THE DES ACTION VOICE
A FOCUS ON DIETHYLSTILBESTROL
Winter 2004 • #99

CDC Teleconference on DES Sons
September 17, 2003

Dr. Forsythe: We're very pleased to have with us two leading DES researchers, Dr. Linda Titus-Ernstoff and Dr. Ed Messing.

I'd like to turn it over now to Dr. Titus-Ernstoff, who will discuss research findings on health risks for DES sons, and then Dr. Messing will discuss medical implications of latest research.

Dr. Titus-Ernstoff: Thank you, Dr. Forsythe, and welcome, everybody. As most of you know, diethylstilbestrol, or DES, is a potent synthetic estrogen that was widely used to prevent miscarriage and pregnancy complications back in the 1940s through the 1960s. The number of men worldwide who were exposed prenatally to DES is unknown, but estimates suggest that the number could be as high as one million or two million. The possible impact of DES exposure on genitourinary anomalies, reproductive outcomes and cancer is of long-standing concern. Much of what we know about genitourinary outcomes in DES exposed men comes from reports based on the Dieckmann sons, men whose mothers participated in the clinical trial of DES in the early 1950s, and also on the Mayo Cohort, a group of men who were identified through a review of medical records at the Mayo Clinic more than 20 years ago.

The possible impact of DES exposure on genitourinary anomalies, reproductive outcomes and cancer is of long-standing concern.

Both of these groups of men, along with three other groups, are now being followed by the NCI's collaborative study of DES. The NCI's study is more than four times larger than the largest previous study, and the results will be available within the next year or two. Possible effects of DES exposure include a higher likelihood of genitourinary infections or inflammations, but few studies have evaluated these outcomes. Genitourinary anomalies have been more extensively studied and an association with DES is almost certain. Several studies have shown that DES exposure is associated with an increased likelihood of minor anomalies of the male genitals including hypoplastic or undescended testicles, epididymal cysts and possibly urethral stenosis. These conditions may be associated with early doses of DES or with especially high doses.

But to keep things in perspective, about 10% of DES exposed men and 8% of unexposed men have been diagnosed with some type of genitourinary conditions. Overall DES exposed men are 1.3 times as likely to have a genitourinary condition when compared to unexposed men. Risk of some conditions such as epididymal cysts may be elevated as much as four-fold in DES exposed men. But importantly, most studies have shown that these anomalies do not interfere with reproductive outcomes in the DES exposed men.

As most of you know, DES exposure has strong effects on fertility and reproductive outcomes in women. Consequently, the influence of DES on these outcomes in men is of key interest. Results from a few studies, including those based on the Dieckmann and Mayo men, provide little evidence of sperm abnormalities, although one study suggested that sperm motility might be lower in the DES exposed men. DES exposure does not appear to be associated, however, with low sperm counts or with Eliasson scores, which seem to be unaffected by DES exposure.

Not surprisingly, much of what we know about reproductive outcomes in DES exposed

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How to Join the DES Daughters Listserv

DES Daughters should check out DES-L, the DES daughters listserv 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 1,000 other DES daughters! Note: this list is operated independently from DES Action.

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men is also based on the Mayo and Dieckmann studies, along with a much smaller study of men whose diabetic mothers participated in the DES clinical trial in England. These studies show no adverse affect of DES on the likelihood of fathering children or on the average number of children fathered. In fact, the Dieckmann study, which is probably the best study to date, suggested that the DES exposed men were more likely to have fathered children, and a similar finding was noted by the small study of British men.

In the Dieckmann study the average number of children, 2.2, was comparable for the DES exposed and unexposed men. Reassuringly, a separate study of the Mayo men also showed similar numbers of pregnancies fathered by DES exposed or unexposed men. Other favorable findings from the Dieckmann study indicate that the DES exposed men fathered their first child about the same age as the unexposed men, were more likely to have fathered a child due to contraceptive failure, and were slightly less likely to have experienced fertility problems, which we're going to define here as taking more than one year to conceive. While these are encouraging results, fertility decreases with age, and it's possible that more subtle effects of DES exposure could become evident as the men grow older.

