DES Action® 40TH ANNIVERSARY
VOICE
We identify, educate, empower and advocate for DES-exposed individuals

Inside

A Focus On Diethylstilbestrol

WINTER 2018 #155

Increased Risk of Breast, Pancreatic Cancer in DES Daughters

A new paper reporting on data from the DES Follow-up Study found an increased risk of three different cancers among DES Daughters compared to women not exposed prenatally to DES. Risk of breast cancer and pancreatic cancer was slightly higher in those exposed to DES, but their risk of clear cell adenocarcinoma (CCA) remained substantially higher.

The finding related to pancreatic cancer risk is new but based on only a few cases that are no longer statistically significant after adjustment for other factors. Meanwhile, DES Daughters had a reduced risk of endometrial cancer, approximately half that of unexposed women. DES Daughters did not show an increased overall risk of cancer when looking at all possible cancer types.

"Thus, we believe that DES exposure is not likely responsible for substantial excess risks of most of the cancer types we were able to evaluate," wrote the study's lead author, Rebecca Troisi, ScD, and her colleagues. Not finding an increased risk for other cancers, especially non-CCA cervical cancer, was reassuring, the authors wrote.

Dr. Troisi told the DES VOICE that she doesn't believe DES Daughters need to take any action related to the pancreatic cancer findings since the disease is so rare and the results were not statistically significant when other differences among the women were factored in.

"I also don't think they are at high risk of breast cancer and the routine screening that is recommended for the general population should be fine," Dr. Troisi said. "They should continue to be screened for cervical cancer," she added, noting that the recently updated guidelines that reduced screening frequency for the general population do not apply to DES-exposed women, who should be followed more regularly.

"DES Daughters' overall cancer risk is similar to the general population," Dr. Troisi said. "I don't think these results should be alarming, and we will continue to follow the women for cancer and report on our findings in the future."

The study was published in *Environmental and Molecular Mutagenesis* in November 2017 (doi: 10.1002/em.22155). The study includes ten additional years of follow-up since the last study on cancer from this follow-up study group.

"This is a more challenging task than evaluating many of the other end-points linked, or thought to be linked, to DES exposure, because there are scores of different cancers and the rates of disease for most are low compared to the rates of many of the adverse reproductive outcomes associated with this exposure," Troisi and her colleagues wrote.

This study includes the largest number of DES Daughters of other long-term studies, but the research population is still small enough that it's not mathematically possible to reliably calculate a

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Did DES Cause This? Fibromyalgia and Hypospadias

DES Action USA frequently receives questions from people exposed to DES who want to know whether the endocrine-disrupting chemical might have played a role in some health condition they have.

In response, the DES VOICE newsletter is introducing a new column called "Did DES Cause This?"

Can DES Cause Hypospadias?

Hypospadias refers to having the opening to the urethra—the hole that semen and urine comes out—in some place on the penis besides the center of the tip, where it normally is. This kind of condition is evident at birth and can cause problems such as

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Gender, sex, sexuality and DES-exposure
Do you have any thoughts or a story to share?

Jacquelyne Luce, Ph.D.
Department of Gender Studies
Mount Holyoke College

How has your exposure to DES shaped your understanding of gender, sex, and sexuality? With a grant from DES Action USA, I am conducting a new research project exploring the relationships between people's experiences of gender, sex, sexuality, and sexual orientation and their experiences of the physical and psychological effects of being DES-exposed. This is an area of study that has not received much prior attention. You can volunteer to be part of it.

Most members of the DES-exposed second generation would have reached puberty between 1960 and 1985, a time of both very strong societal ideas about femininity and masculinity, as well as increasing resistance to expectations about what it means to be a woman or man. New ideas about sex hormones and techniques of genital surgery also emerged during this time period, shaping various fields of intersex and transgender health. The third generation of DES-exposed people is likely to have been born anytime between 1975 and now, experiencing life in a world of both rigid and fluid ideas about gender, sex and sexuality.

My work as a researcher involves seeking out and listening intensely to people's stories about their experiences of the body, health, disability and difference, and situating these within local and global developments in science and medicine. I wonder: How can members of the DES-exposed communities, who lived through the forefront of the women's rights movement, the LGBT rights movement, and the Intersex rights movement, contribute to our understandings of the relationship between bodies and identity? How can the stories of this community help us to better understand the historical ongoing health, advocacy, and research needs of LGBTIQ and gender non-conforming DES-exposed people?

