THE DES ACTION VOICE
A FOCUS ON DIETHYLSTILBESTROL
Winter 1999 • #79

T-uterus Surgery—Update

Reviewed by Sally Keely

"Hysteroscopic metroplasty in diethylstilboestrol-exposed and hypoplastic uterus: a report on 24 cases", by Dr. Olivier Garbin et al. of the Dept. of Gynecology, Center of Obstetric Surgery, France. *Human Reproduction*, Vol. 13, No. 10, 1998, published by the European Society for Human Reproduction and Embryology.

THIS is a report on surgery performed on 24 infertile women to correct uterine abnormalities. 15 of the 24 women were DES daughters. Each patient had a hypoplastic malformed uterus meaning small, narrow, underdeveloped, and/or Y or T-shaped uterus. The surgical technique, called hysteroscopic metroplasty, is basically plastic surgery on the uterus. The goal is to enlarge the uterine cavity and improve the uterine shape by removing tissue inside the uterus, and the procedure is described in detail in the report.

After the surgery, the patients received an x-ray of the uterus and fallopian tubes (hysterosalpingography or HSG). In 23 cases (96%), the postoperative HSGs were "well improved, with real enlargement and improvement of the uterine shapes." Fifteen cases (63%) resulted in a normal uterine cavity.

13 pregnancies occurred, including five in patients with previously diagnosed primary infertility. Compared to previous pregnancies, the miscarriage rate fell from 88% to 12.5% and the rate of term deliveries increased from 3% to 87.5%. Of the 13 patients who became pregnant, there was one miscarriage, one ectopic pregnancy, one premature delivery at 30 weeks, four C-sections, and 6 normal deliveries.

Most significant for us, among the 15 DES daughters in the group, 8 pregnancies occurred with 7 healthy live births. (This statistic was not in the article but given to us by Dr. Garbin in personal correspondence). In other words, of the total group of 24 patients, there were 13 pregnancies, and 8 of these were with DES daughters.

In the Winter 1994 VOICE, Pat Cody reported on early results of a similar surgical technique by Drs. Nagel and Malo. The hysteroscopic metroplasty technique described by Dr. Garbin differs from that of Nagel and Mayo because the Garbin team used a monopolar hook, instead of hysteroscopic scissors, allowing particularly clean incisions. Nagel and Malo obtained four pregnancies (of 8 women treated) in women with a history of recurrent pregnancy loss, but none in cases of primary infertility.

Garbin concludes "we consider that hysteroscopic metroplasty may be offered to many women, including those with malformative hypoplasia or DES-exposed uterus with severe primary sterility. This would be especially applicable for implantation failures in an IVF programme or in those women with an inexplicable history of recurrent pregnancy loss." ■

INSIDE

DES Action Tribute Program

WE'D like to offer a great idea for that person who has everything: the DES Action Tribute Program. Our Tribute Program is a way for you to make your contribution in someone's honor or memory. Holiday gifts, birthdays, anniversaries or memorial remembrances - all are appropriate occasions for a Tribute gift.

When you send your Tribute gift to DES Action, simply enclose a note indicating in whose honor and for what occasion the gift is given. Make sure to include the honoree's name and address as well as your own. We send an acknowledgment letter to you and to the honoree. The amount of the gift is not mentioned. ■

DES Action Affiliates

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

DES Action
USA National Office
1615 Broadway, Suite 510
Oakland, CA 94612

Arizona
4855 East Warner Road, #24
Box 180
Phoenix AZ 85044

California
c/o Dr. Wingard
Community Medicine M-007
Univ. of Calif-S.D.
La Jolla, CA 92093
Box 661653
Los Angeles, CA 90066
4936 Red Creek Drive
San Jose, CA 95136

Colorado
P.O. Box 2645
Colorado Springs, CO 80901

Connecticut
Box 131
Guilford, CT 06437

Louisiana
P.O. Box 804
Chalmette, LA 70044

Massachusetts
P.O. Box 126
Stoughton, MA 02072

Michigan
P.O. Box 2692
Ann Arbor, MI 48106
2205 Rosewood SE
Grand Rapids, MI 49506

