DES Action VOICE

Inside

A Focus On Diethylstilbestrol

SUMMER 2014 #141

DES Son's Research Review

Why Different Studies Yield Conflicting Results

"Urogenital Abnormalities in Men Exposed to Diethylstilbestrol *In Utero*: A Cohort Study," Julie R. Palmer et al. *Environmental Health 2009*, 8:37-1-6, 2009. (http://www.ehjournal.net/content/8/1/37)

Reviewed by Fran Howell

This study confirms that DES Sons are at increased risk for cryptorchidism (undescended testicles), epididymal cysts (benign but painful), and testicular inflammation and infection. It also helps unravel the mystery as to why earlier studies presented conflicting results.

Using information collected by the on-going National Cancer Institute (NCI) DES Follow-up Study, researcher Julie Palmer, Sc.D., from Boston University's Slone Epidemiology Center, analyzed data from three studies of DES Sons. They were done with mailed questionnaires (1994, 1997 and 2001), which asked about abnormalities of the urogenital tract.

The earlier the exposure, the higher the prevalence of anomalies, which holds true for DES Sons because genitalia are most susceptible to harm caused by exposures during the early weeks of gestation.

One study was of a group of DES Sons born at the University of Chicago's hospital; the second was of DES Sons born after their mothers were treated at a private infertility clinic near Boston, and the third was of DES Sons born at the Mayo Clinic in Rochester, MN.

Two of the studies found a link between DES exposure and a higher prevalence of genital tract abnormalities in DES Sons. But the Mayo Clinic results showed no such correlation.

For all three groups, mothers' medical records were available. Upon close examination, Palmer came to understand that the risk for undescended testicles, epididymal cysts and testicular inflammation/infection was the highest for men who were first exposed to DES before the 11th week of gestation, and whose mothers had been given the large cumulative dose of more than five grams of DES.

As it turns out, the protocol for handling so-called problem pregnancies at the Mayo Clinic was generally more conservative than elsewhere. According to Palmer, "The Mayo Clinic cohort differs from the other cohorts in two major ways: only 48% were

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Uterine Fibroids and DES Daughters

Additional Confirmation of an Increased Risk

"Prenatal Diethylstilbestrol Exposure and Risk of Uterine Leiomyomata in the Nurses' Health Study II," Struthi Mahalingaiah et al. *American Journal of Epidemiology*, Volume 179 Issue 4 February 15, 2014.

Reviewed by Kari Christianson

Within the last ten years, several U.S. research articles have investigated a potential link between prenatal DES exposure and uterine fibroids in DES Daughters. These studies had interesting—and sometimes conflicting—findings.

The latest research comes from the Nurses' Health Study II, which recently investigated whether prenatal DES exposure increases the incidence of uterine fibroids (leiomyomata) in women. The women with prenatal DES exposure were found to have a 12% increased incidence of uterine fibroids, particularly among those prenatally exposed to DES during the first three months in the womb.

The study gathered health information from 102,164 premenopausal women for 20 years, from 1989 to 2009. At the start of the study the nurse participants were premenopausal and had intact uteri with no prior history of uterine fibroids or cancer; some of the women included prenatal DES exposure in their med-

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JOIN THE CONVERSATION

Facebook For All

With lots going on in the DES community, you can be part of the information flow 24/7. Social media has changed the face of communicating, and DES Action USA is part of it.

Stay on top of information of interest to the DES community and share your thoughts.

Timely — Accurate — Interesting

Check out the DES Action USA Facebook page where we've been talking about:

- A DES Mother who demanded better education for health care providers saying: "We are still here!"
- New findings that link PCOS to an increased diabetes risk. This is of particular interest to DES Granddaughters as the DES Action Health History Survey showed them reporting PCOS at a higher rate than the national average.
- Some of us get cancer, others deal with infertility or Rheumatoid Arthritis. Scientists now wonder about the combination of DES with other environmental exposures triggering harm in different ways.
- The newest breast cancer screening tool is tomosynthesis (3-D scanning). It may screen dense breasts better, but what are the trade-offs for the extra radiation exposure?

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.

We are a caring and supportive group that has become an important benefit of membership in DES Action USA. To join the support group, send an email to:

DESactionDaughters-subscribe@yahoogroups.com

Once we've checked to be sure you are a DES Action USA member, please join us and participate in the email conversations surrounding the impacts of DES exposure and know your concerns are completely valid. It's empowering knowing you are not alone!

