THE DES ACTION VOICE

A FOCUS ON DIETHYLSTILBESTROL

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Cervical Problems Greater for DES Daughters

Reviewed by Pat Cody

E.E. Hatch et al, "Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States)," Cancer Causes and Control, vol. 12, November 2001.

LAST year (VOICE 85, Summer 2000) we reported on a study from the Netherlands on 5,421 DES daughters who reported a total of 111 gynecologic cancers in 105 women (excluding clear-cell cancer). The authors noted that this was three times the risk that would be found in non-exposed women of this age group.

Now we have a major study from the researchers funded by the National Cancer Institute in response to legislation we helped get through Congress on research and public education. Replies from the 1994 survey were received from 3,222 DES daughters and 1,102 non-exposed controls. The researchers looked at those who reported having squamous neoplasia, which is defined as pre-cancerous lesions of the vagina and cervix that require removal. There are degrees of neoplasia and the authors report on those with moderate to marked neoplasia (CIN 2). They found 95 cases among the DES daughters and 16 in the control group. This works out to about 3% of DES daughters having neoplasia against 1.5% of the unexposed women.

"This study found a two-fold increased risk of high-grade squamous neoplasia in women exposed to DES in utero compared to unexposed women. The risk was highest among women who were exposed within 7 weeks of the last menstrual period, and was not significantly elevated among those exposed at 15 weeks or later . . ."

The findings, as stated in the article:

"This study found a two-fold increased risk of high-grade squamous neoplasia in women exposed to DES in utero compared to unexposed women. The risk was highest among women who were exposed within 7 weeks of the last menstrual period, and was not significantly elevated among those exposed at 15 weeks or later . . .

"Women exposed to DES in utero have a much wider cervical transformation zone than non-exposed women. The increased incidence of high-grade squamous neoplasia observed in the present study may be the result of the increased area of the transformation zone resulting from DES exposure . . .

"Another hypothesis for the association between DES and high-grade disease is that DES exposure may have caused permanent alterations in the immune system leading to lesser ability to fight off a genital infection such as HPV. Treatment of neonatal mice with DES caused profound alterations in the immune system, especially on natural killer cells. Very few studies of immune effects have been conducted in humans, and those that have are inconsistent.

"In summary, the present study found a small but significant increase in the incidence of high-grade cervical and vaginal neoplasia among DES-exposed women followed between 1982 and 1995. The findings, in conjunction with the previous study of the DESAD cohort and the suggestion of a higher risk of cervical cancer among DES-exposed in the Netherlands, underscore the importance of continuing to educate both physicians and the exposed population about the necessity of regular screening among women with a history of in-utero DES exposure." ■

INSIDE

Update on DES Internet Listservs

by Sally Keely (aka "DESxposd")

THERE are now several DES e-mail lists.

DES Action members with e-mail access are invited to join the DES Action Listserv, DAL. The purpose of this listserv is to allow a direct e-mail link between DES Action and our members. This forum is primarily for information sharing, for instance: Legislative alerts, Press releases and news updates, Event announcements, e.g. DES Symposiums, Information from upcoming DES Action **Voice** newsletters.

This low volume list is a benefit of membership. Only current DES Action members may participate. To subscribe, send e-mail to Sally Keely, the list owner, at DAL-OWNER@perilpoint.com. Please include a statement that you wish to join DAL and the full name under which your current DES Action membership is listed. Note: this list has recently moved to a new server, so these are new subscribe directions. All 95 previous list members have already been transferred over to the new site. If you have any questions about the list, please contact Sally.

DES daughters should check out DES-L, the DES daughters listsev and online support forum at http://www.surrogacy.com/online_support/des/. To join the listserv, complete the online application and get ready to share support and information with 1000 other DES daughters!

DES sons will want to join the DES-Sons list for confidential discussions of issues related to DES exposure in males. This list was developed in conjunction with DES Action. To subscribe send blank e-mail to des-sons-request@egroups.com. Direct questions to des-sons-owner@egroups.com.

The DES-Family list welcomes all DES-exposed, their family, and friends. To join, e-mail listserv@sact.com with only the command "subscribe des-family" (without the quotes) in the body of the message.

Charli@egroups.com can help if you have questions.

