

New Study Suggests DES Effects in DES Granddaughters

DES Granddaughters have a higher risk of irregular menstruation, of going at least six weeks without a period and of having a preterm birth delivery than other women in the population whose mothers were not DES Daughters. A new study published in late December in the journal *Reproductive Toxicity* suggests multigenerational effects from DES exposure that scientists have long suspected.

It's also possible that DES Granddaughters are at higher risk for ectopic pregnancies, but that's less certain, reported lead author and DES researcher Linda Titus, PhD, of Dartmouth. Her coauthors included top NIH DES researchers Rebecca Troisi ScD and Dr. Robert Hoover as well as Dr. Arthur Herbst, the first to publish research showing the increased risk of clear-cell adenocarcinoma (CCA) in young DES Daughters.

These long-time researchers chose to study menstruation and pregnancy/birth outcomes because these events are linked to hormonal regulation, which is one of the processes most likely to be affected by a family history of DES exposure.

"These findings are consistent with the notion that prenatal exposure to DES can influence outcomes in the next generation of offspring," the researchers wrote.

Past research in animals has found that effects from prenatal

DES exposure do not stop with the growing fetus. Instead, these effects can carry over into several later generations through epigenetic changes.

Epigenetic changes refer to changes in how genes are expressed—whether they are told to act or stop acting in certain ways—rather than what the genes themselves are. This relatively new area of research has found a wide range of exposures have long-lasting effects in the gene expression of one's descendants.

For example, although the exposure types are quite different, scientists have found that severe trauma from slavery or the Holocaust or starvation during famines has lasting effects on later generations. (DES is a chemical exposure, not one of

trauma or starvation, but the mechanism—resulting from some sort of non-typical experience to the body—is the same.)

In DES research, mouse studies have shown changes in "gene expression as well as an increased occurrence of reproductive tract structural anomalies and tumors in females born to [female] animals exposed to DES in utero."

Often, what happens in mice may not translate to humans. However, with DES, past studies have shown that research in DES-exposed mice has accurately predicted or replicated health outcomes in DES Daughters. The mice findings had therefore raised concerns about "intergenerational transmission of DES effects," the authors explained.

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Does DES Cause Musculoskeletal Problems?

We discussed in the last issue of the *VOICE* whether DES might contribute to a higher risk for hip dysplasia in DES Children or Grandchildren. We reported that there may be an indirect increased risk in DES Grandchildren as a result of possible pregnancy complications in DES Daughters.

In the process of researching

that question, we also discovered research in mice that explored whether prenatal exposure to DES affects musculoskeletal development. Studies in mice cannot directly translate to humans. However, if findings in mice suggest a possible connection between DES and joint problems, it might lead to

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Gender/Sex/Sexuality and DES Exposure

Part 5: Sexual Health, the Body and Sex

Jacquelyne Luce, PhD, Principal Investigator and Lecturer in Gender Studies, Mount Holyoke College

In discussions about women's health education and care, reproductive and sexual health are often very closely related. A number of cisgender (one's gender identity aligns with the sex one was assigned at birth) interviewees in this research project spent many years experiencing pregnancy loss and fertility treatment (often prior to the knowledge about the effects of DES exposure on reproduction). Some interviewees experienced surgeries such as vaginoplasty, hysterectomy, and vaginectomy in order to treat anatomical differences or cancer. Such experiences have been associated with people's experiences or perceptions of

gender (for example, one's sense of being a woman). When I asked one interviewee, who I will call Lisa, whether she thought that having been exposed to DES had influenced her sense of gender, or her sense of being a woman, she responded, "No. More my sexuality." What did she mean?

Lisa was born in the mid-1950s. She tried to get pregnant for nine years before an infertility specialist recommended a hysterectomy upon seeing the significantly altered shape of her uterus and linking it to an emerging profile of women who had been exposed to DES in utero. Lisa has since suffered from what is thought to be DES-related cancer twice, experiencing a partial vaginectomy and radiation treatment. Lisa said that sexual intercourse in her

