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

Inside

A Focus on Diethylstilbestrol

SUMMER 2018 #157

New Research Suggests Higher ADHD Risk in DES Grandchildren

A new study found that 7.7% of DES Grandchildren in the study population have attention deficit hyperactivity disorder, compared to 5.2% of children without any links to DES exposure. After accounting for several other factors, the study suggests that DES Grandchildren have a higher risk for ADHD than the general population.

The study was published in *JAMA Pediatrics*. The research was observational, using data that had already been collected for different purposes unrelated to DES. It therefore cannot show that DES exposure caused ADHD in the third generation. There is a chance that other factors might account for the increased risk, including statistical oddities.

Nevertheless, the study's finding of a positive link between ADHD and DES exposure in the third generation emphasizes the need for further research into ways the DES third generation might differ from the general population. As more studies identify these differences, if they are replicated in additional studies, it will become easier to determine what effects may directly result from DES exposure in the third generation's parents.

How the Study Was Conducted

Researchers first used surveys from the Nurses' Health Study II to look for any associations between neurodevelopmental conditions and prenatal exposure to DES. Among the 47,540 women enrolled in the Nurses' Health Study, 1.8% (856) of their mothers had taken DES while pregnant with them.

Then the scientists examined rates of ADHD, as diagnosed by a physician, among the participants' children. The researchers found that 7.7% of DES Daughters' children had ADHD, compared to 5.2% of children whose mothers were not exposed to DES.

The difference between these percentages is small, but it was statistically significant, which means it's likely the difference is not due to chance.

In relative terms, the children whose grandmothers took DES at any time during pregnancy had about 36% higher likelihood of having ADHD than other children, and a 63% higher likelihood if the DES was taken during the first trimester.

"Although additional studies are warranted, these findings could suggest that the first trimester is a critical exposure window," the researchers wrote.

Those percentages, though they look high, only represent the increased risk over the regular population risk, however. (For example, if 10% of the population has a condition, a group with 63% increased risk means that 16% of those group members would actually have that condition.)

The researchers did not see any difference in risk according to the grandchildren's sex.

Over email, DES Action USA Executive Director Su Robotti

continued on page 6

Did DES Cause Autism? We Need More Studies

Autism spectrum disorders have been linked in hundreds of studies to just about every possible environmental exposure you can think of. That does not mean all those exposures caused autism. More simply, the disability is just common enough—but not too common—that it's not difficult to find relationships with various exposures in observational studies. Observational studies only let researchers learn whether two things are associated—not why they are associated—and hundreds of factors might explain an association.

The vast majority of these exposures do not have enough replicated studies to support a real

continued on page 7

Gender/Sex/Sexuality and Experiences of Being DES-Exposed

Part 3: Reflections on the Categories of DES Daughter and DES Son

April Albrecht (Gender Studies major and LYNK summer research intern) and Jacquelyne Luce, PhD (Principal Investigator and Lecturer in Gender Studies), Mount Holyoke College

It is often assumed that we know what terms like DES Daughter or DES Son mean. Through our archival research and interviews, in which we are focusing on how DES exposure is linked to people's experiences of gender, sex and sexuality, we are noticing how people use these terms in ways that can be expanding or constraining.

In the DES Action Archives we came across a reference to a DES stepmom. Another document referred to a DES father. Putting DES before Daughter or Son is understood to mark that individual as having been exposed to DES, emphasizing the heritability of exposure through biological reproduction. The use of the terms DES stepmom and DES father extends the use of family terms to demonstrate a person's relationship to an affected person. This enlarges the visible community of those who are affected by DES, and challenges the notion that only those who are directly exposed are impacted.