Minnesota
Box 3102 Butler Quarter Station
Minneapolis, MN 55403

Missouri
7647 Carswold
Clayton, MO 63105

Montana
491 Eckelberry Drive
Columbia Falls, MT 59912

New Jersey
Box 762
Fort Lee, NJ 07024

New Mexico
8401 Spain Road NE
Apt. 2-G
Albuquerque, NM 87111

Ohio
27060 Cedar Road, #507
Beachwood, OH 44122

Oregon
1050 NE Butler Market Road, #3
Bend, OR 97701

Pennsylvania
Box 398
Nescopeck, PA 18635

Rhode Island
33 Edward Avenue
Rumford, RI 02916

Texas
8230 Shadowwood Drive
Waco, TX 76712

Washington, D.C. Area
12494 Alexander Cornell Drive
Fairfax, VA 22033

Washington
719-15th Ave. East
Seattle, WA 98112

DES Sons Network
Michael Freilick
104 Sleepy Hollow Place
Cherry Hill, NJ 08003

DES
Third Generation Network
10731 Brookley Road
Glen Allen, VA 23060

DES Action
Canada National Office
5890 Monkland, Suite 203
Montreal, Quebec H4A 1G2

DES Action
Australia
P.O. Box 282
Camberwell, Victoria 3124
14 Edmundson Close
Thornleigh 2120 NSW

DES Action
Belgium
DES Informatiecentrum
Kolkensvijverstraat 18
3201 Langdorp, Belgium

DES Action
Britain
c/o Women's Health
52 Featherstone Street
London EC1 Y 8RT

DES Action
France
Info DES/France
9 Allee de Guignegault
45800 St. Jean de Braye
Reseau—DES France
44 Rue Popincourt
75011 Paris

DES Action
Ireland
Lower Ground Floor 16
20 Cumberland St. 5
Dublin 2

DES Action
Netherlands
DES-Aktiegroep
Wilhelminapark 25
3581 NE Utrecht

DES Action
New Zealand
Prof. Charlotte Paul
Preventive and Social Medicine
Otago Medical School
Box 913
Dunedin, New Zealand

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. ■

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DES Action USA
1615 Broadway, # 510
Oakland, CA 94612
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(510) 465-4011
FAX: (510) 465-4815
Hotline: 1-800-DES-9288
e-mail: desact@well.com
http://www.desaction.org

Executive Director:
Nora Cody

Board Officers
President: Pat Cody
VicePresident: Michael Freilick
Secretary: Karen Renick
Treasurer: Stephanie Kanarek

Contributors:
Nora Cody
Pat Cody
Tricia Gardner
Sally Keely
Cynthia Laitman

Design and Layout:
Sphinx Graphics
Berkeley, CA

Printing:
Inkworks,
Berkeley, CA
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Notes from Nora

DES Legislation Passes!

After more than a year of letter-writing, trips to Washington, and meetings with members of Congress, legislation extending DES research and establishing a National DES Education program finally passed in late 1998. Our original bill (sponsored by Rep. Louise Slaughter and Sen. Tom Harkin) was incorporated into a comprehensive women's health bill.

Rep. Louise Slaughter (D-NY), rose to speak in favor of the legislation and noted:

"This bill contains a vital section extending Federal research and education on the drug diethylstilbestrol, or DES."

The bill also mandates that "In developing and carrying out the national program, the Secretary (of Health & Human Services) shall consult closely with representatives of nonprofit private entities that represent individuals who have been exposed to DES and that have expertise in community-based information campaigns for the public and for health care providers. The implementation of the national program shall begin during fiscal year 1999."

Day of DES Activism Re-scheduled

Because of the successful passage of our DES legislation, we are no longer planning the Day of DES Activism that was to be held early this year. Instead we are urging everyone interested in supporting and learning about DES research to attend the National DES Research Conference (described below). We hope to have a large contingent of DES-exposed individuals at this gathering.

National Institutes of Health to hold DES Research Conference

As DES legislation was passing, the National Institutes of Health began planning for a national research conference on DES, to be held in July 19 and 20, 1999. DES Action was invited to participate in the planning committee and we have already held our first meeting. The public will be invited to attend this important conference, and there will be no registration charge. The conference will be held in the Washington, D.C. area. We will let you know as soon as we can the exact time, location, and registration information. **We encourage all members to attend, learn about DES research, and help determine the priorities for future research.**

DES Action begins to work with Centers for Disease Control

Scientists and public health experts at the CDC - the nation's leading public health agency - spend their days tracking, analyzing, and working to prevent the spread of diseases and health problems. They monitor birth defects and establish registries to determine the toxicity of chemicals in the environment. They also conduct public health campaigns to attempt to reduce such health risks as smoking, lead exposure, and asthma.