twenties had been painful, but she hadn't known that it wasn't supposed to be. She now associates that pain with vaginal differences, specifically having no glandular secretion, which she understands to be related to DES exposure. (This is in contrast to the increased vaginal secretions associated with DES-related vaginal adenosis.) "[At the time of the hysterectomy when I was 29] I was so naive and nobody explained anything to me." She contrasted her experiences of infertility treatment with her most recent cancer care five years ago: "Now I have doctors who have helped me and I think that if I had had that 30 years ago, things would have been a lot different [...] I have a new doctor [who] has *some* experience with DES, *but* she's very active in women's health and sexuality and she's the one who told us about different things to use and to try, like olive oil [a lubricant] and cold cones [a form of vaginal dilator]. You put [cold cones] in your vagina. You put them in the refrigerator and then you put them inside and it cools everything off. Just the damage from radiation and the irritation [...] And, I guess the radiologist really helped, talking about the tissue and the radiation damage and, you know, scar tissue. It really made sense. Before I didn't understand why I would have pain in certain positions. It was because there was so much scar tissue."

Lisa's words resonate with so many other people's experiences in which clinically visible and medical effects of exposure to DES were medically managed, yet other DES-related effects—like painful intercourse—were not addressed. Lisa's recent cancer care, in which sexual health

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Published quarterly by:

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MedShadow Foundation, Inc.

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MedShadow Foundation, Inc.

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ISSN 1522-0389

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Review Discusses Environmental Risks for Breast Cancer

A recent review of existing evidence linking environmental exposures with breast cancer provides insight into the progress of research in risks for breast cancer.

The research review, conducted by Janet M. Gray, of Vassar College Department of Psychology in Poughkeepsie, New York, and her colleagues, appeared in the journal *Environmental Health* in September 2017.

The hefty document is an update of a similar research review done eight years ago and includes more than 40 pages summarizing the most recent exposures linked in any way to breast cancer, though multiple sections cover the same research.

“Epidemiological data strongly support the link between increased risk of developing breast cancer and early developmental exposures to DES, DDT and radiation, as well as adult exposures to oral contraceptives and hormone replacement therapy,” the researchers reported, though the amount of increased risk varies by age, race/ethnicity, geography and other demographic and medical characteristics.

The researchers also identified an increasing body of evidence showing that night shift work increases breast cancer risk. Lack of consistency in sleeping schedules, circadian rhythms and work schedules has been a growing area of research linked to a wide range of health conditions, including obesity, sleeping disorder, diabetes and heart disease.

The review also looked at the possible influence of different environmental chemicals, especially endocrine-disrupting chemicals, on breast cancer risk.

Animal studies have suggested

that exposure to these chemicals might increase the risk of “predisposing mammary tissue to develop tumors,” but that does not necessarily mean those chemicals will cause cancer, or tell us how much exposure might be required to potentially increase risk of cancer.

Most animal studies do not translate well to humans, and it’s remarkably easy to grow tumors in mammal tissue and Petri dishes even when such growth would not occur in a living person. As the researchers note, the current design of these studies cannot yet provide good understanding about how much risk these chemicals might pose, in what doses or by what route of exposure (oral, respiratory, skin absorption, etc.).

One of the review’s biggest limitations is including a broad range of environmental exposures whose link to breast cancer is weaker than the review seems to suggest. In some cases, the amount of increased risk is modest enough that it’s unclear whether the information is actually helpful.

For example, if a specific chemical in the environment that everyone is unavoidably exposed to appears linked with a 10% increase in breast cancer risk, it’s uncertain how to use that information in a meaningful way.


In other cases, the evidence for a particular exposure is weak. That could mean it relies on observational studies that are not carefully enough designed to exclude other explanations for an apparent link.

Or, the evidence could be only animal studies that either use a very high dose of the exposure (much more than a human would encounter proportionally) or which otherwise cannot necessarily

translate to humans. (Many things cause—and cure—cancer in animals that do not appear to cause it—or cure it—in humans.)


The review discussed the already known risk for breast cancer among DES Mothers and, to a lesser extent, in DES Daughters. It suggests a way in which DES Granddaughters might experience an increased risk of breast cancer, but so far no research has shown that such a risk exists.

The primary value of the review is in suggesting what future research needs to explore. Hopefully, by the next review, more well-designed studies will have revealed more reliable information about environmental exposures and risk of breast cancer.

The research did not use outside funding. The authors had no link to pharmaceutical companies or other conflicts of interest. Study: Gray et al. *Environmental Health*. (2017) 16:94. doi: 10.1186/s12940-017-0287-4. 