There has been considerable interest in the possibility that prenatal exposure to DES influences sexual behavior, including sexual orientation. A small number of previous studies of sexual behavior were conducted by psychologists who had access to small groups of DES exposed men, and the results probably are not reliable. A study of the Mayo men found no differences in age at onset of puberty, frequency of sexual intercourse, sexual satisfaction or occurrence of impotency. A report based on the Dieckmann study indicated that DES exposed men were less likely than unexposed men to report a decrease in sex drive lasting at least three months.

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By far the largest study, which was reported earlier this year by the NCI Collaborative DES Follow-Up Group, provided little evidence that DES affects sexual behavior in men, including age at first intercourse, number of partners or sexual orientation. The NCI study and most other reports indicate that the likelihood of marriage is comparable for DES exposed men and unexposed men, although the study of British men showed that the DES exposed were less likely than unexposed men to marry. However, also in the British study, the DES exposed men who had married or were living as married were more likely to have fathered children.

In women, the association between DES and a rare vaginal adenocarcinoma raised the first alarms about the hazards of prenatal DES exposure. Whether DES exposed men have increased risk of genitourinary cancer is not known. Because DES is associated with cryptorchidism (undescended testicles), which increases risk of a testicular cancer, an association between DES and testicular cancer is plausible. Several studies have evaluated this association, but unfortunately the results have not been consistent. The NCI collaborative study suggested that risk may be three to four times greater for DES exposed men, but because the findings were not statistically significant, they may not be reliable. Consequently, although the association is plausible and is of continuing concern, the question has not been answered definitively.

The DES exposed men are still relatively young and have not yet reached the age of highest prostate cancer risk. Consequently, while this is of interest, we don't know whether DES exposure influences risk of prostate cancer. Answering this question is a very high priority of the ongoing NCI collaborative study.

The NCI collaborative group is in the process now of analyzing data based on the last phases of follow up of the DES exposed sons, and the reports will be available soon. This study is several times larger and more powerful than previous studies, and it may produce the definitive report on genitourinary inflammations and anomalies, and reproductive outcomes in the DES exposed sons. At this point it would be premature to offer any conclusions based on this work, which remains ongoing. However, thus far there is no indication that this large study will overturn what is already known about the effects of prenatal DES exposure in men.

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Consequently, we can summarize by concluding that DES exposure in men is associated with an increased risk of minor genitourinary conditions, which don't seem to influence fertility or reproductive outcomes. DES may also be associated with a modest increase of genitourinary infections and inflammation. To date there is little evidence that DES influences sexual behavior including sexual orientation, and previous studies have not shown an association between DES exposure and reproductive outcomes in men. A possible link with testicular cancer is suspected, but has not been confirmed.

And now, Dr. Messing.

Dr. Messing: Rather than repeat a lot of what Linda has just said, I think that I'd summarize a couple of things that should be known, and then maybe explain some of the findings and explain why things aren't known about them. First, the reproductive tract abnormalities that Linda mentioned and have been recognized for 20 to 30 years now are ones which tend to be minor. Epididymal cysts are nodules that arise in the epididymis, which is the tubular structure that attaches the testicle to the vas duct. Sperm migrate through it and become capacitated to become capable of fertilizing an egg by doing this process. It does not appear that these cysts hinder fertility.

An undescended testicle can be a major issue, not only because it requires a surgical repair in most men or young boys, but because it can lead to sub-fertility and has, more importantly, the risk associated with testicle cancer that was just mentioned. The reason that it's been very hard to figure out if the DES exposed men have an increased risk of getting testicle cancer is that the incidence of testicle cancer is quite low, even though it's the most common solid malignancy in men who are in their 20s and 30s. It's still a very rare disease, relatively speaking, and the result is that even if there were a few more patients in the DES-treated rather than the untreated group, the numbers couldn't achieve statistical significance, because they were low and it would require even further studies to really figure out if there is a significantly increased incidence.