Some people exposed in utero may be more likely to hold onto a stricter understanding of DES Daughter or DES Son, upholding an association of the terms Daughter and Son with the sex categories of female and male. For example, one of our interview participants, who we call Ron, changed his gender in his late 20s. We spoke at length about his ideas regarding transgender identities and being intersex. When asked what he would do if he was presented with the categories of DES Daughter or DES Son, he acknowledges:

"It's rough. When I register online for a group and they say, 'Are you a DES Daughter or DES Son?', I will say, 'I'm a DES Daughter,' because that's the closest thing. I don't know what I would do if I had to do it in person. I would try to explain... But I do identify as a DES Daughter to them, because I think if they're doing research and they're looking to put me in a pot, that's the best pot. If I were to say, for instance, that I'm a DES Son, that could conceivably lead researchers to develop inappropriate hypotheses. In the best possible situation I would appear to be an outlier in their data analysis, but in the worst situation I would dilute their population base to the point where they could not have any statistical… you know? I can't do that to their database."

In contrast to the examples of DES stepmom and DES father, which expanded the social dimensions of the terms, Ron places his everyday identity aside, ticking off "DES Daughter" in an effort to acquire appropriate information and to preserve the integrity of any research that might be undertaken. Our question: How might retaining an image of two sexes affected by DES contribute to a lack of appropriate healthcare for DES-exposed people and hinder possibilities for further scientific and medical research into the effects of DES exposure? DES VOICE

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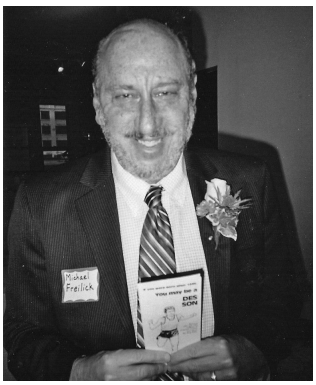
Q&A with Carol Freilick



Carol Freilick's husband Michael, a DES Son ('53) and past president of DES Action, passed away from cardiac arrest on July 6, 2011. As part of our ongoing 40th anniversary retrospective, we asked Carol to share memories about Michael's life and his experiences with DES Action.

Q: How did you learn about your husband's DES exposure?

We actually met through a personal ad in the *Jewish Voice* and went on three dates, and on the third date, we had a conversation about having children. He said to me, "I'm not sure I can father a child biologically." He said his mother took a drug called DES when she was pregnant and it caused a lot of health problems. I had heard of DES, but only in DES Daughters.

I never knew it also affected DES Sons. Ironically, I said "I've had a lot of infertility problems," and the two of us joked, "If this works out, how do you feel about adoption?" From that point forward, we just started dating. Once we cleared the air, it felt like we could really seriously begin dating.

After we were married, we did adopt a healthy newborn named Michelle, now 19 years old, who was a daddy's girl. When Michael went to DES board meetings, he always brought pictures of his family.

Q: Tell us about Michael's involvement in DES Action.

Before I met Mike, he had testicular cancer. When he went through the treatment, he was looking for a support group, and it was around then that he found out his mother took DES. He got connected with DES Sons and then he got more involved with the whole organization.

[DES Mothers] would write letters to DES Action asking about their sons' health problems or support groups for their sons, and those letters were eventually forwarded to Michael, who began answering them. He soon became friends with Fran Howell and Pat Cody and joined the DES Action board representing DES Sons, and then he eventually became president of DES Action.

Q: How did Michael's DES exposure affect his life?

He had so many health problems, but probably the only one that you could possibly consider DES-related was the testicular cancer. [She said they don't know whether the testicular cancer was connected to the DES exposure or not.] He later had bladder cancer that the doctor thought could have been caused by the treatment for his testicular cancer.

My husband was also born six weeks premature with two holes in his heart. Many premature babies have holes in the heart, and we don't know whether he had the heart problem because he was born premature or because of the DES. [Editor's note: DES exposure is associated with premature birth, so it could have contributed to his premature birth.] So his whole childhood up to 12, he couldn't play sports, and he was always sickly.

His parents were told by the doctors when he was around 12 that he needed open-heart surgery or else he would die by age 16, but if they did the surgery, he had a 50% chance of dying during surgery. His parents agreed to the surgery, he survived, and after that, he started to grow taller and stronger.

Q: What has DES Action meant for your family?