Gender/Sex/Sexuality and DES Exposure

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is explicitly addressed by her healthcare providers, offers her new possibilities for understanding her body and experiencing sex. Her new gynecologist’s specialization in women’s health and sexuality is viewed as valuable as, or more than, having specific knowledge about DES. Lisa’s story, along with those of other interviewees, highlights a current need for life-stage appropriate sexual health education and care, which is informed by the very specific bodily and clinical experiences and social histories which have shaped the experiences of sexuality, desire and intimacy of people who were exposed to DES in utero. 

Q&A with Joelle Codde, Born a DES Son

Joelle Codde, a 70-year-old professor emeritus of the Michigan State University College of Education, was assigned male at birth. However, she tells DES Action that being gendered a male never felt quite right. On her journey to understand more, she discovered it was highly likely she was exposed prenatally to DES in 1948–1949. She could never get confirmation because her mother had passed away and the hospital had purged its medical records. She strongly suspects DES played a role in her gender dysphoria, though she also knows the important thing is that she finally, after transitioning in her post-retirement silver years, gets to live life in a way that feels right to her.



Joelle Codde

Tell us about your journey of discovering your likely DES exposure.

I knew at five years old that something was different and that I should have been a girl. As a child and into adolescence I did one thing that so many young people who shared the same feelings did: I prayed every single day to be transformed. I also remember thinking if I were to commit suicide, I would have a 50/50 chance of coming back as a girl.

As I reached my teens I recognized there was nothing I could do to change genders. You live the life you have been given and, although I've thought about wanting to change every single day of my life, I knew the reality was there was nothing I could do.

I then set about living my life to the fullest. We only get one chance at life in this world, and rather than bemoan being assigned male, I accepted it and married, had two children and had a fantastic career. It has only been in the last four

years that I've transitioned genders, and now, although I'm retired, I'm back working again on a new topic I'm passionate about—transgender healthcare.

My transition began in 2015 during a time where I was having a lot of problems with fatigue and just feeling poorly. Diagnosed with anemia, I was referred to a hematologist who noted my testosterone levels were very low and prescribed the testosterone supplement Androgel. Almost immediately, my breasts began developing. Initially, the doctors said it was gynecomastia, a side effect of Androgel.

But my breasts continued to grow and, as my doctor noted, became more feminized. I learned the incoming testosterone was being converted to estrogen via the aromatase enzyme, and it was at that point I thought, "Oh my God, the prayers of a five-year-old boy have been answered!"

Joelle ultimately decided to begin transitioning and switched from testosterone to estrogen. In her research, she viewed a PowerPoint presentation by Dr. William Powers, a family physician in the Detroit area who had treated two transgender sisters in their 50s. Both women had been born DES Sons, were separately put up for adoption, transitioned to female, and did not know about each other until after transitioning.

I started researching DES and the related birth defects. My mother did not have any miscarriages, but her twin sister

had several before my mother conceived me, so it's probable that my mother would have told her doctor about her sister, and that he would have prescribed DES for my mother as a precaution.

I did have a number of health conditions related to DES, but at the time nobody made those connections. It wasn't until just recently that all this started coming together.

At 19, Joelle suffered a testicular torsion—a twisting of the testicle that cuts off blood supply. Without treatment, it leads to gangrene, which happened to Joelle. The surgeon who removed it informed Joelle that it was a testicular deformity that caused the torsion. She's also had hypogonadism (very low testosterone levels) her entire life and has scoliosis. Joelle is also left-handed, which is more common among DES Sons.

How did you learn about DES Action and what led you to join?

When I viewed Dr. Powers' presentation and saw his reference to DES, that's when all the puzzle pieces began coming together. I did a Google search on DES and came up with DES Action. I looked at the website and saw this was the only organization that had a lot of reliable information behind it, so I joined. DES Action has provided me with a great deal of useful information and resources and has given me a place to both refer back to and a place to refer others to.