There is some fairly compelling evidence in animal studies that estrogens given very early in life... do have affects on the prostate gland.

The urethral narrowing problems are ones, which again, normally can be taken care of fairly easily and normally would not hinder fertility, although they might require some sort of intervention if they affect urinary flow, which is where the symptoms would become most obvious. Perhaps the biggest issue is the potential affects of estrogen in the in-utero period, associated with the subsequent growth of the prostate. There is some fairly compelling evidence in animal studies that estrogens given very early in life, or more commonly given when the mice are still inside their mothers, do have definite affects on the pros-tate gland that only become manifest as mice age considerably.

One of the most common problems as normal men age is a non-cancerous enlargement of the prostate, and while this does not tend to occur in mice, in those mice exposed to very early estrogens and DES, it will occur. This is a process that has to be looked for and the men in the Dieckmann cohort who were born in 1950 to 1952 would only be in their early 50s now, and they're just beginning to enter the age range where the prostate enarges, and I think it will take at least a decade or longer to figure out if this is going to be a factor. It should be recognized, however, that this is a common event of prostate enlargement in many men who don't have any exposure to DES. So comparing the two groups will be very important.

The other fairly concerning issue is that of prostate cancer, and again, men tend to get his now when they're in their 60s, 70s or older, although some men in their 50s get it as well. This will be something that we just have to follow. There are theoretical reasons why this could occur. In the rodent studies prostate cancer was not a common event, although, again, rodents don't tend to get this disease naturally, so it would be hard to figure out. I think prostate cancer has to be looked for, and certainly those men who were exposed to DES in-utero probably should be followed for this disease. I think I'll stop here as well.

Moderator: Thank you, Doctor. The first question comes from a participant in Kingston.

Q Dr. Titus-Ernstoff, I am with the DES International Network, and I'm pleased to connect with you and Dr. Messing as well. We've not had a chance to actually talk before,

but I think it might be worthwhile in the future. I have a question briefly. Our network is about five years old, and I'm quite familiar with your research study on psychosexual effects and have been through actually the entire range of studies going back to the 1970s that have looked at psychosexual effects and gender issues in DES exposed people. I wonder if you would briefly just address the question of why it could be possible that although your study seems to be finding "no or very little impact on adult sexual behavior," we have, in fact, in our network found over 100 individuals with known or likely exposure who also have a history of gender variance experiences or transsexualism.

A Sure. I'd be happy to address that. First of all, I think what I'd like to do is talk about why you are seeing something that's very different from what we've seen. I think that we can start with the possibility that some of the people that are in the network do not have confirmed DES exposure. A very important strength of the NCI study is that every single person in that study has DES exposure confirmed by medical records. While medical records may not be infallible, that's about as close to perfection as we can get.

Another extremely important difference between the NCI study and a framework such as a network, where people essentially volunteer or self-identify themselves to participate, is that the NCI study is based on people who are identified through a more objective or neutral process. These are people who were identified not because they had a problem or were concerned about a problem, but because their medical records indicated that they were exposed or they weren't exposed to DES. So there's very little possibility that bias affects the results of the NCI study, simply because we invited people to participate regardless of whether they had a concern about a DES condition. It's possible that what you're seeing, and I would suggest that this is exactly what's happening, is that the network members represent the small proportion of those who were exposed to DES and also have a health problem. But it doesn't necessarily mean that the health problem is related to DES.

I think that these networks and registries are extremely important in terms of reaching people who have problems or concerns. But it is very difficult to derive valid or reliable scientific conclusions based on people who belong to a registry or a network.

Q In the discussion on the CDC Web site talks, for the most part, about epididymal cysts in sons, which seem to be fairly catchable with a good physical exam and self-exam. Are there any other issues related to prevention, particularly signs and symptoms and history and physical exams, that should be looked out for and regular, routine, preventive in otherwise healthy individuals?

