

Dr. Titus-Ernstoff received her Ph.D. in epidemiology from Yale University School of Medicine in 1989. She is a Professor of Community and Family Medicine at the Dartmouth Medical School. Dr. Titus-Ernstoff has served on several breast cancer scientific review panels and served for four years on the Epidemiology Scientific Review Committee of the National Institutes of Health. Her research interests include women's cancers, melanoma and the health effects of DES exposure. She has published over 60 articles in these areas.

Since 1992 Dr. Titus-Ernstoff has led Dartmouth's participation in the National Cancer Institute's collaborative study of DES. As part of that study Dr. Titus-Ernstoff is currently involved in research on the genitourinary and reproductive outcomes in DES sons and is working closely with Dr. Kim Perez to finalize statistical analyses and report preparation on these topics. She recently published a report on the psychosexual outcomes in DES sons and daughters.

Now I'd like to introduce Dr. Messing. In July 1995 Dr. Edward M. Messing, Chief of Urological Oncology at the University of Wisconsin, joined the University of Rochester faculty as Winfield W. Scott Professor and Chair of the Department of Urology. A national leader in the field of urological oncology and principal investigator on numerous NIH grants and contracts, Dr. Messing has brought his clinical and research expertise to all facets of the department. In October 1996 Dr. Messing was also named Acting Director of the University of Rochester's National Cancer Institute's Designated Cancer Center. Upon appointment of a full-time Director in 1997 Dr. Messing has continued his role at the center as Deputy Director. Dr. Messing also co-authored the 1997 article on the effects of prenatal DES exposure on men.

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.

L. 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. 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 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.

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.

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. That's about all I have to tell you tonight. Thank you.

A. Forsythe

And now, Dr. Messing...

E. 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.

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 effects 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 prostate 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 enlarges, 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.

A. Forsythe

Thank you, Linda, and thank you, Ed. John, we'd now like to open up the lines for questions.

Moderator

Thank you, Doctor. The first question comes from a participant in Kingston. Please go ahead.

W

Yes. I guess that would be me. 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.

L. Titus Ernstoff

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.

Moderator Thank you. Our next question comes from a caller in Santa Monica. Please go ahead.

M Hi. My mother took DES for my sister as well, and I know she participated in a class action suit for DES women, and I'm wondering if there's been any sense of doing that with men as well.

L. Titus Ernstoff I don't have any idea. I'll turn that over to Dr. Messing.

E. Messing I have no idea either. I think it would be difficult to figure out the condition for which one could claim that this is justified. Now, all of that said and done, I'm certainly not a lawyer, and I guess more to the point one could make an argument that the monitoring that I think might be advisable for DES exposed men dealing with prostate disease, for instance, and perhaps testicle cancer do require some increased surveillance and might require some expense on their part, but I think it would be hard to pinpoint a tangible way in which men currently have been hurt by this in order to justify some sort of class action suit, which I think normally requires a damage or some sort of monetary loss to be recoverable. I think I'll stop there.

Moderator Thank you. Our next question comes from a caller from Pittsburgh. Please go ahead.

- M Hi. Most of the research on DES sons appears to have focused on prenatal exposure to DES. I'm wondering what studies have been conducted that have looked at exposure through beef consumption. As you're probably aware, DES was continued to be permitted in beef through 1979 and then probably has been included in beef for at least through the mid to late '80s because stockpiles were allowed to be continued to be used in beef, and the FDA currently allows estradiol as an injection in cattle, and estradiol is chemically similar in many ways to diethylstilbestrol, so I'm wondering what research has been done on the impact of exposure through beef consumption.
- L. Titus Ernstoff I'm actually not familiar with that area. That's a huge area of investigation. There are many sources of what are called environmental estrogens, and people have worried, of course, about DDE and DDT in terms of estrogenic effects in men. I know those chemicals have been studied, but I'm not specifically aware of studies of the impact of DES or estradiol in beef. Dr. Messing, do you know anything more about that?
- E. Messing I know very little more. I know of two vague references to it. One is actually if beef is bad you can think about poultry, which is even worse. There have been reports of families adjacent to a poultry farm in Puerto Rico where this was clearly an issue, mostly in daughters. Whether it was ante-natal or postnatal exposure is, of course, unclear, since this continued after the children were born and their mothers were taking care of them while exposed to this. I can't comment further about that, but clearly it's an issue.
- The other issue is that there has been a relative rise over the past 30 to 40 years in testicular cancer internationally, and this is not simply a reporting artifact because medicine reporting is better now, because this is a disease that really does not go away and is a very serious one. Certainly one of the theories behind it is continued exposure, be it antenatal or after birth, to environmental estrogens that are of greater quantity than they had been. I don't know any specific research studies that would address this issue, and I really am not sure that there's been any good, quantitative information otherwise either from epidemiologic studies.
- L. Titus Ernstoff Dr. Messing, I have a question for you, actually. Do you think there is a remote possibility that estrogens in the environment could be protective in terms of prostate cancer in men?
- E. Messing Well, there is certainly, again, indirect evidence. To those who are in the audience, prostate cancer tends to be a disease related to the male sex hormones, androgens, although the specific levels of testosterone in the blood don't directly correlate with developing the disease. There's clear-cut evidence that people in countries which are exposed to certain dietary factors, which include, as Linda mentioned, phyto or natural estrogens, these are estrogenic-like compounds in herbs and other materials, tend to

have a lower incidence of getting prostate cancer, and as their dietary habits change, they get a more westernized diet, prostate cancer becomes more common. Thus exposure to estrogens may protect against prostate cancer.