Michael enjoyed helping people. He also spoke at our local high school's health classes once a year about testicular cancer and self-examinations. One of the boys who heard his lecture went home and told his parents that he had felt a lump. They went to the doctor, and he had testicular cancer, but because it was treated early, he did well. Michael always felt he had saved a life, and it became important to him to get the word out to listen to your body and do self-exams.

Michael always said that men don't like to talk about things, but he was a big advocate of talking about your health issues, going to the doctor and getting things handled before they got out of control. DES Action gave him the self-satisfaction of feeling like he was saving lives.

Sometimes men would write letters and say, "I have a microphallus. Is that normal?" So many were describing the same

Carol, Michelle and Michael

continued on page 5

Early Members Share Memories and Hopes

In honor of the 40th Anniversary, we've asked some of the early members of DES Action to reminisce about the early years and how being involved with DES Action changed their lives. Who did we miss? Please send in your suggestions and we'll do our best to include as many as possible. Email Karen@desaction.org

Kari Christianson, '49

I had known since 1972 that I'd been prenatally exposed to diethylstilbestrol throughout my mother's pregnancy and that because of that exposure, I had precancerous and structural changes to my reproductive tract. I had talked about my DES experiences with family and friends, but until Joyce Bichler moved to Minnesota and organized a meeting about DES exposure in January of 1980, I had never knowingly met another DES Daughter. Meeting those other DES Daughters and forming a DES Action group in Minnesota became a light shining on the darkness of my fear. I have never forgotten how important it was to share my DES story and to have others understand.

I realized other DES Daughters needed the information offered by DES Action, too. Our stories of DES harm included cancer, infertility, problem pregnancies, frequent abnormal exams and questions about what other health problems might be related to DES exposure. DES Action offered information for all women and men exposed to DES prenatally and generationally. More importantly, DES Action shared our stories with the research community. For 40 years, DES Action has given voice to our DES experiences and our concerns about the harmful health and reproductive effects of all endocrine disruptors and inappropriately used medications.

An understanding ear, advocacy and accurate information have been the hallmarks of DES Action USA throughout these four decades. I cannot imagine my life without this advocacy and the information DES Action has provided to all of us who have been affected by DES.

Jill Murphy '64

Finding DES Action and connecting with other exposed individuals was invaluable. I have made lifelong friends across the globe, and while we don't focus on DES as much now, it is our common bond. Looking forward, I'd love to see DES Action create a "virtual museum" of the history of DES with video from doctors, mothers, children and researchers talking about this medical tragedy. We have always said this should never happen again, and I think such a curated place could remind medical professionals, the FDA and legislators that the first promise for them is to "do no harm."

Kristen Butler '67

My mom co-founded the Boston chapter of DES Action in the late 1970s. I remember it helped her grow from being a shy person who didn't like conflict into a fearless advocate for DES Mothers and Daughters. Her experience taught her how to do medical research and speak up to our family's doctors. She passed these skills on to me, and I think watching her and other DES-exposed women fight to expose the truth about DES helped inspire me to get a degree in journalism and work as a reporter.

In the future, I hope DES Action will support more research into how things like the HPV virus, hormone replacement therapy and the impact of menopause (on ease of screening) affects DES Daughters. I also hope DES Action will advocate for the prevention and treatment of medical trauma from DES effects, such as cancer, infertility and a lifetime of mentally dealing with constant medical surveillance and recurring false-positive test results. Such research would benefit all of society and help push the medical care system toward more patient-centered care for all conditions and diseases.

Karen Fernandes, '49

When my mom told me about my exposure in the early '70s, I never really knew other than my gyn exams that I had anything to worry about. But I had ectopic pregnancies in 1970 and 1976, lost my ovaries by age 26 and had a hysterectomy at 35. I called DES Action and talked with Pat [Cody], and it was an eye-opening conversation about what I needed to do and how I needed to care for myself. She was just amazing.