Do you have a story tell? Would you like your experience included? We are looking for volunteers who are interested in sharing their thoughts about the connections they make between being DES-exposed and their gender identity, notions of biological, hormonal or chromosomal sex, and sexuality (including sexual orientation and preference).

We will conduct interviews by phone and video conference, recording these with your permission. We will anonymize everyone who shares their story in order to protect your privacy. These interviews will be like open-ended conversations. You don't have to prepare for them in any special way. We are not looking for any particular "answer." Instead, your participation will help us shape our research, and the larger themes we explore.

We will be sharing the ongoing thoughts that emerge from this research with you via VOICE and the DES Action website. If you would like to receive more information about the project or you would like to schedule an interview, please call me at 413-538-3369 or email me at jluce@mtholyoke.edu, and write "DES Action Study" in the subject line. DES VOICE

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Q&A with a Member: Dealing with the Guilt and Anger

Joann Linthicum

As a DES Mother, Joann Linthicum gave birth to two daughters exposed to DES while Joann was pregnant. Both had been angry or shocked when they heard about their exposure to the drug, Joann said, and she wanted to share her story as one of the millions of women misled into taking a drug with no benefit and plenty of harm.

Q: Tell us about the experience of finding out about the harms of DES.

A: In 1973, when my first daughter was about 10 years old, I happened to turn the TV on and saw a DES Daughter who had cancer. I remembered that before my pregnancy with my first daughter, I had lost a pregnancy about 6 weeks along. When I became pregnant again, my OBGYN told me he would give me something to prevent miscarriage. I called my OBGYN to find out if the medication I had taken was DES. It was, but he told me I would have taken it for 3 months, not the 9 months that would have really led to problems.

However, when my oldest daughter was 13, a test showed she had adenosis and needed to see the gynecologist every 6 months for a while. She was never able to have biological children, but she adopted a boy and a girl. With my second child, a daughter born in 1965, I did not take any medication during the pregnancy.

But while pregnant with my third child, a daughter born in 1967, I had some cramping early in the pregnancy and was given DES for four months. She later had two miscarriages, then a son, and then two more miscarriages before she had a second son. We learned she had the T-shaped uterus, a problem with one of her Fallopian tubes, and an incompetent cervix. She was therefore on complete bed rest for more than four months during both pregnancies. During her second son's pregnancy, she was hospitalized at seven months gestation and gave birth to her son two months early. My fourth child, a son born in 1969, had no problems; I took no medication during his pregnancy.

Q: In what ways has your exposure to DES impacted your life?

A: Over the years, I have experienced anger with the OBGYN, who I didn't feel was being truthful to me and who then didn't check my records to see if he had given me DES while I was pregnant with any other of my children he delivered. I wonder how many other mothers he gave this medication to without telling them. I have also dealt with guilt, especially with my first daughter, because I feel like she has not been able to have biological children because of what I took while pregnant. I also feel the heartache of my other daughter losing four children and thinking of her holding one born prematurely (at 5 months) who also died. I have heard that doctors also knew (though perhaps not all of them) that DES didn't prevent miscarriage—but then it created reproductive problems in the daughters. How ironic is that?

I was angry with the pharmaceutical companies that produced this medication, and my daughters did have a lawsuit and received some remuneration for what they went through.

Q: How did you find out about DES Action and what have you gotten out of your membership?

A: Perhaps it was when I first saw the story on TV in 1973 that I became a member of DES Action. I have written several letters over the years sharing my story: one in 1996 and one in our local newspaper before then sharing some of my story under different names.

DES Action has been very helpful to me through all these years, just knowing that I haven't been alone in this. I am sad, however, for those who have had pregnancy problems and never knew the reason why, when it was DES-related. I plan to continue my membership, and hopefully my daughters will continue when I am no longer here. Research is so important, and it is important for all of us to know what is being done in this field. I do need to add that God has also been very important in my life in getting through the challenges that all of us face. DES VOICE

Q&A: Another Man's DES Journey

Rich Carey (exposed in 1949) saw another DES Son's story in the newsletter and it inspired him to share his story. He hopes other DES Sons will make their stories heard as well.

Q: How did you learn about your DES exposure and what was the experience like?