Pat Cody and I visited the CDC's headquarters in Atlanta twice last year, meeting with staff at their National Center for Environmental Health to discuss how they might carry out a National DES Education Program. We have been pleased by their grassroots orientation, public health outlook, and their sincere desire to help spread awareness about DES. Designing such a program is complex, however, and we are still in the early stages. We will keep all members posted as this exciting work progresses. ■

Join DES Action's New Online Listserv

All members with e-mail access are invited to join DAL, DES Action's new online network, or "listserv." To subscribe, send e-mail to DAL-request6:35:34elelists.com. In the body of the message write only the command "subscribe YourFirstName YourLastName" without the quotation marks. Please use the first and last name under which your DES Action membership is listed. When you receive a confirmation request, simply hit reply and send.

Breast Cancer and Hormones - Another View

"Physiologic effects of steroid hormones and postmenopausal hormone replacement on the female breast and breast cancer risk"
Annals of Surgery, November, Vol .228 (No. 5):pp 638-651.
Authors: Isha A. Mustafa, MD and Kirby I. Bland, MDBrown University School of Medicine Department of Surgery

Reviewed by Cynthia J. Laitman, M.S., Author, **DES: The Complete Story** Managing Editor, Annals of Surgery

THIS article constitutes an exhaustive review of medical studies on hormones and breast cancer. The authors acknowledge the widespread concern that women who use hormone replacement therapy (HRT) may increase their risk of breast cancer, and have undertaken this in-depth review to help clarify what is truly known about possible risks. They present their findings in two parts—1) general background information about hormones and the female breast and 2) particularly, breast cancer risk and hormone replacement therapy. The following represents a summary of their findings. However, none of the data included specific information on DES exposed women and we still do not know whether these results may be different for women exposed to DES.

Part 1. Background: Hormones and the Female Breast

Known risk factors. Well established risk factors for developing breast cancer include young age at first period, older age at menopause, and becoming pregnant for the first time after the age of thirty.

Pregnancy. Studies have shown that pregnancy seems to have no effect on survival or recurrence of disease in women who have breast cancer at pregnancy or who have had the disease before becoming pregnant.

Obesity. Obesity in premenopausal women is associated with a decreased risk of breast cancer. In postmenopausal women, it is associated with an increased risk. Scientists have yet to explain this seeming contradiction.

Oral contraceptives. In studies of the effects of oral contraceptive on breast cancer risk, it is difficult to compare European studies with American studies since different types of estrogen are used. In Europe, many women use estradiol, a synthetic estrogen which has been shown to increase breast cancer risk. In the US women use conjugated estrogens which have not been shown to increase cancer risk. In addition, European doses have sometimes been twice as high as those in the US.

In a 1986 US study sponsored by the Centers for Disease Control (CDC), nearly five thousand women with breast cancer were compared with a similar number without breast cancer. The number of women taking oral contraceptives was about equal in both groups leading the researchers to conclude that even 15 or more years of oral contraceptive use did not lead to an increased risk of breast cancer.

Part 2. Postmenopausal Hormone Replacement and the Risk of Breast Cancer

The menopause affects bone density, the heart and circulatory system, muscles and nerves, and the urinary tract as well as the genitals and reproductive organs. In postmenopausal women, from 25% to 44% of women have bone fractures as a direct result of osteoporosis (loss of bone density from reduced levels of estrogen in the body results in bones so fragile, they literally break under the body's weight or with minimal impact).

Benefits of hormone replacement therapy. HRT protects against osteoporosis and reduces the risk of heart disease in women compared to women who do not take HRT. From a public health point of view, these health benefits are considerable since heart disease still ranks as the number one cause of death in women and osteoporosis substantially impairs the health and quality of life for millions of women.

For most women, the authors state, the greatest benefit of HRT centers around quality-of-life issues. HRT relieves hot flashes, menopausally related insomnia and concentration problems, and drying out of the urinary tract and vaginal mucus membranes (the last two conditions are associated with urinary tract infections and pain on intercourse).

In the Nurses Health Study (a ten-year study of over one hundred thousand nurses) the risk of breast cancer increased by 43% in women who used HRT. However, it is not clear if this

increased risk was a true rise in breast cancer risk, or whether these women lived long enough (being spared heart disease as a result of the benefits of HRT) to develop breast cancer they would have gotten anyway. However, in an analysis of a subset of three groups of women (one group never used hormones, another group consisted of current users, and a third group had used HRT in the past) researchers concluded there was no increased risk associated with past use or length of time hormones were used. Current hormone users did have a higher incidence of breast cancer but this could have been due to the fact that this group had far fewer pregnancies and were more likely to consume alcohol.