Lastly, announcing the newest DES related listserv, DES-Pregnancies. DES daughters who are pregnant, trying to conceive, or contemplating pregnancy are invited to join via the list website http://www.onelist.com/subscribe/despregnancies. You will need to register with onelist, if you aren't already. Contact ladonnakat@aol.com if you have trouble subscribing.

DES Action Affiliates and State Contacts

DES Action Affiliates

Each affiliate was created and nurtured by volunteers. Write to them if you want information or would like to volunteer.

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Sisters Study on Breast Cancer

WORKING out of their office in Research Triangle Park, North Carolina, a pair of NIEHS researchers are laying the groundwork for what may prove to be a landmark study of the possible interplay between genetics and the environment in the development of breast cancer. Principal investigator Dale Sandler, acting chief of the institute's Epidemiology Branch, and colleague Clarice Weinberg, chief of the Biostatistics Branch, plan to recruit 50,000 female volunteers aged 35-70 whose sisters have been diagnosed with breast cancer and follow their health over a period of time. Eventually the researchers will evaluate the 1,500 or so of the women that they estimate will develop breast cancer during the initial five years of follow-up, analyzing environmental, genetic and health data captured at the outset of the study...

Besides collecting biologic and environmental samples such as blood, urine, tap water, and household dust, researchers will also use questionnaires to gather a multitude of data about health history, past environmental exposures, and lifestyle.....

To execute such an ambitious study, the research team will need large numbers of participants. Though Sandler and Weinberg expect recruiting the large cohort necessary to generate a statistically viable group to be a challenge, they plan to surmount this hurdle by going after precisely the participants with the most motivation to enroll and stay enrolled – women who have a sister with breast cancer.

"To execute such an ambitious study, the research team will need large numbers of participants."

"First-degree relatives, especially sisters, have about two times the risk of developing breast cancer as the average woman," Sandler says. Sisters of breast cancer patients are also likely to be within the same age range (and therefore at an age when they are at risk for developing breast cancer) and likely to have been exposed to the same environmental risk factors during early childhood. And of course they share many of the same genes. Sandler says sisters are also likely to share genetic polymorphisms (slightly different versions of a gene) that might affect the way a person's system handles carcinogens or repairs DNA...

In focus groups of women of diverse socioeconomic, racial, and lifestyle backgrounds, Sandler and Weinberg have discovered that the women have one thing in common: as sisters of breast cancer patients, they share a common concern over the disease. That makes them more likely to want to participate in the study and more willing to comply with the demands of the study...

The researchers are building a web site for the project, developing a marketing plan to attract study participants (including ads in women's magazines and cancer publications), finalizing questionnaires, and securing scientific review of the study design...Women enrolled in the study will provide periodic updates and will be given follow-up questionnaires. "By starting with a cohort of women and following them over time, we'll be able to look at many conditions of concern to women in addition to breast cancer, like osteoporosis and thyroid and autoimmune disorders," Sandler says. ■

Editor's note: The Sister Study is not yet open for enrollment. Please contact Dr. Sandler, the Principal Investigator, if you have questions about the plans for the Sister Study. Her e-mail is sandler@niehs.nih.gov and her phone is (919) 541-4668. Watch the web site at www.sisterstudy.info for details about enrolling in the study.

Note: We receive many inquiries from DES daughters about various aspects of menopause. This article, while not about DES daughters in particular, is a useful discussion. See also the report on page 7 on an osteoporosis drug that Eli Lilly wants to market.

Perimenopause: an Invented "Disease"

By Tony Scialli and Adriane Fugh-Berman. *Reprinted with permission from the November/ December 2001 issue of Network News, published by the National Women's Health Network*

THE latest media event is perimenopause, yet another time in a woman's life when the characteristics of her menstrual cycle give her a chance to be considered abnormal. Menopause itself is an arbitrarily defined non-event useful primarily for targeting a group of women for pharmaceutical marketing. Perimenopause increases both the number of women eligible for unnecessary tests and treatment, and the duration of their eligibility for special attention from pharmaceutical companies.

What is Perimenopause?