Find us on Facebook

twitter

MISSION STATEMENT

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

DES Action VOICE

Published quarterly by:

DES Action USA
P.O. Box 7296
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ISSN 1522-0389
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DES Sons Research Review

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exposed before the 11th week of gestation and very few were exposed to 5 grams or more" of DES.

Palmer's dose and timing analysis of the three studies answers the mystery as to why the Mayo Clinic's results regarding DES Sons conflicted with the others. Dose and timing matter.

Also, Palmer points out that according to animal studies, when the synthetic estrogen DES was given during pregnancy, the male offspring had higher than expected incidences of undescended testicles and epididymal cysts. Researchers theorize from those studies that normal descent of the testes is, at least in part, under hormonal control. So getting the same results in human studies was not a surprise to Palmer, since animal work is often a predictor of the human experience.

She also notes that interestingly, "timing of in utero exposure to DES has been shown to be a predictive factor for structural anomalies of the cervix and vagina in DES-exposed daughters." The earlier the exposure, the higher the prevalence of anomalies, which holds true for DES Sons because genitalia are most susceptible to harm caused by exposures during the early weeks of gestation.

Palmer was particularly interested in the association between prenatal DES exposure and the increased risk for inflammation/infection of the testes. She speculates that some DES Sons may have been born with a small structural abnormality, such as a minor obstruction that could explain their greater testicular inflammation/infection risk. Palmer calls for follow-up on this point.

Findings in this study, Palmer says, can be extended to current concerns of endocrine disruptors in the environment. She notes an increase in the prevalence of undescended testicles being seen in recent years in the general population. Some scientists are looking at both genetics and environmental factors for a cause. According to Palmer, these research results regarding DES appear to lean toward the possibility that genital anomalies may have something to do with increased estrogen exposure before birth.

Palmer notes the importance of continuing studies on these groups of DES Sons as they age. She says it makes sense to watch for an increased possibility of benign prostatic hypertrophy (enlargement of the prostate gland) and prostate cancer among DES Sons, because both conditions occur more often in men as they age. DES VOICE

Uterine Fibroids

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ical histories.

This report suggests that early DES exposure in the first trimester may be associated with a small, but statistically significant, increased incidence of uterine fibroids. Uterine fibroids are benign tumors that may cause pain and bleeding, as well as infertility and pregnancy problems. Uterine fibroids are the leading reason for a hysterectomy.

Struthi Mahalingaiah, M.D., Assistant Professor of Obstetrics and Gynecology at Boston University School of Medicine, indicates that two factors may compromise these results from the Nurses' Health Study II, which links DES exposure to an increased uterine fibroid risk: 1) participants may receive more thorough gynecological exams, which result in an increased detection of uterine fibroids among the study participants, and 2) recall bias, meaning DES exposure was suspected but could not be confirmed.

Interestingly, the National Institutes of Health (NIH) Sister Study by the National Institute of Environmental Health Sciences (NIEHS) had similar findings in 2010 and 2012 among their participants with prenatal DES exposure. (VOICE issues #124 and #132) These two studies reported the early development of uterine fibroids, before the age of 35, among women who listed probable DES exposure in their medical histories. The women listing definite DES exposure did not show an increased risk for uterine fibroids. The Sister Study follows the health of over 50,000 women whose sisters had breast cancer.

An earlier NIEHS study, published in 2005, found more and larger uterine fibroids among women exposed prenatally to DES than found in unexposed women. (VOICE #105) This relatively small human study confirmed NIEHS findings linking DES exposure to the development of uterine tumors in mice.

However, research by the National Cancer Institute (NCI) DES Follow-up Study did not find an increased incidence of uterine fibroids among DES Daughters in a study published in 2005. (VOICE #104) There are fewer participants in the DES Follow-up Study than in either the Nurses' Health Study II or the Sister Study. However, the NCI study participants have medical record review confirmation of prenatal DES exposure, often including when the DES was administered in a pregnancy and total dosage. This study also uses a group of matched unexposed control participants.

Uterine fibroids are benign tumors that may cause pain and bleeding, as well as infertility and pregnancy problems. Uterine fibroids are the leading reasons for a hysterectomy.