A *(From Dr.Messing)* I presume you're talking about a DES son, and I think the two that I think are justified, although you can make an argument that they're justified in all teenagers, young adults and up until about age 50 anyway, is examining the testicles. Certainly if you have a history of an undescended testicle, even if it was brought down, you are at markedly increased risk for developing a tumor in that testicle, and even the opposite testicle that was normally descended is at a considerably increased risk, although not as great as the undescended one that was brought down. So certainly in those groups of men there's no question that testicular self-exam is critical. Testicle cancer is a highly curable disease, but the treatments can be moderately drastic, and if left alone it's very difficult to cure....

The second is the issue dealing with prostate disease, that of course is a complete unknown. ...Both screening and testing for prostate cancer...is still a debatable issue as to whether it really winds up saving lives or note. I happen to believe that it does...Screening involves an annual rectal exam and a blood test, and since currently there is no blatant sign of increased prostate cancer risk for DES exposure, I think waiting until one is 50 years of age to do that would be justified....

(Editor's note: Readers can find many other interesting questions and answers from this conference at the CDC web site —www.cdc.gov/des) ■

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Third Teleconference: What Do Animal Research Findings Reveal About Future DES Health Effects

Summary by Nora Cody

THIS teleconference featured John McLachlan, Ph.D., Director of the Center for Bioenvironmental Research at Tulane & Xavier Universities. Before coming to Tulane, Dr. McLachlan spent two decades at the National Institute of Environmental Health Sciences. He has studied DES for over thirty years and has published over 150 journal articles. Our readers know Dr. McLachlan as a pioneering researcher and a true friend to our community who has taken a keen interest in helping DES-exposed people for his entire career.

Dr. McLachlan's remarks are difficult to summarize succinctly, and he spent most of the call taking questions from callers. Here is my best effort at summarizing key elements of his remarks.

"Currently, the work that I think is most prominent and most promising is that which investigates how DES can change the gene regulation or the gene in a way that can be passed through multiple generations of cells, and perhaps through generations of different animals. This I know is an issue of great interest to many people....

"The reproductive tract development in the mouse – development of the vagina, uterus, and cervix – is something that essentially occurs in the last trimester of mouse pregnancy and in the first five days of newborn life. In the human, this whole process occurs in the first trimester of pregnancy. So, why look at neonatal and prenatal mice? Well, the biology is actually very, very similar in both cases....

In response to a question about menopause:

"When we did animal studies and gave pregnant mice DES in a variety of different doses, one of the things we observed, and published several papers on, was that there isn't a menopause, per se, in mice or rats, but that they do have what's called a reproductive senescence. They age out and they no longer ovulate.... We were able to see that these animals would cease reproducing, essentially become mouse menopausal. This would happen at earlier times with more DES exposure. So it wouldn't surprise me if there were changes in the human hormone profile or onset or severity of menopause with DES exposure, since it does cause such a profound organizational change in different parts of the endocrine system. I don't know of any data that has looked directly at that.

Q Could you give us an overall view of the effects of DES on third-generation mice, both male and female, and what do the human studies show?

"These are actually studies that I was conducting with my colleague, Retha Newbold, at the NIH before I left for Tulane eight years ago, so I know them very well.

"What was shown in that series of papers, looking at both male and female grandchildren, if such a thing can exist with mice, was that they both had what seemed to be normal fertility, but that some females ended up with changes in the vagina and uterus that were very suggestive of cancers seen in the first generation. The males were also of normal fertility, but had defects in their reproductive systems, primarily in the prostate, seminal vesicle, and to a lesser extent the testicle, that were suggestive of a cancerous change.

"Again, this was similar to what the first generation had, but not in as high a percentage. What struck us, though, and what strikes everyone who has done similar experiments, is that the changes seen occurred in the same organs in both the first and second generations, suggesting that something must happen to the genetics of that animal that could be passed on. Many laboratories are working furiously right now trying to figure out what those molecular events could be." ■

Letter to the Editor

Dear Editor,

I am a DES daughter who had breast cancer almost 8 years ago and many other problems including not having children. Recently I had a thyroid nodule enlarge and this led me to ask for a look-see throughout my body. An abdominal CT scan revealed a kidney tumor.