The story of perimenopause is closely connected to the hoopla around menopause itself. Menopause is when menstrual periods stop permanently. Unlike the menarche (first menstruation), however, a woman's last period is not dramatically announced, nor can it be predicted or diagnosed by lab tests. Determined retrospectively and by an absence, menopause is defined as the time after which no menses occur for 12 months. But rather than ceasing abruptly, menstrual periods commonly space out prior to stopping altogether. As women age, it is normal to progress from having periods about once a month to having them every two, three or more months, following which cycles start up again. Menstrual periods are unlikely to start again after being absent a full year.

"Perimenopause increases both the number of women eligible for unnecessary tests and treatment, and the duration of their eligibility for special attention from pharmaceutical companies."

If menopause is an arbitrarily defined point on the continuum of normal changes in ovarian function, perimenopause is both vaguely and variously defined (under some definitions, this "phase" could last 20 years). As women get older, their ovaries become less sensitive to follicle-stimulating hormone (FSH), which stimulates the maturation of an egg and the release of estrogen. With continued aging, the response to FSH may diminish to the point that an egg does not mature, ovulation does not occur, and hormone levels are not high enough to cause uterine bleeding. Lack of bleeding does not signify a complete lack of eggs or even a complete lack of hormones, but only an amount of estrogen or progesterone too low to cause the uterine lining to bleed.

During the years prior to her last menstrual period, a woman's response to FSH is not uniform. Varying levels of hormones may change menstrual-related symptoms and bleeding intervals. Some variability is normal throughout the reproductive years. The 28-day cycle is a myth—normal cycles can vary from 25 to 34 days or more, with few women experiencing the same interval cycle after cycle. In the years prior to menopause, however, variability can become more extreme. Associated symptoms such as mood changes, breast tenderness and bloating can also be highly variable. It is this period that has become known as perimenopause.

The term perimenopause became popular among health care providers and the media only a few years ago. Creating a medical term has invited medical researchers to take ownership of the condition and thereby to study it. Unfortunately, such studies require that criteria be invented for defining a condition, and particular creativity is involved when the condition itself is invented.

Some researchers have

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defined perimenopause as the 10 years prior to the last menstrual period; but of course this definition can only be made in retrospect. Other definitions start perimenopause at age 40, under the assumption that the average age of menopause is around 50. But this ignores the fact that the normal age range of menopause is from 40 to 60. One of us heard a lecture defining perimenopause as the first break in menstrual cyclicity, with "early perimenopause" defined as less than three months without a period and "late perimenopause" as more than three months without a period. We wondered if "pre-perimenopause" would soon join the lexicon.

There may be no agreement on when this elusive condition begins, but the symptoms it encompasses include an ever-growing list. Perimenopause has become a new disease. Symptoms attributed to it include irregular periods, heavy periods, light periods, cramps, hot flashes, night sweats, memory loss, sleeping problems, mood swings, anxiety, irritability, lack of libido, vaginal dryness, frequent urination, migraines, bloating and breast tenderness. Not one of these symptoms is specific to the "perimenopausal" age group (irregular periods, for example, are common among adolescents, athletes and lactating women). Instead, the list is a compilation of symptoms attributed variously to menopause, menstrual cycle changes, pregnancy—and just being a woman.

Irritability or mood swings, for example, have been attributed to women's jumpy hormones for eons; such labels have long been used either to overmedicate women or to dismiss their complaints. Hormones may be one factor in influencing moods, but personalities, relationships and stress are probably far more important. (One Network friend, whose doctor pushed her to go on hormones after skipping exactly one period, was asked if she suffered from irritability; she responded that her partner certainly thought so, but that the "condition" predated the relationship.)

The growing number of symptoms or conditions attributed to perimenopause allows its purveyors to cast their diagnostic net over as many women as possible. Their justifications for lumping discordant symptoms can border on the absurd. An article in the *Female Patient* (a pseudojournal funded by drug companies and distributed free to doctors) titled "Perimenopause: surviving the transition to menopause" notes that problems with perimenopause include fertility or infertility. Well, that about covers the bases: who escapes one of those two categories? In the same article, a researcher is quoted as saying, "The one consistent thing about perimenopause is its inconsistency," a statement one may as well make about life.