A: It was during the third year of my marriage (in 1978). We were trying to get pregnant to no avail. Right off I thought it was my fault as I couldn't seem to hold an erection due to my microphallus, or that it was related to testicular stress caused by a terrible bout of the mumps that my older brother (born in 1945) told me about from my early life. My mother, a surgical nurse, told me I had had the mumps but had not described how stressful the illness was on my body.

When I told my mother that my wife and I were having trouble getting pregnant, she told me she took DES while pregnant with me. She had accumulated all the research and never shared it with me. She said, "I didn't tell you because I thought you wouldn't get married. I will go to my grave knowing that my taking DES during your pregnancy to prevent a miscarriage will haunt me the rest of my life!" To say the least, I was dumbfounded and my wife was angry. I felt angry and betrayed as well.

Q: In what ways have you been affected by your DES exposure?

A: I always knew I was different because my genitals were small (smaller than my brother's, for sure). I was embarrassed to take showers during PE class because of it.

I also remember I didn't seem to have the same excitement of teenage hormones bouncing around to make me attracted to girls. It caused me to be extremely shy and reserved around my male friends who were experiencing those urges. I even had thoughts of homosexual tendencies.

Once I was told by my mother about DES, I went to an endocrinologist at a reputable clinic to be further evaluated. His nurse asked me when I had a vasectomy because there were no sperm in my sample I submitted. Of course, I had not had that operation. The doctor did a digital exam and told me my prostate was underdeveloped so my semen would be clear. He tested my testosterone levels and felt I needed an injection. But he later said I didn't need to continue it, and medical investigation seemed to go nowhere.

Finding out about DES early in my marriage had an extreme psychological effect on my sexual behavior. "I couldn't have children, so why have sex?" I thought. Sex for pure enjoyment waned (even though I had foolproof birth control), and then mutual masturbation evolved, but eventually waned also. We went through sexual behavioral therapy, hypnosis therapy and numerous marriage counseling sessions to figure out what was going on in our intimacy; nothing seemed to work.

Q: How did you find out about DES Action USA and what led you to join?

A: I went online to investigate DES usage and was primarily interested to see if there was any research on Sons. All I could find were volumes of information on Daughters. DES Action USA offered what research was available for Sons.

Q: Can you describe what it's like to be a DES Son when so much research focuses on effects on DES Daughters?

A: I was totally frustrated! How could there be little or no research on Sons? Sons have just as much a right to know what this drug has done to us physically. Now I know that DES was an endocrine disruptor. Maybe this could account for my lack of sexual desire throughout my life? There could have been a chemical reason for my behavior! It would have been nice to KNOW that fact earlier! I know my DES exposure is a done deal. What I really want to know more about is information about the possibility of how endocrine disruptors affected me prenatally. I just need to know!

Q: If you could make one improvement to DES Action USA, what would it be and why?

A: As Tom Shrifter, another DES Son mentioned in a past issue, I would like to see more information for DES Sons and have an available online support group for us. Being a member now, I hope I can be kept abreast of this research. DES Action USA must continue to provide this information and keep physicians up to date on the research the organization finds.

How Does DES Affect Developing Reproductive Systems?

We never knew exactly, until now

Mice have been used in medical research studies for decades. Drugs are routinely tested on mice for safety and effectiveness before testing on humans. But a mouse's reproductive system isn't identical to a human's, and quite often the outcome can be misleading.

In an exciting new development, scientists have successfully found a new way to study how DES affects a developing human fetus. Researchers can take developing human fetal tissue grown in a lab and transplant it into another animal's uterus to watch it develop. When researchers expose that animal to DES, they come as close as possible to seeing what happens when human fetal tissue is exposed to DES during development.

DES-Related Changes

In one such recent study, scientists saw exactly how DES affected the development of a human fetus's female reproductive tract. They saw four major changes that occurred compared to normal developing fetal tissue. They also discovered that DES stimulated two genes (in tissue where they don't belong) that create proteins affecting estrogen and progesterone behavior in the body.

These results tell researchers for the first time what proteins to look for to understand how DES affects the developing human reproductive tract. That means they can now use the same technique to tell if abnormal development might occur in the human female reproductive tract when exposed to other estrogen-based endocrine disruptors.

BOTTOM LINE: The researchers could observe exactly how DES changed fetal tissue in ways that could affect future disease risk. They can now look for these changes with other chemicals.