I was a nurse and in the right place at the right time in Tulsa, and I had access to a medical library. I read all the DES articles from the 1930s forward. To me, knowledge is power, and I needed to read all about it. Then I told Pat I'd like to become more involved.

I established DES Action Oklahoma and ran that for a couple years, getting my feet wet in activism, and then I opened up DES Action Texas after we moved to Texas. Then DES Action invited me to be on the board, and I was very honored.

Being a member of the board was very important to me. It put me on my road to activism, and it hasn't stopped. For me, as a nurse, teaching is part of what I do, and I am still surprised how much education doesn't include DES. So I'm continuing to teach in all these different connections, and it's my work with DES Action that really launched me into public speaking. I would never have thought about speaking otherwise.

I believe the mission of DES Action should be to keep the story of the DES tragedy alive. We can't let it be forgotten. We have to keep it out in the forefront. We have to push for more research and education for healthcare providers, and we have to keep funding coming in for research because that's the only way we're going to know more.

Nancy Ferer, '51

I was active in the founding of DES Action New Jersey and did work for the group for many years. I met many wonderful women and men through these efforts, and I hope we helped the DES-exposed in this state. DES VOICE

Q&A with Carol Freilick

continued from page 3

symptoms that he could at least write back and say, "That's not uncommon. I hear that from a lot of DES-exposed men." People would feel better if they knew they weren't the only one.

Q: What do you want people to remember most about Michael?

His biggest hope and goal was that people would pay attention to symptoms in their bodies and seek medical attention at an early stage so they could get help for whatever medical problems they may have before it was too late. Early detection and early intervention was his big thing: If people would pay attention to their body, ask questions and seek medical attention, he would feel his goal of helping people would be met.

Q: What do you think Michael hoped for the future?

Through the years there has always been conversation that DES Action was going to fold, and he didn't want that to happen. He didn't want people to forget this drug and the problems from it, and that we don't know how many generations could potentially be affected by it. So what were his hopes for DES Action? That it didn't just go away after X amount of years because people didn't know their grandmother or great-grandmother took the drug. He wanted the communication to continue through the generations because no one really knows when the effects will end.

What I want people to know is that we miss him, and somehow or other, we hope that what he did in the past is being paid forward. If he helped a DES Son by answering questions for him and making him feel better about his own physical problems, then maybe that DES Son can help another person and just pay it forward. DES VOICE

Long-Term CCA Survival Rates Higher in DES Daughters

A recent study in the *New England Journal of Medicine* updated data on survival rates of DES Daughters who developed clear-cell adenocarcinoma when they were young. The research was led by Arthur L. Herbst, M.D., the same physician-researcher who discovered and published the earliest papers on the link between DES exposure and CCA.

In the new study, Dr. Herbst and fellow researchers followed 695 patients who had been diagnosed with CCA and were listed in the Registry for Research on Hormonal Transplacental Carcinogenesis. Dr. Herbst set up the Registry in 1971 specifically to track and gather data on CCA cases and better understand the disease in women exposed prenatally to DES. The Registry began at Massachusetts General Hospital but then moved with Dr. Herbst to the University of Chicago.

The women, with an average birth year of 1955, were followed through 2014. Their average age at the time of diagnosis was 22 years old, and 80% were diagnosed between 15–30 years old. Documented evidence of prenatal DES exposure existed for 415 of the women.

Over a follow-up period of more than two decades, 219 of the women died. The researchers calculated the 20-year survival for CCA to be about 69%, which did not differ between those with and without DES exposure.

The five-year survival rate, however, was slightly higher for DES Daughters with CCA, even after accounting for age and the tumor stage and molecular makeup. Those exposed to DES had an 86% five-year survival rate compared to 81% for those without DES exposure.

However, some patients without documentation may actually have had prenatal DES exposure, especially since the course of their disease followed that of DES Daughters' disease so closely. With completely accurate records, then, the difference in survival rates may actually be larger, the researchers wrote.

This difference in survival rates suggests that DES-related CCA may somehow differ biologically from CCA in those without DES exposure. Research is needed to better understand genetic mutations, changes in the tumor's genetics and epigenetic changes related to CCA, the authors wrote.