FSH Fallacies

In their search for proof that perimenopause exists, researchers and clinicians have hit on measuring FSH in blood as a way to "diagnose" the perimenopause. This is a useless test for this purpose (although perhaps appropriate for an invented disease). The primary purpose of the blood test is ceremonial: it allows health care providers to make scientific-sounding pronouncements. You may be feeling fine, "but the blood test shows that you have severe menopause" (for high FSH). Conversely, you may be having bothersome symptoms and be told, "The blood test is normal, so maybe you should see a psychiatrist" (for low FSH).

The use of FSH as a measure of ovarian aging does have some scientific basis. FSH is produced by the pituitary gland in response to low levels of estrogen and inhibin, another ovarian hormone. During a woman's reproductive life, her estrogen and inhibin levels are low when no eggs are maturing. Increased FSH stimulates eggs to mature in preparation for ovulation. Many years after menopause, when estrogen levels are very low compared to premenopausal levels, FSH levels increase because the pituitary gland keeps trying to stimulate eggs to mature.

At menopause and during the years prior, estrogen levels are not necessarily low, although they are more variable. If estrogen levels go up and down, FSH levels, in their see-saw relationship with estrogen, go down and up. A woman's FSH blood test result reflects her FSH level at the moment the needle is in her arm. It may be completely different 90 minutes later.

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FSH testing is useful in women who may be having trouble becoming pregnant. An FSH result on day 3 of a spontaneous menstrual cycle can predict whether a woman's eggs have aged beyond the likeliness of successful pregnancy and birth. In the early part of the cycle, estrogen and inhibin levels are rising, and FSH should be at its lowest. If the ovary does not respond normally to FSH, the pituitary will produce more and more in an effort to stimulate the ovary. Women with elevated FSH values on day 3 are unlikely to become pregnant (or, if they do become pregnant, they are unlikely to carry the pregnancy very long). An elevated FSH can be disappointing, but it can also save a woman from spending large sums of money on assisted reproductive technologies that are very unlikely to be successful.

Hormone levels may vary more sharply before menopause. Women may have symptoms (breast tenderness, mood changes) that they never had before, or never had to the same degree. They can have both high estrogen (breast tenderness) and low estrogen (hot flash) symptoms in rapid succession. In fact, hot flashes are not directly related to estrogen levels—after all, girls have low estrogen levels and no hot flashes—but may be related to rapidly falling estrogen levels. Women who suddenly stop estrogen therapy rather than tapering off, for example, often have severe hot flashes.

But what if a woman finds the increased variability of these years to be disturbing? If symptoms such as heavy bleeding, bloating, breast tenderness, mood changes or hot flashes are troublesome, they can be managed. It is acceptable to consider treatment, even for a non-disease. Treatments may include pharmaceuticals, herbs, dietary supplements, dietary changes or exercise.

"Many women have no 'perimenopausal' symptoms at all, and many others have mild symptoms that are not troublesome. Most women feel absolutely fine simply knowing that these symptoms are a normal part of life and not evidence of poor health. Perimenopause is no more a disease than is peripuberty, and we might be a lot better off if the term would just go away."

Then again, many women have no "perimenopausal" symptoms at all, and many others have mild symptoms that are not troublesome. Most women feel absolutely fine simply knowing that these symptoms are a normal part of life and not evidence of poor health. Perimenopause is no more a disease than is peripuberty, and we might be a lot better off if the term would just go away.

Tony Scialli, MD, is professor, Department of Obstetrics and Gynecology, Georgetown University Hospital, and editor of Reproductive Toxicology. *Adriane Fugh-Berman, MD, is assistant clinical professor, Department of Health Care Sciences, George Washington University School of Medicine, and a board member of the Network.*

Editor's Note: Recently the press had a report on the newest effort to tap into the women's health market. It is a "Revival Menopause Home Test," which costs $59.95 and whose makers urge women to use it every six months starting at age 35. Cindy Pearson, director of the National Women's Health Network, advises women not to waste their money. "Menopause is not a disease and not a medical emergency. There's no need to do a test for it even if the test were particularly accurate, which this isn't." For a balanced article on "Menopausal Hormone Replacement Therapy" available free from the National Cancer Institute, call 1-800-4-CANCER (1-800-422-6237).

