, privacy), nor should everything go on the open Web. Digitization is very time- and labor-consuming, so we focus on digitizing for preservation (e.g., old audiovisual formats) and to promote collections in our care. That is more of a sample, rather than the whole collection. I am currently perusing a major grant to digitize a sizable portion of the YWCA of the USA records in the archives, but even so, not all of the collection will be digitized.

More practically, when we physically process a collection, we organize the records and take basic preservation steps to ensure that the collection will be around and accessible for future generations. Due to the generosity of DES Action, I am on the cusp of hiring a temporary staff person who will process the DES Action records. When that person is done, they will create a finding aid, which we will post online so that anyone looking for DES Action records will know that we have them, that the collection is open for research and exactly what is in the collection. Researchers can come to the campus and visit the materials directly or they can ask for research copies, which are provided for a nominal cost.

To learn more about the Sophia Smith Collection, visit www.smith.edu/libraries/libs/ssc. DES VOICE

Myers and Kari Christianson

"The DES records tell an important story of an initially small organization that grew to national prominence and which has celebrated successful campaigns for the health of women, men and children."

New Study Reveals Prenatal DES Exposure Linked to Endometriosis

By Virginia Pelley

Endometriosis, a condition in which the endometrial tissue lining the uterus is found outside of it and which causes chronic pelvic pain, painful periods and pain during sex, affects 6 percent to 11 percent of women of reproductive age in the US, yet doctors know very little about what causes it.

To further understanding about early-life factors that might contribute to the development of endometriosis in adulthood, researchers in Washington state compared 310 women diagnosed with endometriosis with a control group of 727 over a 5-year period for this study, the results of which were published in *Fertility and Sterility* in October.

Intrauterine DES exposure was associated with twice the odds of endometriosis, says study co-author Kristen Upson, Ph.D., MPH, IRTA postdoctoral fellow at the National Institute of Environmental Health Sciences of the National Institutes of Health, although she adds that "this association was not statistically significant," because the sample of DES-exposed women in the study was relatively small.

A previous study, however, observed that women exposed to DES in utero were 1.8 times more likely to develop endometriosis than women not exposed to DES in utero, she notes, and she says that this latest study supports that earlier finding.

"The key finding was that soy formula feeding during infancy was associated with more than twice the increased risk of endometriosis in adulthood," says. "But our data also suggested an increased risk of endometriosis with prematurity and maternal use of DES (exposure to DES in utero from the participant's mother's use of DES while pregnant with the participant)."

Upson points out that during the fetal and infant periods, there is rapid development of the uterus and the organs involved in the production of hormones.

As part of their explanation of the significance of exposure to endocrine disruptors such as DES during fetal development, the researchers wrote, "Given the rapid tissue differentiation and complex hormonal, cellular, and molecular mechanisms that occur during the fetal and infant periods, these developmental periods are susceptible to hormonal disruption. Studies of animal models have demonstrated the ability of early-life hormonal disruption to permanently alter the uterus and HPO axis [Hypothalamic Pituitary Ovarian axis, which must be properly functioning together for normal menstruation to occur] during development, resulting in changes that persist in adulthood."

"We don't have a clear understanding as to why endometriosis develops in some women, but not in others," Upson says. "The most widely accepted theory about the development of endometriosis postulates that endometriosis occurs when the uterine lining that is shed during menses travels backwards into the peritoneal cavity instead of leaving the body, and the displaced uterine tissue persists and grow outside the uterus.

"Additional factors promote the persistence and growth of this tissue, including factors related to the immune system, inflammation, blood supply formation and tissue survival, and these factors are influenced by hormones produced by the ovary," she explains.

Early-life factors, such as DES, may disrupt development, resulting in changes that persist in adulthood that may increase the risk of endometriosis, she says, which makes sense considering what we already know about the effects of DES on reproductive organs.

"DES is a well-established transplacental estrogenic carcinogen," Upson continues, noting the well-documented link between DES exposure and clear cell adenocarcinoma (CCA) in DES daughters. "Scientific evidence from laboratory animal studies has demonstrated the persistent effects of early-life DES exposure on the reproductive tract in adulthood."

Scientists are more willing than ever before to acknowledge the role of endocrine disruptors in a growing number of health issues. The Endocrine Society released a statement in late September calling for further study, "arguing that the benefits to society will far outstrip the costs." So we hope that studies of the probable link between DES exposure and endometriosis continue to help determine whether DES granddaughters face the same risk as their mothers. DES VOICE

Funding note from Upson: "The Women's Risk of Endometriosis Study, which provided the data for this study, was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and my work on this project was funded by NICHD, National Institute of Nursing Research, and was supported in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences."