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New Study Suggests DES Effects in DES Granddaughters

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Previous studies have already found limited evidence of intergenerational effects, such as a higher risk for hypospadias in boys born to DES Daughters and a higher risk of menstrual irregularities in girls born to DES Daughters. These menstrual irregularities could potentially increase DES Granddaughters' risk for infertility or ovarian cancer. Researchers previously reported a possibly increased risk of ovarian cancer (not CCA, which is linked to DES exposure in DES daughters), but the finding was based on only three exposed cases in DES Granddaughters, so the findings must be considered preliminary.

This study used data from combining two groups of DES Granddaughters and unexposed granddaughters of women involved in earlier DES clinical trials. The results reflect findings in a first questionnaire from the women (baseline) and in a follow-up an average 8.8 years later.

Among the 796 DES Granddaughters and 469 unexposed women in the study, the average age of first period was similar (12.5 and 12.7 years old, respectively).

However, at the start of the study (baseline), DES Granddaughters were 1.2 times more likely to have irregular periods or not to have a period for at least six weeks. The risk for irregular periods occurred mainly in DES Granddaughters whose mothers (DES Daughters) had observable changes in their inner vaginal lining (epithelium).

"Associations with established DES-related outcomes [such as CCA] are generally stronger in prenatally DES-exposed women who are also affected by vaginal epithelial changes," the researchers wrote. "Thus, in addition to being a marker of early and high-dose

exposure, vaginal epithelial changes may also serve as a marker of DES effects on the developing fetus."

For DES Granddaughters whose mothers had vaginal epithelial changes, risk of irregular periods was 1.3 times greater than daughters of unexposed women. But DES Granddaughters whose mothers lacked vaginal epithelial changes had no increased risk of irregular periods.

The risk of going at least six weeks without a period at all at baseline was higher in DES

few occurred overall.)

In the baseline group, risk of infertility was increased approximately 1.75 times among DES Granddaughters after (but not before) taking into account BMI, but the finding was statistically weak.

No other calculations of infertility, based on age or in the follow-up group, showed increased risk, and it's too early, based on current evidence, to determine whether fertility problems actually are more likely among DES

These menstrual irregularities could potentially increase DES Granddaughters' risk for infertility or ovarian cancer.

Granddaughters as a group, even if their mothers (DES Daughters) did not have vaginal epithelial changes. However, risk remained more evident in daughters of DES Daughters with vaginal epithelial changes.

In the follow-up group of 416 of the original participants, DES Granddaughters were also 1.5 times more likely to have preterm deliveries. (In other words, for every two unexposed women who give birth prematurely, three DES Granddaughters would give birth prematurely.) This risk increased to almost 1.7 after the researchers adjusted the calculation to take BMI and infertility into account.

There was no statistical difference in age at first pregnancy, likelihood of a live birth or miscarriage rates in first pregnancies between DES Granddaughters and unexposed granddaughters.

Although ectopic pregnancies occurred more often in DES Granddaughters than unexposed women, the numbers were too small for this risk to be statistically significant. (That is, the researchers could not rule out the role of chance in the findings because so

Granddaughters.

"A more complete assessment of infertility will be possible when the women are older," the researchers wrote.

The researchers only asked the follow-up group about endometriosis, thyroid conditions, sexual orientation (homosexual or heterosexual) and birth weight, but only birth weight was statistically different in DES Granddaughters.

Their average birth weight was 109 ounces, compared to 116.6 ounces in unexposed women, but this finding was not surprising given known pregnancy complications among DES Daughters. The researchers did not ask about bisexuality, asexuality or gender identity.

"The intergenerational transmission of DES effects has implications for the influence of other pharmaceutical and environmental endocrine-disrupting chemicals on human health," the researchers concluded.

The study was funded by the National Cancer Institute. The authors had no conflicts of interest. Study: *Reprod Toxicol*. 2018 Dec 27;84:32-38. doi: 10.1016/j.reprotox.2018.12.008.

Is Common MRI Contrast Dye Safe? What You Need to Know

Gadolinium-based contrast agents can linger in the body years after an MRI

Note: This is an excerpt from an article which first appeared on DES Action's sister site, MedShadow.org, discussing risks associated with a contrast dye called gadolinium that's sometimes used during MRIs. According to Dr. Gary Levine, a radiologist who specializes in breast screenings at MemorialCare Breast Centers in Laguna Hills, California, DES Daughters with dense breast tissue should get 3-D mammograms followed by a bilateral breast MRI, with and without contrast dye, six months later. You can watch an interview with Dr. Levine in the Members Area of desaction.org.

