

Mouse Study Shows Link to Third Generation Effects

Reviewed by Molly Berigan Spira

"Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol,"

by Retha Newbold et al,
Carcinogenesis, Vol. 19, No. 9,
September 1998.

In a study conducted by scientists at the National Institute of Environmental Health Sciences, Wake Forest University, and Tulane University, a link was found between the initial DES exposure in mice down through their second generation daughters to a third generation of female grandchildren. From two to eleven per cent of these "granddaughters" developed benign and malignant tumors in their old age. (The non-exposed mice in the comparison or 'control' group had no tumors). The report indicated that the range and prevalence of these abnormalities increased with age.

The study used mice for the investigation, a common practice as the reproductive organs of these subjects closely reflect those of humans, yet their shorter gestation and lifespans allow for more immediate study. Dosages and timing of exposure were correlated to match those experienced by women who were initially exposed to DES—"DES mothers." Three separate groups of mice were exposed at different stages of gestation at varying dosages. These offspring were

then raised to sexual maturity, mated to un-exposed control mice, and then gave birth to third generation "granddaughter" mice.

Tumors of the uterus were the most commonly seen abnormalities in these third generation offspring. The authors report "an increased incidence of malignant reproductive tract tumors, including uterine adenocarcinoma in DES-lineage mice but not in corresponding controls." The results of this study suggest that all developmental exposure periods were susceptible to the adverse effects of DES, and that tumor formation, whether benign or malignant, is transmitted to the next generation.

As seen in the human population of DES daughters, the fertility rates of the DES daughter mice were well below normal, but the fertility rates of the third generation were not affected. Explanations for the "mechanisms involved in the transgenerational events" are unknown. The authors surmise that DES could alter the germ cells of the exposed fetus so that its offspring would be affected.

This study did not address the effects on the offspring of DES son mice, the sons of the DES daughter mice, nor on any effects on bone tissue or other organ systems. These and other studies will be conducted under the auspices of these same scientists. Their report concludes:

"While the occurrence of reproductive tract tumors in DES lineage mice does not predict a similar outcome in DES-exposed humans, continued close surveillance of the prenatally DES-exposed cohort and their offspring is warranted. Using the animal model, we can now systematically analyze the genetic/epigenetic changes caused by DES, which will aid in the comparison of similarities and differences between the mouse and human. Ongoing mechanistic studies with the experimental DES-exposed animal model may thus prove useful in identifying specific genetic/epigenetic changes that lead to tumor development and thereby provide markers of early detection and prevention of human disease.

"In summary, this report describes irreversible changes in the female genital tract that are transmitted to other generations. These results indicate that the cascade of events that led to the appearance of tumors may well begin before birth and perhaps before conception. Additional studies on prenatal and developmental exposures are essential for an accurate assessment of risks that can be attributed to specific environmental agents. However, these experimental studies will contribute to our understanding of some of the mechanisms underlying the genetic predisposition to cancer."

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Each group was created and nurtured by volunteers. Write them if you want information on their activities or can volunteer.

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About DES

DES (diethylstilbestrol) is a synthetic form of the female hormone estrogen. From 1938 to 1971, several million pregnant women in the U.S. were prescribed DES, especially if they had a history of previous miscarriage or slight bleeding or had diabetes. DES was given in pills, injections and suppositories and sold by over 200 drug companies under their own brand names.

DES exposure can lead to health problems:

- DES mothers have a slightly increased risk for breast cancer
- DES daughters have a 1 in 1,000 risk for a rare vaginal/cervical cancer, clear-cell adenocarcinoma. This is the reason all daughters need regular gyn exams. They also are at risk for reproductive difficulties: infertility, ectopic pregnancy, miscarriage and premature delivery, and should always receive high-risk pregnancy care.
- DES sons have an increased risk for undescended testicles, cysts on the epididymus, and possibly for infertility

DES Action, the major consumer group working on this issue since 1974, has special publications, physician referral lists, attorney referral lists, this quarterly newsletter, and a hot-line: 1-800-DES-9288.