This study also showed that among women who developed breast cancer during the study, those who currently used HRT had a lower risk of dying from their disease than breast cancer patients who had used HRT in the past or who had never used HRT. (This, surprisingly, implies a possible beneficial effect of HRT with respect to breast cancer, but more research needs to be done.) In another study of life expectancy among women with a family history of breast cancer who used hormones compared to women without a family history of breast cancer, researchers found that lifetime risk of breast cancer increased by about 50% in the family history group. However—the life expectancies of both groups of hormone users (those with and those without a family history of breast cancer) were virtually identical.

In addition, the authors surprisingly conclude that HRT might actually be acceptable for women who have had breast cancer. They point to the unexpected finding in the Nurses' Health Study which showed improved survival among breast cancer patients who used HRT compared to those who did not use it. They do state that many questions remain about the use of HRT in breast cancer survivors including, type of tumor, receptor status, and duration of time since diagnosis. They also emphasize that breast cancer occurs in a complex biological environment where hormones are but one of a number of factors. They state that the "complex interaction of factors may be more important than any one factor, including estrogen."

"Although many questions about hormone use and breast cancer still remain, HRT may actually confer health benefits which outweigh possible risks."

Conclusion. In sum, this exhaustive analysis of available data reveals that evidence thus far shows minimal or no increased risk of breast cancer as a result of hormone replacement therapy. The only group of women who would not benefit from HRT, say the authors, are women at greatest risk for breast cancer and lowest risk for heart disease.

They make the point that women who use HRT tend to be of a higher socioeconomic background, have more frequent health checks (including mammograms), tend to lead healthier lifestyles (including exercising more and eating less fatty diets) and take more vitamin supplements. They point out that regular exercise and a low-fat diet may reduce the risk of breast cancer, independent of the use of hormones. Studies are now underway to clarify whether HRT increases breast cancer risk independent of lifestyle habits.

They conclude that the benefits of HRT may outweigh the risks for women with no personal history of breast cancer, and although it remains the standard of care to discourage hormone use in women who have had breast cancer, future studies may even change this standard.

Although many questions about hormone use and breast cancer still remain, as a woman in menopause, I derive reassurance from this review. Hormone replacement therapy — far from being the menace that our fears and our experiences with DES may have led us to believe — may actually confer health benefits which outweigh possible risks. Future research has yet to reveal the full story.

Our present state of knowledge may be imperfect, but it is what we have to work with. The bottom line is that the responsibility is ours. Each of us has to make our own decisions, design our own lifestyles, and — hopefully— each of us will reap the benefits of good health. ■

How DES Changes Body Systems

Reviewed by Pat Cody

"Fetal exposure to DES results in de-regulation of Wnt-7a, during a critical period of uterine morphogenesis," by Cary Miller, Karl Degenhardt, and David A. Sassoon. Nature Genetics, 20:3, November, 1998.

THIS important study shows that DES exposure during a critical developmental period in mice appears to suppress a gene, Wnt7a, that controls reproductive tract development. In turn, this suppression causes changes in the uterus and vagina that are similar to those found in women exposed to DES before birth. Scientists at the Mt. Sinai School of Medicine in New York found that defects in the reproductive tracts of DES-exposed mice are similar to those found in mice who do not have the Wnt7a gene. This gene is one of a family that regulates cell interactions in the development of the body, as well as specific organs in living organisms from fruit flies to humans.

The researchers exposed pregnant mice to 200 micrograms/day of DES. They then compared samples of reproductive tract tissue from the female offspring of these DES exposed mice with similar samples from Wnt7a mutant mice and a control group of mice whose mothers had not been exposed to DES and were not lacking the Wnt7a gene. Both the DES exposed mice and the Wnt7a mice showed similar changes in the outer and underlying tissue, and the smooth muscle in the uteri. These similarities suggest that the geneWnt7a is somehow involved in the changes seen in DES daughters. In fact, the scientists saw that **DES exposure blocks the expression of Wnt7a in the uterus during a time period critical to uterine development in mice.** They also saw structural changes in the reproductive tracts of the DES and the Wnt7a mutant mice that included poorly formed oviducts and vaginal fornices (the area in the vagina near the cervix) as well as hardened areas and abnormal glandular material in the vagina.

"This work reveals that DES, and possibly other environmental agents, work by disturbing the delicate balance of factors that guide the development of the embryo..."