By Jennifer L.W. Fink

The FDA approved the first gadolinium-based contrast agents (GBCAs) in 1998. Since then, the heavy metal-based contrast agents have been used to assess more than 300 million patients worldwide, according to the American College of Radiology (ACR). The agents help physicians spot problem areas on MRIs and are used in approximately 70% of all MRIs performed in the United States. If you've ever undergone an MRI "with" or "with and without contrast," you've probably been exposed to gadolinium.

Typically, when gadolinium is injected into the body, most of it—as much as 98%—is excreted by the kidneys within 24 hours. A bit more leaves the body via feces. If a patient's kidneys aren't working well, gadolinium can build up in the body and cause problems.

Poor kidney function plus exposure to GBCAs can cause nephrogenic systemic fibrosis (NSF), a rare disease characterized by a hardening and darkening of the skin and other body tissues. Since

2006, physicians have tested patients' kidney function prior to MRIs and withheld GBCAs if the kidneys weren't working well. As a result, gadolinium-related "NSF is just not a problem anymore," says James Carr, MD, vice chair for research in the department of radiology at Northwestern Medicine.

Gadolinium can also cause allergic reactions. Approximately one in 1,000 people will develop an itchy skin rash after injection of GBCA; in most cases, the rash goes away in about an hour without causing any further problems.

About one in 10,000 people have a severe allergic reaction; they may develop swelling of the mouth and lips and have a hard time breathing. Anyone who has ever had an allergic reaction to GBCA should not receive it again—unless there's a dire emergency. Then, "you do what you need to do," Dr. Carr says.

A 2014 scientific paper that showed evidence of gadolinium deposits in the brain, years after scans, ignited concern about the long-term safety of GBCAs. In 2015, the FDA issued a public safety alert and called for more scientific study.

Last year, the agency began requiring warning labels on GBCAs and advised hospitals to share information about GBCAs with patients and family members. To date, researchers say there's no evidence linking gadolinium deposits to health problems. Research is ongoing.

What to Do If Your Healthcare Provider Orders an MRI

If your healthcare provider orders an MRI, ask these three questions to get the information you need to make an informed decision:

1. Are you ordering an MRI with or without contrast? The answer will likely depend on the part of the body being examined. Contrast agents aren't typically used to check joints. They're almost always used when the heart or abdomen is being examined.

If your test won't include contrast, you don't have to worry about gadolinium at all.

2. Are there any other tests that could give you the same information? One way to avoid gadolinium exposure is to avoid MRIs with contrast. So, ask your provider, "Is this MRI scan absolutely necessary?" says Mahadevappa Mahesh, PhD, chief physicist at Johns Hopkins Hospital and a professor of radiology. Another imaging scan such as an ultrasound might be able to reveal the information your physician desires.

This question is especially important if you've had an MRI in the past year or so or expect to need one in the future. At present, "it's not known whether there's a certain threshold of doses you have to get before you see gadolinium deposition," Dr. Carr says, but the studies that have shown evidence of gadolinium deposition all involved subjects who'd received four or more doses of gadolinium over time.

3. What kind of contrast agent will I be receiving? Chemically speaking, two different forms of gadolinium are used as contrast agents: macrocyclic and linear. (The terms refer to the agents' molecular structure.) Available studies suggest that linear agents are more likely to be retained in the body, so "a lot of clinics are moving from the linear type to macrocyclic," Dr. Mahesh says. **DES VOICE**

What additional research on DES do you still want to see done?

I want to see a solid scientific link between DES and gender in DES Sons. I want to confirm that what I think is true is actually true. And I want the medical community, in particular, endocrinologists who treat transgender and gender-variant patients, to better understand this issue.

What is your hope for the future as someone who was likely exposed to DES?

I'm now happier and feeling better than I have at any time in my life. My wife says I have that sense of well-being that I never had before. And, for the first time in my life, I know how it feels to feel great about yourself and what a positive sense of well-being actually feels like.

Why I felt compelled to transition genders and whether or not DES triggered it, I'll never know for sure. But now I'm going

to live the best life I can and do it as a woman. And I'm going to use my voice as both a transgender woman and an academic to be an advocate for our community.

and this just fits in with the history of pharmaceuticals and other things that have gone on, such as thalidomide.