Published quarterly by
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ISSN 1522-0389
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Design and Layout:

Sphinx Graphics
Berkeley, CA

Printing:

Inkworks,
Berkeley, CA
A collectively owned
union shop.

DES Action to Begin Member Network on Internet

DES Action is beginning a member network (listserv) on the Internet. For those of you familiar with the DES Daughters online network, please note this will be a separate network for DES Action members only.

We plan to use this network to communicate more easily with our members, particularly on matters requiring rapid response such as legislative action alerts. Because we realize that many of you do not have access to the Internet, we are committed to providing the same information to all members. Those who register for the Internet Network will receive some of their member information via e-mail; those who do not will continue to receive information via standard postal mail.

Some of our ideas for the Member Network:

- Legislative updates and requests for you to send letters about DES legislation
- Renewal notices online—your first reminder to renew could come via e-mail, saving time, money and natural resources
- Quick access to doctor and attorney referrals
- Members would have the ability to post questions to DES Action

This list will be established as a secure list, with no outsiders having access to the network. Registration would be screened and monitored by DES Action, and only members will be allowed to join.

"We plan to use this network to communicate more easily with our members."

If you are interested in participating in our online network, please send an e-mail from the address you wish to subscribe to HYPERLINK mail to:
majordomo@lists.teleport.com.
 In the body of the message write only the words **SUBSCRIBE DES-ACTION-L**. We will then send you a list of terms and conditions and ask for your agreement before enrolling you in the online network.

Internet Resources

Online Support Group for DES Daughters

TASC, The American Surrogacy Center, hosts DES-L, an online support group for DES daughters. The purpose of this listserv is to provide support and exchange information with other DES daughters (currently over 500 members) via the internet. Besides communicating through e-mail, DES-L offers an online bulletin board, live chat sessions, and virtual seminars (at which professionals such as physicians, attorneys, psychologists, and researchers are available to discuss your questions and concerns).

"The purpose of this group is to exchange information, provide support, and post DES related announcements."

DES-L's webpage at http://www.surrogacy.com/online_support/des/ has DES articles, links to other DES websites, and an application to join the listserv. Hope to "see" you there.

DES newsgroup

There is also a DES newsgroup—check to see if your

server carries it. It is called **alt.support.des** and it is a newsgroup for DES exposed daughters, sons, and moms. The purpose of this group is to exchange information, provide support, and post DES related announcements.

DES Action website and e-mail

And don't forget that DES Action has a website at <http://www.desaction.org>, and our e-mail address is desact@mail.well.com.

Hope to see you on the internet!

New York State Examines Assisted Reproduction

by Judith Turiel, Ph.D., author, *Beyond Second Opinions: Making Decisions about Fertility Treatment*

LAST July, as the world's first in vitro fertilization baby celebrated her 20th birthday, scientists displayed to the public several generations of cloned mice. Once again, attention turned briefly to prospects for human cloning as a treatment for infertility. What's missing from this picture? Regulation and monitoring of treatments performed daily, right now—including procedures we may someday recognize as steps toward the reproductive future. The need to protect patients who undergo fertility treatment is of particular concern for people exposed to DES. Not only have we been harmed by a previous generation's state-of-the-art reproductive treatment, but that harm often means that individuals who wish to have a baby must make decisions about current medical interventions. Unfortunately, along with non-exposed fertility patients, we face inadequate information about risks and benefits of these interventions, as well as inadequate oversight of this medical specialty.