Study: Why Many DES Daughters Aren't Getting the Pap Smears Crucial for Their Health

By Virginia Pelley

Women with a history of DES exposure know—or should know—that their elevated risk for reproductive health problems means that they need to be vigilant about getting regular Pap smears. DES daughters' greatly increased risk of clear cell adenocarcinoma is well-documented, and Pap smear screening is the primary method for identifying this kind of tumor development.

But despite this generally heightened awareness, common obstacles prevent many of the DES-exposed from getting the health screens so important to maintaining their health, researchers have found.

For their study, the results of which were published in the *Journal of Women's Health* in the spring, researchers used national cohort data from the National Cancer Institute (NCI) DES Combined Cohort Follow-up study from 1994, 1996, 2001 and 2006 to figure out why women in this population weren't getting regular Pap smears.

"In 1994, DES-exposed women were less likely to report noncompliance, while in 2006, they were more likely to be noncompliant," says study lead author Elizabeth Camp, Ph.D., a professor at Baylor College of Medicine in Houston. "In the paper, we suggest that there may be screening fatigue in this cohort of women, especially as they age. We also noted that primary care physicians may not be aware of the yearly Pap smear recommendations for this high-risk group of women."

Co-author Stanley Robboy, Ph.D., professor of pathology and obstetrics and gynecology at the Duke University Medical Center elaborates on the screening fatigue likely affecting DES daughters: "As more than 30 years have elapsed since the link was made between DES exposure in utero and the development of cancer in the daughters, many daughters likely feel that due to their extensive earlier screening, the time may have passed when clear cell carcinoma might arise," he speculates.

But, he points out, "The entire field has shifted regarding screening for the average population, but most clear cell cancers will be HPV-related. The most sensible preventive measure for DES-exposed women remains Pap smears with annual gynecological exams including digital palpation of the vagina and cervical surfaces and Schiller staining of the mucosa" to identify any problems while they're in early, treatable states.

Least surprising—and perhaps most worrisome—regarding the study, among the 2,861 DES-exposed and 1,027 unexposed respondents was that a lack of health insurance contributed to infrequent Pap smears.

The authors wrote that they hope increased awareness among doctors about the factors preventing the high-risk, DES-exposed population from undergoing regular gynecological screenings will help them better tailor their care plans in terms of early detection of cervical and vaginal adenocarcinomas.

To read the abstract, go here: http://1.usa.gov/1RWDpxV or search for it at PubMed.gov. DES VOICE

The American Cancer Society changed its guidelines for breast cancer screening frequency in October—although they noted that the DES-exposed need more individualized recommendations in their new printable guide, "Guidelines for the Early Detection of Cancer." Find it here and talk to your doctor about how often you should be screened: http://bit.ly/1MED6mQ

DES Action® VOICE

DES Action USA
178 Columbus Avenue #237182
New York, NY 10023

www.desaction.org

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Research Reveals DES Effects on Male Reproductive Organs

By Virginia Pelley

Increasing incidences of male reproductive problems such as testicular cancer, low semen quality, undescended testis and hypospadias (abnormal development in which the opening of the urethra is on the underside of the penis instead of at the tip) are a growing concern in the medical community. Of particular interest to scientists is determining how the reproductive system is affected by exposure to environmental chemicals such as BPA.

There appears to be a connection between exposure to environmental estrogens and deteriorating male reproductive function, but they're not sure why, researchers wrote in their paper published in the *International Journal of Clinical and Experimental Pathology*.

The use in decades past of DES, a synthetic estrogen, provides the only evidence we have about the effect of estrogen on human beings. So Chinese researchers treated testis (male sex gland) cells with DES to better understand the mechanisms that might affect their development—in turn offering insights into how exposure to EEs might affect male reproductive organs. In doing so, they were able to show that DES impaired how testis cells are put together as well as how they shrink and reproduce.

In essence, this paper provides mechanistic insight for the increase in undescended testicles seen in DES-exposed sons, whose exact numbers are unknown but is estimated to be between 1 million and 3 million in the US alone. It also identifies a pathway that's disrupted in the cells of the gubernaculum (the fibrous cord connecting the testis and scrotum) by DES exposure and suggests that the effects on the gubernaculum are not mediated by a classical estrogen receptor but by the G protein-coupled estrogen receptor or GPER.

Estrogen receptor GPER was identified less than a decade ago, so researchers are only beginning to understand what it does.

Therefore, their conclusion that DES affects the expression of GPER in testis cells could lead to better understanding of how exposure to the drug causes abnormalities as well as how to eventually treat them. DES VOICE