I am in the middle of this new crisis, but it was found because of the abdominal CT scan.

A review of the literature shows that DES causes kidney tumors in animals, and there are in the literature stories of an 18 year old DES daughter with kidney cancer, and three men treated with DES (and lupron) for prostate cancer that went on to get kidney cancer.

I think it prudent for DES daughters to get abdominal CT scans every 4-5 years, like a colonoscopy, to make sure we don't grow abdominal tumors.

Also, if you are a DES daughter with kidney tumors or thyroid masses, benign or malignant, I would like to talk to you.

Please write me at DLBerkson@aol.com, or at 10420 Charette Cove, Austin TX 78759

Sincerely,

Lindsey Berkson

Editor's note: Ms Berkson is a consulting scholar at the Center for Bioenvironmental Research at Tulane and Xavier Universities and the author of Natural Answers for Women's Health Questions (Simon and Schuster, 2002), *Hormone Deception* (Contemporary/McGraw Hill 2001), and *Healthy Digestion, the Natural Way* (John Wiley, 2000). ■

An Award for Good Work

EACH year the Public Relations Society of America gives out awards to recognize excellence among public relations practitioners. This year, in the Public Service category, the CDC contractor Porter Novelli won the Phoenix Award for "Centers for Disease Control and Prevention's DES Update Campaign." The award was given out in November in Atlanta.

We know the award was well deserved, because of the splendid materials that presented to a national audience the facts and figures about DES: what it is, how it concerns you, and what you can do to get more information and references. As many of you know,

- special informational binders were mailed to our members,
- five teleconferences provided information on various aspects of exposure,
- press releases and media appearances launched the campaign in March 2003.

If you have not done so already, check out the CDC's DES web site at www.cdc.gov/des. ■

We always need the names of physicians who are informed about DES and sensitive to the needs of their patients. If you have such a referral, let us know!

Progress in DES Lawsuits Abroad

THE long-standing effort of two French cancer daughters to receive compensation from UCB Pharma moved forward in November 2003. The High Court of Nanterre found UCB Pharma responsible for the health effects of DES, and rejected their efforts to make the daughters bear the costs of the law suit. The Court ordered that each of the daughters receive at this time 16,000 ($20,160) euros pending completion of a study of their claims. It also ordered UCB Pharma to pay 5,500 ($6,930) euros in court costs. ■

DDT: The Devil in the Details

By Nora Cody

THE November/December 2003 issues of *San Francisco Medicine,* the journal of the San Francisco Medical Society, carried a thoughtful overview article "From "*Silent Spring* to Scientific Revolution" by John Peterson Myers Ph.D. He is a co-author of *Our Stolen Future* and began his report with these words:

"Four decades ago in *Silent Spring* (1962), Rachel Carson wove together a fabric of evidence suggesting that parts of the modern chemical revolution were having unintended consequences, undermining human and wildlife health in unexpected ways.... Her thesis...launched the modern environmental movement. It stimulated formation of a new branch of government focused on environmental impacts. It led to bans of DDT and, since then, a host of other chemicals...."

Dr. Myers later refers to a study about DDT published in *The Lancet* as recently as July 14, 2001. The authors of that work, led by Matthew P. Longnecker, report on a significant association between DDE (the metabolite of DDT) in maternal blood serum and the occurrence of pre-term birth and small-for-gestational-age children. They used birth records and stored serum from 1959 to 1966 and had complete data for 2,380 children. They concluded that "The findings strongly suggest that DDT use increases pre-term births, which is a major contributor to infant mortality."

My thought when I read this was – this may explain why so many pregnant women with a history of pre-term delivery and/or still births, were given DES in those years, and, for that matter, in earlier years when DDT use was rampant. And it took until 2001 to make the link between DDT and prematurity. ■

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