"Idiopathic [unknown-cause spontaneous] clear-cell adenocarcinoma may be more likely to progress quickly or recur earlier, whereas clear-cell adenocarcinoma associated with DES exposure may be more likely to recur later," the authors speculated.

They noted a similar pattern seen in certain estrogen-receptor positive breast and endometrial cancers. They also noted the higher risk of death for DES Daughters who developed CCA, compared to the general population of women who never developed CCA.

That risk persists even through age 65, though not as dramatically as during women's 20s and 30s. The higher risk among women ages 35–49 is primarily due to cancer recurrences, but older women's increased risk "may be due to other life-threatening health conditions in the population of women who were exposed to DES," they wrote.

They continued with a call to continue surveillance of DES Daughters with CCA.

The research was funded by the National Cancer Institute and can be found at doi 10.1056/NEJMc1800097.

Higher ADHD Risk in DES Grandchildren

continued from page 1

asked the researchers why they chose to look specifically at ADHD. Lead author Marianthi-Anna Kioumourtzoglou, ScD, a professor of environmental health at Columbia University Mailman School of Public Health in New York, said they had planned to look at neurodevelopmental outcomes in general.

"In our study population, we did not have many outcomes. We only had information on autism spectrum disorder (ASD) and ADHD," Dr. Kioumourtzoglou wrote. "Due to the rare exposure (only 1.8% of the mothers used DES during pregnancy), we decided to start our analyses looking at ADHD because we had more identified cases than for ASD." She added that they hope to look at other outcomes in the future, but they are still determining how to proceed.

What Past Research Has Found

Previous research in animals has revealed differences in the neurology and development of third- or fourth-generation offspring when their parents or grandparents had been exposed to endocrine disruptors. Those findings cannot be directly applied to humans, however, because rodent brains, for example, may be too different from human brains to compare.

It's also difficult to determine what doses of DES are most appropriate to use in rodent research to represent an exposure similar to what humans would have. Many toxicology studies use very high dosages that do not accurately reflect dosages in humans.

That said, previous research has already identified other conditions in humans that are more common among those whose parents were prenatally exposed to DES.

For example, DES Granddaughters are more likely

to have delayed menstruation, irregular periods and fewer live births than their peers. DES Grandsons have a slightly higher risk of hypospadias—an abnormal placement of the urethra on the penis. And birth defects appear slightly more likely to occur in DES Grandchildren than in those without a family history of DES exposure.

These Studies Cannot Show Causation

The human findings above, however, are from studies with several limitations. The most important of these limitations is that the studies are observational and therefore cannot show causation. It will require multiple additional studies to learn more about whether these conditions definitely represent third-generation effects from DES exposure.

Observational studies also carry the risk that other factors the researchers don't know about—and therefore cannot account for—may explain differences seen in DES Grandchildren. Researchers try to adjust their calculations to consider other factors, such as socioeconomic status and smoking during pregnancy.

But it's impossible to know all the ways that children born to DES Daughters and Sons may be different from other children, regardless of the DES connection.

In this most recent study, the strongest finding suggesting possible causation is the increased risk among those whose mothers' DES exposure was in the first trimester.

The study was funded by the National Institutes of Health and the Escher Fund for Autism. Find it at doi 10.1001/jamapediatrics.2018.0727.

Did DES Cause Autism?

continued from page 1

connection. Some, such as having an older father or the mother having an infection during pregnancy, have more evidence than others, and likely do play a role in the development of autism. And it's been long established that a rubella infection during pregnancy can cause autism.

However, substantial evidence has shown that genetics play a role too, both in terms of family inheritance and in terms of random mutations unrelated to family history. It's unclear how much genetics contribute and how much environmental exposures might contribute to autism development, but researchers have identified at least 100 genes involved with the whole spectrum of disorders. Most likely, as many scientists believe, "autism spectrum disorders" is literally a broad range of often very different disorders that share symptoms but may not share causes. The diversity in symptoms and experiences among autistic people supports this hypothesis as well.