Conflicting research reports, like these investigating a DES exposure link to an increased risk for uterine fibroids, reminds us that prenatal DES exposure remains an interesting, if frustrating, puzzle for researchers to continue untangling. While also frustrating for the DES-exposed community, just know that you are witnessing the evolution of science in action. Each study uses valid research techniques, but a variety of factors may result in different outcomes. Eventually the puzzle pieces will come together for an understanding of the harms caused by DES and all endocrine disruptors. DES VOICE

YOUR VOICE

This article, by DES Action USA member Cecelia Volk, is another in a series of personal stories to be published in the VOICE. We hope you enjoy reading about the spirit of our members who are living good lives in spite of, and with, DES exposure.

Do you have a DES story that shares useful information for our readers? Please email us at info@desaction.org for details about submitting it.

Cecelia Volk

I always knew my mother had been given some medicine to "strengthen" her uterus after she suffered a miscarriage with her first pregnancy. It wasn't until 1975, however, that I discovered I was a DES Daughter with the classic "cockscomb" cervix.

From that time on I carefully monitored my gynecologic health as my research (at the time and continual information through DES Action) showed all the possible DES effects on young women.

I had many colposcopies through the years, but with no suspicious findings I stopped having them on a regular basis several years ago. That said, I continued regular visits for Paps.

I chose not to have children because of my DES exposure, so I do not know if that would have been an issue.

Last October was to be just another regular screening exam.

While reviewing my Pap results, the doctor (who, in my opinion is one of the best DES specialists in New York City and is affiliated with one of the top medical centers here) said the Pap had "atypical" cells. So an HPV screening was done and it came back positive.

I found this interesting, as several years earlier I had an HPV test that came back negative. I wasn't surprised, because I suspected I'd been exposed to HPV in college (yes, the sex, drugs and rock roll era!).

With all the stress I was experiencing at my job, I figured my immune system was lowered, allowing HPV to get the upper hand, just as chicken pox had popped out as shingles a few years before. So I underwent further testing.

The colposcopy results looked normal (weird!), but the biopsy came back with both CIN I and CIN III, a low grade and a high-grade lesion. As it was explained to me, those were not a carcinoma, but on the "steps" to it.

So I underwent a LEEP procedure. The top part of my cervix was "shaved" and there was no pain or discomfort as the cervix was numbed. The LEEP results confirmed the biopsy.

My one-month post-exam was normal! At two months post-LEEP I consulted with a specialist in gynecologic oncology who told me there is no need for a hysterectomy and the results of his colposcopy, Pap, and "scraping" were normal.

My six-month post LEEP exam and colposcopy were normal, but I am still HPV positive. I assume now it is "out" and I will have to be more vigilant.

I will speak to my doctor about seeing him more frequently, just to catch any changes early. I have a nine-month post-LEEP appointment for the end of August.

How DES exposure and HPV interact is a good question. I'm glad I had that HPV test done so I can stay on top of it. DES Action USA has been with me every step of the way. Truly, a resource to trust—and I am thankful. Being a DES Daughter means I stay alert and act when anything unusual turns up. It's gotten me this far and I'm confident this approach will serve me well in the future, too.

Editor's Note: DES Daughters may actually have an increased risk for HPV because many have a wider cervical transformation zone than unexposed women. That's where most of the pre-cancerous lesions develop. It is speculated the larger area in DES Daughters makes them more susceptible to HPV.

We have heard from DES Daughters who say they tested positive for HPV, only to be told later it was a false positive based on their DES-exposed tissue. Our suggestion is to question any unusual test result. There may be additional information available about which strain of HPV has been detected, if nothing else. Also, having the most accurate facts about test results is helpful in treatment decision-making. DES VOICE