Hopefully, this method of growing specific types of developing fetal tissue in lab animals can help researchers also learn how DES affects other types of fetal tissue, such as the male reproductive tract.

The Study's Procedures

The researchers grew human fetal reproductive tracts inside special female lab mice. (It was only fetal female reproductive tract tissue—not a whole human fetus—transplanted into each lab mouse.) The mice's ovaries had been removed, and they lacked a thymus gland. (Without a thymus, the mouse has no T cells, a type of immune cell, so it won't reject transplanted cells.)

The transplanted human fetal reproductive tracts were from 9.5 to 22 weeks gestation and were grown for one month inside the mice. Half the mice continuously received DES through injections; the other half did not.

The researchers watched how the fetal cells differentiated as they grew. (During differentiation, human cells develop into the type of cell they will become in the fully formed human. Cells differentiate into lung cells, brain cells, heart cells, muscle cells, etc.)

What DES Exposure Did

Normal development and cell differentiation occurred in the human tissue in the mice not receiving DES. The human tissue development looked similar to what would be seen inside a human.

In the mice receiving DES, however, several structural changes occurred in the human tissue. The researchers observed four specific changes in particular: First, more glands developed in the endometrial and cervical tissue. Second, the outer tissue lining of the Fallopian tubes had more folding than normal. Third, the vagina's outer tissue lining developed into very thin, flattened cells. Finally, the vaginal tissue experienced abnormal gland development and enlargement.

In addition, a gene (PGR) was activated throughout the DES-exposed developing human female reproductive tract that creates a protein controlling how progesterone affects the body. The scientists also found expression of the ESR1 gene in the cervix and main body of the uterus when it is typically found only in a different part of the uterus in unexposed tissue. Scientists know that the ESR1 gene creates a specific estrogen receptor, which is a protein involved in diseases such as breast cancer, endometrial cancer and osteoporosis.

The study was led by Gerald R. Cunha, of the Department of Urology at the University of California in San Francisco. It was first published online in October 2017 in the medical journal *Differentiation*. DES VOICE

CV Risks For DES Daughters

You'll find details about the CV study on the desaction.org homepage.

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urinary tract infections and sexual problems.

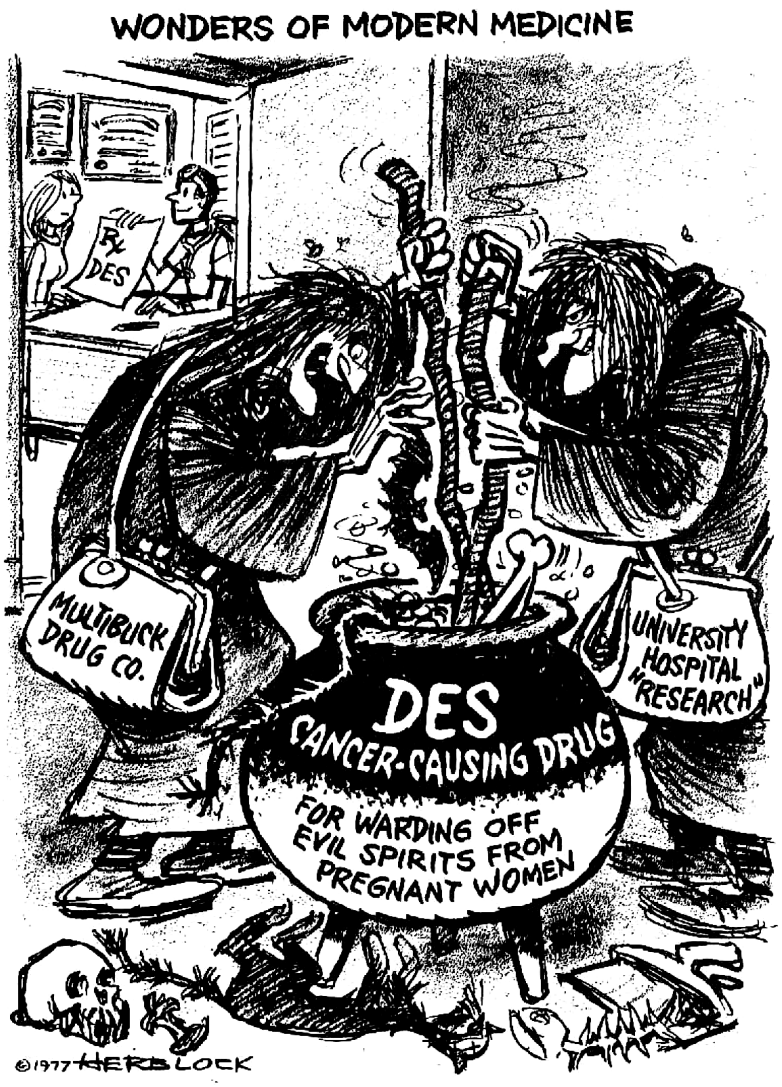
A mild case of hypospadias might mean the urethral opening is on the tip but further down than it should be, maybe almost on the underside of the penis. In a more severe case of hypospadias, the urethral opening is somewhere else along the shaft of the penis. It could be on the top or the underside, but it could be in the middle of the penis or even further back.