Another Drug Women Don't Need

By Pat Cody

NOT too long ago, Eli Lilly found a "disease" they termed Pre-Menstrual Dysphoric Disorder (PMDD)—and, not surprisingly, a cure for it: Sarafem, a re-worked version of Prozac. Now they have proposed another medication, Forteo, this time for osteoporosis. The *New England Journal of Medicine* (in its issue of May 10, 2001) carried a report on it, "Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis," by R.M. Neel, M.D. and 11 co-authors. This study was supported by Lilly, and consisted of daily injections of a parathyroid drug teriparatide (trade name Forteo) to postmenopausal women diagnosed with osteoporosis. The women also received 1000 mg. of calcium and 1200 IU of Vitamin D. The women were divided into three groups: 541 got Forteo at a dose of 20 ug a day, 552 got 40 ug a day, and 544 women received a placebo. Over a median observation of 21 months, the researchers report that 14% of the women in the placebo group had new vertebral fractures compared with 5% and 4% in the two Forteo groups. Bone mineral density increased by 2-4 percentage points in the groups on Forteo over the placebo group.

However, the study was stopped when a study on rats given Forteo showed the development of bone cancer with an increase in risk relative to the strength of the dosage. Dr. Sidney Wolfe's Health Research Group testified in July before the FDA Advisory Committee on Endocrinologic and Metabolic Drugs. In a strong statement from Peter Lurie, M.D., M.P.H., Deputy Director of the Health Research Group, he stated that:

"'We therefore believe that the risk-benefit assessment tips against approval of the drug in women . . .' Yet—the FDA Advisory Committee unanimously approved putting this drug on the market."

"The rat carcinogenicity data are some of the most striking animal carcinogenicity data we have ever seen. Osteosarcomas (bone cancers) occurred at frequencies of 0%, 5%, 35% and 52% (for control vs. placebo group, low dose, middle dose and high dose) of males and in 0%, 7%, 20% and 38% of females. No "no-effect level" for osteosarcomas was established because tumors were present at even the lowest dose level. Osteoblastomas were also statistically significantly increased in males and in females.

These data present a compelling case for the carcinogenicity of teriparatide for several reasons:

1. The increases in tumors are substantial and statistically significant.
2. The increases are dose-related.
3. No no-effect level was demonstrated.
4. The higher the exposure, the shorter the time to tumor initiation and death.
5. The increases in tumors occur in both genders.
6. The exposure levels are small multiples of human exposure; at 18 months the lowest dose was only approximately 1.6 times (based on area under the curve) or 5 times (based on maximum concentration) the exposure in humans.
7. Osteosarcomas are very rare tumors in experimental animals; the FDA safety review states that they were seen in control animals in past rat carcinogenicity studies at rates of 0.3% (1/360) in males and 0.0% (00/360) in females.
8. The tumors are mechanism-based; teriparatide causes increases in bone formation and thus, bone is where one would expect to see tumors.
9. Parathyroid hormone-induced osteosarcomas have been observed in other rodent studies; FDA's Draft Guidance for Industry on Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis (May 2000) mentions positive studies in two rat strains and one mouse strain.

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. . . Moreover, the rat study may actually have underestimated the incidence of bone tumors. Tumors were detected either by clinical detection of a bone nodule or by microscopic evaluation, but only four bones were examined routinely under the microscope. The limits of clinical detection are illustrated by one tumor that was fatal yet was only detected upon microscopic examination . . .

Dr. Lurie concludes, in referring to women, that "the absolute fracture reductions are not large; many of the fractures are symptomatic and there was no overall impact on the patients' quality of life. Moreover, there already are four drugs approved by the FDA for the treatment of osteoporosis. We therefore believe that the risk-benefit assessment tips against approval of the drug in women . . ."

Yet—the FDA Advisory Committee unanimously approved putting this drug on the market. ■

STUDY ON LONG TERM EFFECTS

We want to tell our readers about an excellent review article by Prof. Shanna Swan of the Dept. of Family and Community Medicine, University of Missouri, Columbia MO. This report *"Intrauterine exposure to diethylstilbestrol: Long-term effects in humans"* is in a Supplement on *"Hormones and Endocrine disrupters in Food and Water"* published in 2001 by the Acta Pathologica, Microbiologica et Immunologica, Scandinavia (APMIS). The Acta is a journal produced by the Scandianvian Societies for Medical Microbiology and Pathology in Denmark. We have received their permission to reprint a few copies for our members. If you would like one, send us $1 in cash or stamps (no checks!) to cover postage.

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