Fascinating History

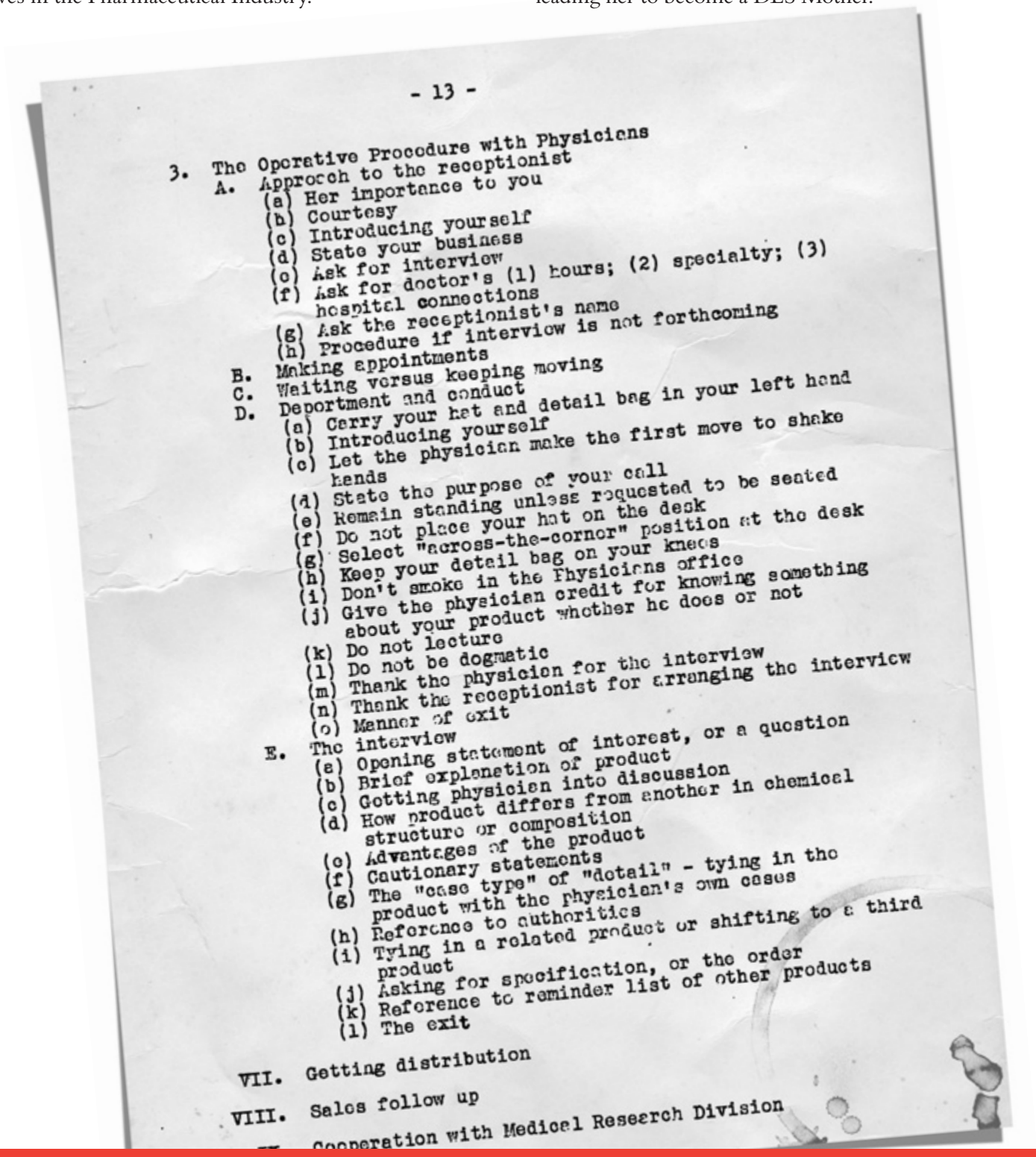
Drug companies promote their products to doctors via an army of Drug Detailers. Thanks to the American Institute of the History of Pharmacy at the University of Wisconsin, we now know what was expected of these Drug Detailers back in the 1940s—during a time when DES was heavily marketed to prevent miscarriage.

The rules of deportment were strict. This is from 1944 describing Sales Training of Professional Service Representatives in the Pharmaceutical Industry.

According to Institute experts, Drug Detailers carried a sample case, often called a detail bag, a list of drugs to promote, an advertising portfolio, clinical notes and samples.

Because DES was not patented and was inexpensive to produce, doctors heard about it from Drug Detailers representing a variety of different pharmaceutical companies.

Quite possibly a "detailman" using this protocol visited the doctor before a pregnant woman had her appointment—leading her to become a DES Mother.