Researchers have been looking at whether prenatal DES exposure is linked to defects in the male reproductive tract since the mid-1970s. A study in *Science* in 1975 identified several conditions that occur more often in males exposed to DES, including hypospadias. Additional studies after that one similarly found a higher incidence of hypospadias in both DES Sons and DES Grandsons than in the general population.

The three most common developmental problems occurring in DES Sons are undescended testicles, hypospadias and a microphallus (smaller than usual penis). These problems only occur in about 5% to 8% of the general population, but they occur in DES Sons about 15% to 32% of the time, according to a 2013 study in Birth Defects Res C Embryo Today (doi:10.1002/bdrc.21035). Another study in 2008 found that DES Sons were 3.7 times more likely to have hypospadias than males not exposed to DES.

It's still not clear how much greater the risk is of hypospadias in DES Grandsons, but the total number of DES Grandsons affected is small.

Verdict: The evidence is clear: DES can cause hypospadias in both DES Sons and DES Grandsons.



From the first issue of the VOICE, Winter 1979.

Does DES Cause Fibromyalgia?

Fibromyalgia is a medically mysterious and complex condition, an autoimmune disease that causes chronic pain throughout the body. It affects approximately 2–3% of the population, and few therapies treat it effectively.

No studies to date have specifically looked at fibromyalgia and DES exposure, though a 2010 study based on the DES Follow-up Study found no increased risk of autoimmune diseases in general among those exposed to DES. In addition, several ongoing DES Daughter and Son studies collect data on all medical conditions and health problems that DES Daughters experience. Comparing the rates of DES Daughters' conditions to those of the general population shows researchers which conditions occur more often in those exposed to DES. If fibromyalgia occurred more often among DES Daughters or Sons, the data would have revealed an association by now. Yet no studies have shown a link between fibromyalgia and DES exposure.

Verdict: The evidence suggests fibromyalgia and prenatal DES exposure are not related.

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moderate or small increased risk for different cancers.

The Study Protocol

Of the 7,439 daughters in the original continuing cohort study of the DES Follow-up Study, 6,905 participated in this study, including 4,822 exposed prenatally to DES and 2,083 not exposed. The women not included in the study had declined participation, could not be located, died or developed cancer before the follow-up data collection began.

The study population was made up of two groups, one beginning in 1978 and the other beginning in the early 1990s. The first group had been tracked for approximately 34 years, and the second group had been tracked for approximately 17 years.

After the first questionnaire in 1994, the participants filled out questionnaires every 5 years through 2011. Cancer diagnoses reported by the women were confirmed, when possible, through pathology reports and tissue slides, but all cases of cancer reported by the women were included in the analysis. The researchers did, however, exclude cases of skin cancer and non-CCA cervical cancer because of inconsistent data on them in past studies.

During the follow-up period, 335 DES-exposed women and 159 unexposed women developed their first-ever invasive cancer (but remember that this follow-up study included 4,822 exposed prenatally to DES and 2,083 not exposed). The rate of cancer cases was nearly the same in the DES-exposed and unexposed groups, and similar to the number of cases in the general population.

The researchers then adjusted their calculations to take into account differences among the women in educational level, smoking, alcohol consumption, number of pregnancies, number of live births, menopausal status, use of hormone replacement therapy, body mass index (BMI, a measure of weight), and a history of cancer in their parents or siblings.