In a letter to me from Dr. Sassoon, one of the authors of this report, he wrote that

"This work reveals that DES, and possibly other environmental agents, work by disturbing the delicate balance of factors that guide the development of the embryo... By merely disturbing the levels of Wnt7a, and not mutating the gene, a pre-cancerous state can be induced. As such, the study of DES is not merely an historical footnote...but also provides for a new way to understand how cancer can be caused by environmental agents...

"It is gratifying to be able to demonstrate that basic research can often have a large impact on clinical issues. In reviewing the historical timeline on DES...it was shocking that it was ever used. We have treated DES in the lab as plutonium (gloves, masks, labcoats, etc.).

This study is especially interesting in light of recent research showing a 'third generation' DES effect in mice (see VOICE 78). Both of these studies demonstrate the need for further research into possible genetic effects resulting from exposure to DES. ■

Report from the Tall Girls

OUR Winter issue 75 described the "Tall Girls" of Australia who were given DES as children so that they would not become "too tall." One of the Tall Girls, Tricia Gardner of Yarraville, Victoria, Australia, writes about their problems.

" The women are now suffering a variety of reproductive and infertility problems. Most of us never made any connection between the 'treatment' we received and DES. We were either too young to understand the drug name which was labeled 'stilboestrol' and later to make any connection to the term DES and the effects on DES daughters. Enquiries to gynecologists led to very little further information. We are a distinct group of people who are suffering similar reproductive problems like the DES daughters without the structural defects of the reproductive system that they have suffered. The Tall Girls group has developed a database of 135 women and the following statistics have been developed from phone testimony or questionnaires...These histories are far from complete or definitive, but certain trends are apparent. Of the 135, one in three have ovarian cysts, one in three have had problems with fertility, one in five have endometriosis, one in six a miscarriage, one in ten fibroids, one in ten have had a hysterectomy. We believe that these figures are a reason for concern.

We have had contact with two American women similarly treated as children, who have the same reproductive and health problems as their counterparts in Australia - they have found us. It concerns our group that there are also a large contingent of women in America and Europe who are at risk and probably wondering why they are having many reproductive and health problems. They are also at double risk if their mothers were given DES.

I have read an article recently sent by a Tall Girl in America written by the Boston Sunday Globe dated March 5, 1967. It mentions that the 'treatment' was thought about in the 1940's but 'treatment was put off for fear it might interfere with fertility.' The article then states..."The work at the Children's Service of the Mass. General Hospital ...and other leading centres from Boston to Melbourne, Australia, indicate the therapy is safe." Unfortunately, the trial was still at too early a stage to convey this comforting information. **It also did not have any real significance in reducing height."** ■

Down History Lane...

THIS letter appeared in the May 1998 issue of Environmental Health Perspectives, published by the National Institute of Environmental Health Sciences .

"In the course of a literature review, I encountered a report published in 1933, which described the first synthetic estrogen. At that time, an incorrect version of the chemical structure of estrone was in use, but the first synthetic estrogen was derived from it, namely, 1-keto-1,2,3,4-tetrahydrophenanthrene. Estrogenicity was demonstrated by changes in vaginal cytology in ovariectomized rats. Two parts of the discussion section of the paper are beautiful to read, as follows:

"a report published in 1933... describ(ing) the first synthetic estrogen... demonstrated... changes in vaginal cytology in ovariectomized rats."

'This result is of importance, for 1-keto-1,2,3,4-tetrahydrophenandthrene is the first compound of known chemical constitution found to have definite oestrus-exciting activity. There is thus provided the first step in the task of defining the molecular conditions necessary for this type of physiological activity, and there are grounds for hoping that substances of a much higher order of activity will be found before very long...

'The observation that oestrogenic properties of a low order are possessed by suitable extracts of such a variety of materials as peat, brown coal, lignite, coal tar and petroleum is of interest, but in view of the fact that many such materials are known to contain carcinogenic constituents, the clinical use of such extracts without very stringent

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refinement is scarcely to be entertained.'

"This seminal paper therefore mentions synthetic estrogens, a test for estrogens, hopes for structure-activity relationships among estrogens, naturally occurring estrogens, the anticipated clinical application of estrogens, and a relative risk estimate, with carcinogenicity being weighed against estrogenicity. Within 3 years, the same group had defined bisphenol A as an experimental estrogen. Sixty years later, the United States Congress mandated an ordered study of synthetic environmental estrogens."

John Ashby, Zeneca Central Toxicology Laboratory, Cheshire, United Kingdom.

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 200 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).

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. ■

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Organization
US Postage
PAID
San Francisco, CA
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National Office
1615 Broadway, Suite 510
Oakland, CA 94612
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