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3. The Operative Procedure with Physicians
   A. Approach to the receptionist
      (a) Her importance to you
      (b) Courtesy
      (c) Introducing yourself
      (d) State your business
      (e) Ask for interview
      (f) Ask for doctor's (1) hours; (2) specialty; (3) hospital connections
      (g) Ask the receptionist's name
      (h) Procedure if interview is not forthcoming
   B. Making appointments
   C. Waiting versus keeping moving
   D. Deportment and conduct
      (a) Carry your hat and detail bag in your left hand
      (b) Introducing yourself
      (c) Let the physician make the first move to shake hands
      (d) State the purpose of your call
      (e) Remain standing unless requested to be seated
      (f) Do not place your hat on the desk
      (g) Select "across-the-corner" position at the desk
      (h) Keep your detail bag on your knees
      (i) Don't smoke in the Physicians office
      (j) Give the physician credit for knowing something about your product whether he does or not
      (k) Do not lecture
      (l) Do not be dogmatic
      (m) Thank the physician for the interview
      (n) Thank the receptionist for arranging the interview
      (o) Manner of exit
   E. The interview
      (a) Opening statement of interest, or a question
      (b) Brief explanation of product
      (c) Getting physician into discussion
      (d) How product differs from another in chemical structure or composition
      (e) Advantages of the product
      (f) Cautionary statements
      (g) The "case type" of "detail" - tying in the product with the physician's own cases
      (h) Reference to authorities
      (i) Tying in a related product or shifting to a third product
      (j) Asking for specification, or the order
      (k) Reference to reminder list of other products
      (l) The exit

VII. Getting distribution

VIII. Sales follow up

Cooperation with Medical Research Division

DES Grandchild Research Resonates Through Aptly Titled Article, "Uncertain Inheritance"

"Uncertain Inheritance: Transgenerational Effects of Environmental Exposures," *Environmental Health Perspectives*, Volume 121, Number 10, October 2013. (http://ehp.niehs.nih.gov/121-A298/)

Reviewed by Kari Christianson

Epigenetics is a relatively new kid in the classroom—or in this case the research lab. It's the emerging field of scientific study that examines alterations of gene expression that can be passed down through generations. We are talking here specifically about how genes work by turning on and off at appropriate times. This should not be confused with gene mutation, because the genes are not changed, they just operate incorrectly.

It's rare that a day goes by without word of a new study finding potential health problems caused by environmental exposure to such chemicals as bisphenol acetate (BPA), phthalates, dioxin, DEET, tributyltin, etc. What's especially troubling is that future generations can be harmed, not just those who are directly exposed to a chemical commonly found in the environment. Up to this point, most of these studies have relied on rodent models for study, because tracking generations of humans for health effects is difficult and costly.

This article in the National Institute of Environmental Health Sciences (NIEHS) publication *Environmental Health Perspectives* (EHP) accurately points out that *human research already does exist*. The article states, "… Some reports have linked nutritional deficiencies from famine and exposure to diethylstilbestrol (DES)—to effects that persist among the grandchildren of exposed women."