However, the overall cancer rate remained similar between the exposed and unexposed groups and showed no increased risk for DES Daughters when looking at all cancers together. Then the researchers looked more closely at individual cancer types.

Specific Cancer Findings

The most common cancer across all the study participants was breast cancer. Before taking into account differences among the women, the researchers found an approximately 17% increased risk of breast cancer among DES Daughters of all ages combined, compared to unexposed women. For women ages 40–49, that risk increased to 33% greater.

However, when the researchers adjusted for the women's ages and the other factors listed above (education, smoking, etc.), the risk of breast cancer in DES Daughters was no longer higher than the risk in unexposed women.

What does that difference mean? It means that the overall increased risk seen before any adjustments (17%) is likely due to some of those other characteristics, such as age, weight or other health conditions. It's possible, the authors suggested, that DES is worsening one or more other risk factors, thereby leading indirectly to a slightly increased risk of breast cancer.

DES Daughters developed clear cell adenocarcinoma over 27 times more often than unexposed women. However, these cases occurred at older ages than previously seen, including one case at age 39. The researchers also found four cases of vulvar cancer and two cases of vaginal cancer (non-CCA), but it's not clear if there's an increased risk for these cancers.

Meanwhile, pancreatic cancer occurred about twice as often among DES Daughters than among unexposed women in one of the two comparison calculations made. In the other comparison, the findings were not statistically significant. Most of the pancreatic cancer cases occurred in women over 50 years old, and doubled risk is based on only a handful of cases. It's therefore considered a preliminary finding that requires more study.

There are no officially recommended screening tests for pancreatic cancer, and there are usually no symptoms until the cancer has advanced to other organs. Then the symptoms will depend on where the cancer has spread.

If you are a DES Daughter, you should speak with your doctor about whether to get screened for pancreatic cancer and when. You should bring in this article or the original study to show your doctor. However, keep in mind that your doctor may not recommend screening since the increased risk is low, the finding is preliminary, and there are no guidelines for standardized or routine pancreatic cancer screening. If your doctor is uncertain of what to recommend, contact the nearest large academic medical center for more information.

Other cancer types analyzed, based on those reported by the women, included ovarian cancer, non-Hodgkin's lymphoma, colorectal cancer and leukemia. When the researchers looked at the dosages DES women were exposed to, they did not find any differences in cancer risk based on a lower or higher dose.

DES Daughters had no greater risk of death from cancer or any other cause than unexposed women. The overall similar cancer risk between DES-exposed and unexposed women is similar to findings in a different 2010 study in the Netherlands, the authors explained.

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DES Action's 40th Anniversary! Celebrate With Us!

2018 marks the fourth decade since DES Action USA became a reality: 40 years of identifying, educating, empowering and advocating for those affected by DES exposure.

In the Spring and Fall VOICE newsletters, we will have short profiles of the early women and men of DES Action USA. Many women have already been nominated, but we want to hear from you, too. If you want to be included or recommend someone, please email Karen Calechman at Karen@DESAction.org.

Join Us on Facebook Live

See us live on the DES Action USA Facebook page! Each month we will hold a Facebook Live event where you can participate with questions and revisit the video later. Already in January Su Robotti interviewed David Fuehrer of Stupid Cancer. Check out the video of this Facebook Live on our homepage.

Upcoming topics for Facebook Live include new research on the effects of DES on DES Daughters, Sons and Grandchildren, which mammograms are best for dense breasts and learn about the experiences of the third generation.

February 27, 7 pm ET

Documentarian Judith Helfand will talk about her life as a DES Daughter, including surviving cervical cancer and eventually becoming an adoptive mother. Helfand's 1997 Peabody Award-winning film, *A Healthy Baby Girl,* explores mother-daughter love, family renewal, survival, political awakening and community activism.

March 21, 6 pm ET

Susan E. Bell, Ph.D., noted author of *DES Daughters: Embodied Knowledge and the Transformation of Women's Health Politics*, will talk about her research and writing about DES Daughters who developed cancer, had concerns about fertility and motherhood, and suffered other medical and/or reproductive difficulties. Dr. Bell is the Department Head and Professor of Sociology at Drexel University.

We have much more in store, and we will promote each Facebook Live on Facebook, Twitter, on our DES Daughters Yahoo Group, on our website and in our DES Action eMail Alerts. We hope you'll join us! DES VOICE