The state of New York has taken an important governmental step, addressing serious problems plaguing fertility medicine. A New York State Task Force on Life and the Law focused, over several years, on assisted reproductive technologies (ART), as practiced within the state's fertility clinics. In April, the Task Force issued a

report, summarizing its findings and recommending state law and health policies for this field (other topics have including life-sustaining medical treatments, organ and tissue transplantation). The Task Force has done its homework, gathering information from every ART program in the state, interviewing doctors and patients, as well as delving into the medical literature. The report is comprehensive and thoughtful, identifying a range of troubling medical activities and legal uncertainties—all of which certainly exist throughout the United States. Although the recommendations fall short of regulating doctors' clinical activities (i.e., their medical interactions with patients), the Task Force report provides a well documented government analysis, legitimizing concerns expressed by DES Action and other consumer health advocates about many aspects of IVF and its spin-offs.

In June, the Task Force convened a day-long meeting to discuss the report. As the morning session began, voices of protest filtered into the cool, staid Manhattan headquarters of the New York Academy of Medicine—a demonstration, along 5th Avenue, by members of Resolve, the consumer organization that focuses on infertility, unhappy that the Task Force recommended against mandated insurance coverage for IVF-related treatments. This issue would appear more formally—yet still passionately—during the New York City Resolve

Director's presentation later in the day. Insurance was, of course, but one topic filling the crowded agenda, which included speakers and panels on:

- ethical issues in assisted reproduction
- clinical practice issues, including informed consent; patient screening and selection; multiple gestation and fetal reduction; introduction of new medical procedures
- use and disposition of frozen embryos
- commercial issues, including advertising; use of success rates; money-back payment plans
- parental rights and responsibilities, including gamete and embryo donation; gestational surrogacy

Opening remarks set the stage for that agenda. New York State commissioner of Health Barbara DeBuono stressed a concern not only for patients undergoing treatment, but also for offspring born following ART—a concern ranging from serious health problems of prematurely born multiples to legal rights regarding access to information about one's genetic background in cases of egg or sperm donation. She emphasized the pressing need for preventive efforts (e.g., measures to reduce sexually transmitted diseases) and for improved public understanding of assisted reproduction. She issued what doctors might consider a threat—that the medical profession in New York has one last chance to regulate potentially harmful

clinical activities (e.g. transferring too many embryos in order to increase "success" rates, one cause of large multiple pregnancies) before the government takes action. The Task Force's Executive Director, Carl Coleman, followed with an overview of the three differing types of recommendations detailed in the report: legislation, regulatory policies and professional guidelines. Just how to tame what some critics describe as the "wild west" of fertility medicine is, not surprisingly, a matter of dispute. The Task Force determined that the quality of informed consent is poor for many patients and egg donors, cited dangers of fertility clinic advertising and refund plans, and summarized the need to establish legal rights and responsibilities for all individuals—including offspring—involved in various gamete donation and surrogacy relationships. Aside from the contentious issue of insurance (which cannot be separated from the larger unresolved problem of providing equitable access to high quality health care for everyone in this country), a major stumbling block is, as always, monitoring and

regulating what doctors actually do, day to day, within their offices and clinics. Interestingly, one of the most striking disagreements at this meeting pitted one doctor, whose presentation adamantly and defensively praised the specialty's history of self-policing efforts, against another doctor who stated bluntly that professional guidelines do not provide true regulation.

The Task Force did not recommend true regulation of New York's doctors—for example, through legislation or state policy on the maximum number of embryos that can be transferred each cycle, or age limits for certain treatments (regulations that exist in several other countries), urging instead stronger guidelines and monitoring within the profession. However, professional guidelines and peer discipline have not adequately protected fertility patients during ART's first two decades. So what should be next steps to follow the work already accomplished by this Task Force? Beyond implementing recommendations in New York State, the report should be "exported" as a model for other states, not to mention the federal

government (pressured for two decades by abortion politics to stay away from assisted reproduction—but that's another story!). And whatever the legislative and regulatory steps, another of the Task Force's recommendations—increased public understanding—is essential. DES-exposed women and men can readily appreciate the risks of unproven reproductive treatments that turn out to be neither safe nor effective. We can take an active role in pressuring legislators and other government officials to establish strong safeguards for fertility patients, at the state and federal levels, including following through on the New York commissioner's threat to regulate how doctors use current and future reproductive technologies. And all fertility patients—DES-exposed and not—can work with their individual physicians to pay more vigilant attention to "doing no harm," and to determining who can, in fact, be helped by medical intervention. That is, to always weigh carefully, on the best information available, the risks and benefits of any fertility treatment. ■