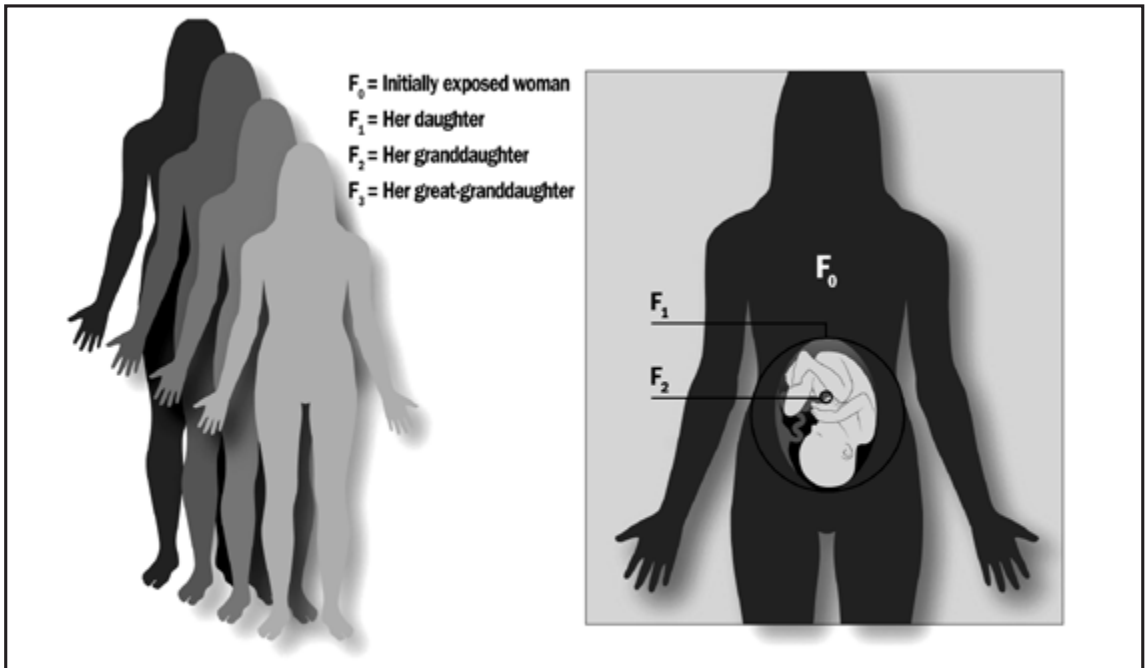
Much more research to understand epigenetic effects is definitely needed to grasp generational threats of environmental exposures. The NIEHS is answering this challenge by funding new study initiatives for research into transgenerational effects in mammals.

This fascinating "Uncertain Inheritance" article highlights the important place DES research has among scientists working to unlock epigenetic mysteries. Of course, those of us in the DES-exposed community are not surprised that prenatal and generational DES exposure offers significant insight for human epigenetic research.

Linda Titus, Ph.D., a Principal Investigator with the DES Follow-up Study, was interviewed because of her research focus on DES Grandchildren. Her comments provide insights and cautions to what current DES research studies add to the science of generational DES exposure.

Quoting from the article, "Another key line of human evidence in the field comes from multigenerational studies of DES. Those data come from a pair of National Cancer Institute studies: the DES Follow-up Study, which tracks health outcomes among women who were exposed to DES and prenatally exposed children, and the DES Third Generation Cohort Study, which tracks the male and female grandchildren of the originally exposed women.

"According to Linda Titus, a professor in community and family



When a pregnant woman is exposed to an environmental agent, the exposure extends not only to herself (F_0) and her unborn child (F_1), but also to the germ cells developing within the fetus (F_2). Animal studies have demonstrated chemical effects that extend a generation further still—to the F_3 generation, the first generation not directly exposed to the original agent. Human studies to date have shown effects only through the F_2 generation. Joseph Tart/EHP

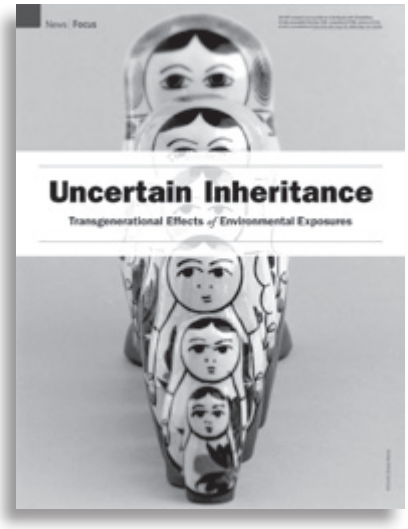
medicine and pediatrics at the Geisel School of Medicine at Dartmouth, grandsons of the DES-exposed women had a modestly higher risk of any birth defect, mostly urogenital defects, although the findings weren't statistically significant. Granddaughters, meanwhile, had a higher frequency of hip dysplasia, irregular periods, older age at menarche, and potentially an increased risk of infertility. There was also a higher risk of ovarian cancer among granddaughters of exposed women, but since that finding is based on just three cases, she says, it must be considered preliminary."

Later in the article, "Titus says that conclusive evidence of transgenerational epigenetic mechanisms in humans will depend on findings in F3 generations. 'Even if new studies confirm outcomes in DES-exposed grandchildren, we can't be sure if they are due to epigenetic changes,' she says. 'A true assessment of heritable epigenetic changes requires studies of great-grandchildren, which will be the first generation without DES exposure.'"