That brings us to DES exposure, also a just-common-enough—but not extremely common—experience that makes it challenging to identify real associations with different conditions, unless many studies together have shown it. Interestingly, however, despite the hundreds of studies looking at autism and other environmental exposure, not a single one looks at autism and DES exposure.

Some hypotheses have suggested that germ-line disruptions or epigenetic changes to the genes—both related to disruptions to genetic material in the womb—could cause autism. But evidence for this is sparse and weak, usually requiring jumps from several different studies to stitch together a hypothesis with solid evidence.

And it's highly unlikely that one single thing causes autism in anyone regardless. Even rubella does not cause autism in every person prenatally exposed to an infection. More likely, a fetus will have a collection of risk factors, and certain combinations or one extra factor will tip the scales during developing the condition.

Is it possible DES could be one of those factors? There is no evidence to rule it out. Only one study, published in 2011, even mentions autism among DES Sons and Daughters. Even there, it is mentioned only once, in a list of more than 30 conditions identified in at least some DES Sons. Many of the other conditions in the list have already been found to be unrelated to DES.

Rebecca Troisi, one of the co-investigators of the DES Follow-Up study at the National Cancer Institute, has not seen evidence either.

"I'm not aware of any research—human or animal—on DES and autism," she told the VOICE. "While individuals who have autism (both DES-exposed and unexposed) might be less likely to answer the questionnaire, I haven't seen it reported on our open list of conditions that we ask about in every follow-up."

Again, that doesn't rule it out. It is possible that in at least a small number of people, DES exposure could be one of multiple factors that, along with a genetic risk or other contributors, tipped the scale. If so, however, no one has identified a biological mechanism for how DES would do so. It's unlikely to be a major contributor in the midst of other factors; if it were, a "signal"—a pattern that shows up in reports over time—would exist. So far, there hasn't been a high number of people exposed to DES reporting autism that is greater than the usual rate in the population. DES VOICE

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Facebook Live Interviews

In honor of DES Action USA's 40th Anniversary, we continue our showcase of leaders of interest. Join us.

Upcoming

August 27, 8pm ET: Fran Howell (left), former Executive Director, DES Action USA, and **Kari Christianson** (right), retired Program Director, DES Action USA, will discuss the history of DES and the formation of DES Action with current Executive Director Su Robotti.

September, Date/Time TBA: Linda Titus, MA, PhD, Professor of Epidemiology, Pediatrics and The Dartmouth Institute/NIH's National Cancer Institute DES researcher, will talk with Su about the third generation (DES Grandchildren).

Insurance Codes for DES-Related Medical Visits

Many DES Daughters have asked us what codes their doctors should use to ensure their insurance company and/or Medicare appropriately pays for the visit and does not leave them with a big bill. Most offices currently use the most recent version, ICD-10, though some may still use ICD-9. No specific code exists for DES exposure since exposure affects people differently, but several codes can be used for the problems associated with exposure.

Special thanks to Karen Fernandes, DES Daughter and registered nurse, who provided these codes to us.

No ICD-10 code is yet available for the third generation.

- C52 is applicable to female patients.

ICD-10-CM C52 is grouped within Diagnostic Related Group(s) (MS-DRG v34.0):

- 736 Uterine and adnexa procedures for ovarian or adnexal malignancy with mcc
- 737 Uterine and adnexa procedures for ovarian or adnexal malignancy with cc
- 738 Uterine and adnexa procedures for ovarian or adnexal malignancy without cc/mcc
- 739 Uterine, adnexa procedures for non-ovarian and non-adnexal malignancy with mcc
- 740 Uterine, adnexa procedures for non-ovarian and non-adnexal malignancy with cc
- 741 Uterine, adnexa procedures for non-ovarian and non-adnexal malignancy without cc/mcc
- 754 Malignancy, female reproductive system with mcc
- 755 Malignancy, female reproductive system with cc
- 756 Malignancy, female reproductive system without cc/mcc