When I did the research on the

I did have a number of health conditions related to DES, but at the time nobody made those connections. It wasn't until just recently that all this started coming together.

I'm hoping to improve transgender healthcare in medical education so that doctors and medical students will have a better understanding of how to treat transgender and gender-variant patients. My mission and goals in life now are to see that we are all treated with care and compassion and with the dignity and respect we all deserve.

How, if at all, has your likely DES exposure affected how you view the medical system, pharmaceutical industry or government regulation?

The pharmaceutical industry has done a lot of bad things over time,

chemist who created DES and the lack of testing in general and testing in humans, I thought, yup, that explains so many things. In some sense, I wish I'd known this so long ago because maybe there would have been something I could have done—a lot of people have litigated this—but I don't have proof so I wouldn't get anywhere with it.

Then again, I think this happened to me—learning about DES and the transition—just at the right time in my life. I would have loved to have transitioned and started this process when I was 15 and blocked the testosterone but at the same time, I've had a good life. **DES VOICE**

Does DES Cause Musculoskeletal Problems?

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studies in humans to see if a similar association exists.

One study found that prenatal DES exposure was linked to changes in bone mineral content and bone area for both male and female mice's femoral and lumbar bones. However, the associations varied by DES dosage and by sex.

Like other endocrine disruptors, DES has a greater effect at both higher and lower doses than it does in more in-between, "medium" doses. (In research terms, this is called a U-shaped dose-response curve because graphing it would show a U shape where exposure and effects are associated.)

Interestingly, male mice tended to show decreased bone mineral

content from the same exposure that led to increased bone mineral content in female mice. Having a higher or lower bone mineral content than typical is linked to different health conditions. For example, in humans, high bone mineral density often indicates degenerative disease, and low bone mineral density can increase the risk of fractures.

"Results suggest that environmental estrogen contaminants can have a detrimental effect on the developmental lumbar bone growth and mineralization in mice," the researchers concluded.

That study, published in 2012, built on similar findings about bone mineral density differences in DES-exposed mice in 2008. However, not much research has occurred since, and DES Action

USA is unaware of any similar research occurring in humans.

Therefore, it is not possible to conclude that prenatal DES exposure causes musculoskeletal problems in general in people. However, some theoretical evidence exists suggesting it's possible, so researchers could still discover a link in future studies.

SOURCES: Effect of in utero exposure to diethylstilbestrol on lumbar and femoral bone, articular cartilage, and the intervertebral disc in male and female adult mice progeny with and without swimming exercise. 2012. doi:10.1186/ar3696

Diethylstilbesterol has gender-specific effects on weight gain and bone development in mice. 2008. doi:10.1080/15287390801988947.

DES VOICE

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Catch Up With Our Facebook Live Interviews

Did you miss any of the Facebook Live interviews that DES Action hosted in 2018 as part of our year-long 40th anniversary celebration? It's not too late to check them out! Members can log into the DES Action website and watch any of the Facebook Live videos below.

Dave Fuehrer, founder of StupidCancer and an app which includes a section for the DES-exposed community.



Judith Helfand, DES Daughter and the Peabody Award-winning filmmaker behind the documentary *A Healthy Baby Girl*.

Susan Bell, author of *DES Daughters: Embodied Knowledge and*

the Transformation of Women's Health Politics in the Late Twentieth Century.



Michael London, a DES lawyer familiar with past and current litigation related to DES.

Jacquelyne Luce, PhD, researcher of the project "Embodying Trans-generational Exposure: Gender/Sex/Sexuality and Experiences of Being DES-Exposed."



Nita Karnik Lee, MD, an oncologist specializing in gynecologic cancer, including clear-cell adenocarcinoma, which is linked to DES exposure.

Susan Helmrich, DES Daughter and cofounder of the DES Cancer Network.

Fran Howell, former DES Action executive director, and Kari Christianson, retired DES Action program director.



Linda Titus, PhD, a Dartmouth professor researching third-generation effects on DES Grandchildren.

Gary M. Levine, MD, a radiologist and mammogram specialist familiar with screenings for DES Daughters.

Su Robotti, DES Action Executive Director, and **Karen Calechman**, DES Action Community Manager.