The EHP article concludes, "The growing evidence that environmental exposures might induce a myriad of effects that persist transgenerationally leaves open questions about where human evolution is headed." Animal studies point to female avoidance of mating with male animals exposed to certain chemicals, thus raising the question of evolution. Additionally, some exposures add the risk of infertility or tumor growth, which also affects success in producing future generations.

Scientist Dave Crews, Professor of biology and psychology at the University of Texas at Austin, adds, "We're all combinations of what we inherit and what we're exposed to in our own lives. And right now you can't find a human or animal on the planet without a body burden of endocrine-disrupting chemicals."

To which those of us who are DES-exposed say, "Don't we know it!" DES VOICE



There's good reason we recognize the nesting doll image depicted on the cover of this article—it's often used to represent potential adverse health effects across generations. Researchers in The Netherlands used it as the logo for their questionnaires and published studies. Viewing a picture of nesting dolls, it's easy to see why adverse generational effects could exist, but proving the 'what' and 'how' of generational harm is challenging.

Annual Pelvic Exams Questioned

But Not By DES Daughters

Some in the medical community have lost faith in the value of annual pelvic exams for detecting cervical cancer in women who have no symptoms and who are at average risk for the disease. That takes DES Daughters out of the equation with our increased risk not only for clear cell adenocarcinoma (CCA) of the cervix, but also of the vagina.

The issue arose in July when the American College of Physicians released what has become a controversial new guideline stating pelvic exams are unnecessary for most women. This is in contrast to the screening guidelines of the American College of Obstetricians and Gynecologists (ACOG), which call for annual pelvic exams (but not yearly Pap smears – DES Daughters excepted).

The debate is expected to continue into the foreseeable future, so here's help in defining terms.

- A pelvic exam involves feet into the stirrups so the doctor can first look at the genitals for anything unusual before inserting the speculum. Then a visual inspection is done of the vagina and cervix, followed by the doctor using a gloved hand pressing from the inside and with the other hand on the abdomen pushing down to feel for unusual masses on the ovaries and uterus. A similar palpation is done in the rectum to look for tenderness or growths.
- A DES Daughter pelvic exam also includes specific feeling (palpating) around the surface of the vagina to detect any growths that could be CCA. This extra component of the screening is especially important.
- During the pelvic exam, a Pap smear may also be done. It entails cervical cells being gently scraped off the cervix with a tool similar to a Q-tip. The specimen is sent to a lab for analysis.
- A DES Daughter Pap smear scrapes cells from both the cervix and the vagina. After hysterectomy DES Daughters should still have Paps done with cells taken from the vagina.

Women can have just a pelvic exam or a pelvic exam coupled with a Pap screening. It's important when scheduling to be specific about what you want, so you know what you are getting.

DES Daughter guidelines continue to call for both a pelvic exam and a Pap smear every year. DES VOICE

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Do We Have Your Current Email Address?

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Cutting Drug Company Influence Over Doctors May Be Tougher Than Expected

Drug makers heavily promoted their products, including DES, to doctors with gifts, trips, lavish meals and other monetary incentives to influence the prescribing of this drug to pregnant women. It clearly succeeded, given the millions who were exposed despite published research proving DES didn't work.

So DES Action USA joined a coalition of groups in support of the Physicians Payments Sunshine Act. When it became law, there were high hopes it would limit the strong influence drug manufacturers have over doctor prescribing habits.

With mandatory tracking now of pharmaceutical money going to each doctor, the expectation was that physicians would be cautious in accepting too much, knowing the amounts will be made public.

While we await release of the list later this year, we have a small inkling that doctors may not be ready to give up the goodies just yet.

A journalist with MedPage who covered the Pharmaceutical Research and Manufacturers of America (PhRMA) annual meeting last month reported that drug companies claim no change in their financial dealings with doctors.

According to David Pittman, the CEOs of Pfizer and Celgene each shook their heads "no" when asked during a news conference if doctors seem more hesitant to interact with pharmaceutical companies now that the new law is in place.

Of course, this characterization of the Sunshine Law's impact comes from firms that lobbied hard against it. We'll have to wait until September 30th to get our first look at the flow of money to doctors from drug makers.

DES Action USA will continue working with coalition partners to monitor the new law and push for changes, if needed, to loosen the grip pharmaceutical companies have over the drugs our doctors prescribe. DES VOICE