Letters to the Editor

DEAR Editor:

I know that none of us would readily invest in Eli Lilly. However, recently my husband and I started to do some research on mutual funds. I'm sure more than a couple of us invest in them to varying degrees. Please make sure you get a list of companies within the stock portfolio of

every mutual fund you invest in. These lists were not always available, but almost all of the diversified ones do invest in pharmaceutical companies.

I for one would like to make sure that company does not receive a dime for me—nor do I want to make any money from any of the work that they do. By

the way, it looks like I'll finally be able to settle my case in a few months—since Eli Lilly will be giving me a substantial sum. I definitely do NOT want to give it back. They owe us, not the other way around!

Florida reader

continued on page 7...

Notes from Nora

Cause for Concern and A Call to Action

The front-page article in this issue reports on one of the most important studies to appear in many years. When I first heard about the third generation effects discovered in mice, a sinking feeling came over me. As a mother of young children, I am acutely aware of the emotions that will overtake many readers as they digest this news, and wonder what the future may hold for their precious children.

As I digested the report, my dismay turned more and more to anger and then, to a desire to do something. Clearly we must make sure that there is no delay in beginning the research that will determine if what happened to these mice will happen to our children and grandchildren.

The findings of this study are significant. However, I want to remind our readers and all DES-exposed individuals that this is just one study. And that 89-98% of the mice did not experience tumor activity. Those who did, experienced tumors late in life.

We ask that you continue to be vigilant about your own health care and access to care for DES exposure that is thorough and informed.

We also ask that you continue to push for support for legislation still pending in Congress—SR 834/HR 1788, "The DES Education and Research Amendments." Contact your U.S. Senators and House Representative TODAY armed with these new findings.

But we must do more

DES Action is proposing a Day of DES Activism on Capitol Hill in early 1999. We need to go directly to our representatives, who determine the funding and priorities for the National Institutes of Health, and insist that they immediately establish research on the third generation of humans exposed to DES. In addition, we will push for increased funding for all forms of DES research so that we can uncover every effect of this drug. The results of this new study give the lie to claims that DES is old news, with all effects already known.

In order to proceed with plans for this **Day of DES Activism**, I need to hear from you. I need to know how many members can spare the time and the expense to travel to Washington, D.C. in January or February, and spend a day meeting other DES-exposed individuals and visiting with your representatives. Please keep in mind that Congress is not in session on the weekend; the Day will have to be on a Tuesday, Wednesday, or Thursday.

If you think you can possibly attend the **Day of DES Activism**, please contact me as soon as possible:

- Fill out and return the form below (if you don't want to cut your newsletter, make a photocopy and send that)
- Send me an e-mail message that states: "Put me on the list for the Day of DES Activism." Include your full name and postal address in the message.
- Call me at 1-800-DES-9288.

You need not commit today—just let me know if you are interested in receiving further updates as we make our plans. ■

Day of DES Activism Sign-up Form

YES! Put me on the mailing list to receive updates on planning for the Day of DES Activism in early 1999. I will do my best to get to Washington, D.C. to join with other DES Action members.

Name: _____

Address: _____ City: _____ State: _____ Zip: _____

Telephone: _____ e-mail: _____

Return to: Nora Cody, DES Action
1615 Broadway, Suite 510, Oakland, CA 94612

Book Reviews

by Molly Berigan Spira

Wanting a Child—Twenty-two writers on their difficult but mostly successful quests for parenthood in a high-tech age. Jill Bialosky and Helen Schulman. Farrar, Straus, 1998, 269 pp. \$24.00

I used to say, "there's always hope"...but now I'm not so sure.

Falling into my protective mothermode, I caution all readers of these wonderfully woven stories, that tears will very likely fall. Mine came in the first moment of the first story. The recognition of your child—the first time you see her, the first time you conceive of her—not physically, but in your mind—she is yours and you wonder if life will be complete without her.

It is said that having children makes us true adults, makes us be the best we can be. The

accounts in this book are written eloquently, by writers who found themselves either without child or seeking children they know to be theirs. And those who were successful define that moment of resolution as if they had found the kingdom of heaven.

The writers are professional and the experiences varied—from the single woman who in one moment knows that she will be an adoptive mother of a daughter from China before she ever even gazes into her eyes, to the two gay women who had vials of frozen sperm shipped to their home via Federal Express—offering perhaps the funniest recounting and visualization of parents-to-be. The last installment will ring true to DES daughters as Jill Bialosky, the co-editor and a poet, shares our struggle and honors her life, her children, and this book with her story.

Wanting a child is one thing, but there are no guarantees. I was hesitant to recommend this book at first glance: success is perceived as securing that child,

through whatever means, and most everyone has a happy ending. Women and men in the midst of infertility struggles may find this a difficult read. I know I did. I found myself having to put the book down and cry—either comparing my situation with theirs (mine often without the same results) or crying for them and their struggles. I was often very glad I was not to be asked to carry their same burdens.

These stories are not for the faint of heart, but they will show you that you are not alone. And that there is always hope. ■



LETTERS TO THE EDITOR from page 5...

DEAR Editor:

I would like to share my story to demonstrate that there are responsible and compassionate doctors. My mother had four miscarriages. In 1953 she became pregnant again. My parents lived in a small rural community and the GP was her doctor. He told her about DES and then regularly drove 200 miles to get the prescription for my mother because it was not available locally. No cost for this. He believed he was doing the right thing. He prescribed bed rest and

regularly visited my mother. I think the bed rest actually did the trick (nine years before, my mother had delivered my brother without any problems).

Eventually he retired and moved to Florida. In 1968 he became aware of the DES problem. He and his wife called all the patients he prescribed DES to—not many, given the nature of his practice. My mother told me about this call years later. He urged my mother to make sure I was examined and told her about the cancer

risk. I was 16 when he called, but for some reasons my mother did not tell me about the DES risk until I was 18. She says she did not want to frighten me.

When I was 26 years old, this doctor was visiting in the area and made an effort to see me as a DES daughter he had delivered. He asked me what effects I had, and when I told him he began to weep. I will never forget that moment. This is a far cry from the "fires and floods" I have been reading about with dismay.

Maryland daughter

First report from long-term NCI study: No New Cancers in DES Daughters

Cancer Risk in Women Exposed to

Diethylstilbestrol in Utero

by Elizabeth Hatch et al, *Journal of the American Medical Association*, Vol. 280 No. 7, August 19, 1998.

THE first results from the National Cancer Institute's long-term follow-up study of DES daughters are in. Researchers report **no increase in any type of cancer** except for clear-cell adenocarcinoma of the vagina and cervix. The rate for other types of cancer was similar for DES-exposed women and for the control group, women not exposed to DES.

Clear Cell Adenocarcinoma

Among the 4,500 exposed women in the study, who were followed from 1978-1992, three cases of clear cell adenocarcinoma developed. This is a rate 40 times greater than the general population, confirming earlier research findings. Because (in the absence of DES exposure) clear cell adenocarcinoma is most common in women in their 50s and 60s, scientists want to follow DES daughters for another 10 to 20 years to see if there is a rise in their risk for this rare cancer following menopause.

Continued Follow-up

Scientists also want to continue to follow this population for some time since the women are still young and more time will allow for a more thorough evaluation of cancer risks, such as breast cancer, which is more common in older women.

Other aspects of the study which have yet to be reported include the effects of DES on fertility and pregnancy outcome, effects on DES mothers, and health risks for DES sons. We await further results from the NCI and will report them as soon as they become available. ■

T W E N T I E T H

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