Since, in epidemiological studies, one of the things most closely associated with developing prostate cancer is consumption of a large amount of red meat and fatty foods, and people who consume them would eat DES impregnated cattle, there may be conflicting influences on prostate cancer development. It would be hard to figure out that association. But in answer to your question, theoretically there could be a protective effect or even an effective therapy based on it. I don't think there's clear evidence and the little evidence there is would be against that.

- L. Titus Ernstoff Thank you.
- Moderator Thank you. Our next question comes from the line of a caller at Dana Point. Please go ahead.
- M Are there any significant co-morbidities outside the genitourinary tract, such as colitis, rheumatoid arthritis and other conditions?
- L. Titus Ernstoff That's a very interesting question, and I think what you're talking about is the group of diseases that we call autoimmune diseases, colitis and rheumatoid arthritis and diseases of that nature. Actually, we are beginning to study autoimmune diseases in the DES sons and daughters in the NCI study, so I hope we'll have an answer to your question before too long, and I hope the answer will be no, but we'll see.
- E. Messing I'm unfamiliar with it, so I can't comment further.
- Moderator Thank you. Our next question comes from the line of a caller in Zephyr Hills. Please go ahead.
- W Yes. I have a question, please. My son, I was a DES mother, and it wasn't found until he was 40 that his testicles did not develop. What I was wondering, they did the testosterone test on him, but I worked in the medical field, and what I was wondering, is it important to monitor the testosterone and the estrogen level? Because from what I understand if the estrogen level creeps up sometimes that can destroy the testosterone. I may be wrong. I don't know.
- E. Messing I guess I'm the one who should be answering.
- L. Titus Ernstoff I'm hoping.

- E. Messing Well, it's a little more complicated than that. Actually, in men the vast majority of estrogens come from the testicles. There are other sources that produce it, but the vast majority come from the testicles, so it would be a bit complex. Certainly, a testicle that has a specific abnormality will produce an abnormally high amount of estrogens and then testosterone will go down. Similarly, in people, men, who have higher levels of estrogen for some reason, the feedback system in the brain is similar in both men and women and the brain will recognize increased amounts of estrogens and it will send a signal where result is that the testicles will be shut down. So things like that can occur.
- I've not heard of it in the reverse way; that is if people's testosterone goes down that causes an increased estrogen. Sometimes these occur in combination though, for instance, in certain conditions the estrogens are not metabolized appropriately so they build up to a higher level and that will suppress testosterone. I'm not sure if that answers your question.
- Clearly, with men who are having sexual performance problems or a variety of other problems or in men who are obviously having trouble with fertility, then checking hormonal levels is quite important because correcting them may be necessary to help their fertility or sexual problem and clearly, in understanding the cause of it. I hope that helps your question anyway.
- Moderator Thank you. Our next question comes from a caller in Round Rock. Please go ahead.
- W Good evening. I'm a DES mother. I took 50mg, up to 200mg a day before my son was born. He was born with a detached stomach, which was herniated through his diaphragm by the esophagus and twisted, and I've always wondered if something like this was a result of the DES that I took. Have you had any studies along this line?
- L. Titus Ernstoff Actually, we haven't. Dr. Messing, do you want to answer this? I was just going to say I'm not aware of any studies, and most of the effects that we would expect to see would be in the genitourinary tract. It's probably a very sad coincidence. And because it's such a rare outcome, it would be very difficult to study it in a scientific way and produce a legitimate answer to your question.
- E. Messing I concur exactly, and certainly in the animal studies I'm aware of, at least in making sense about this there's not clear cut evidence that for a herniated stomach and diaphragm developmental problems that sexual hormones would be responsible. It is possible, however, that first, these are much more common, these types of abnormalities are much more common in premature infants, and it is certainly possible since many of the women receive DES to avoid a threatened miscarriage it is possible that just because of prematurity there is a higher risk of this association (non reproductive congenital anomalies and in utero DES exposure) developing.

But I am unaware of it, and it doesn't make a lot of sense from what I understand about embryology. I would stop there.

- Moderator Thank you. Our next question comes from a caller in Tucson. Please go ahead.
- W Yes. I'm a DES exposed daughter. I have a 24-year-old son who was diagnosed with an abnormality in the reproductive organs. I'm not sure if I'm saying this correctly, a varicocele vein, something to that effect. My question is this: What does research show about the effects of DES on sons of DES exposed mothers?
- L. Titus Ernstoff We're probably not going to be able to clarify this question. I thought she said she was a DES daughter?
- W Yes, I am.
- L. Titus Ernstoff Okay. So your mother was the one who took DES?
- W My mother took DES while she was pregnant with me. I have a 24-year-old son who I said has been diagnosed with this abnormality.
- L. Titus Ernstoff Yes. Right. I believe that abnormality has been seen in the DES sons. But as far as I know, no one has yet studied what I would call the third generation or the grandsons. Dr. Messing, do you know anything about that?
- E. Messing No. I don't have an answer to that, but you should know that in several studies done in military recruit populations, around 10% of ostensibly normal men in the United States, in Western Europe and in Israel have varicoceles. So while this could be associated with the indirect DES exposure and certainly can be associated with obviously documented DES exposure, it is also not a terribly uncommon event, and so it's hard to tell without a controlled study whether it is related or not.
- L. Titus Ernstoff Actually, I'm looking at a table of previous study results, and there doesn't seem to be evidence of an increased risk of varicocele in the sons, so that makes it even less likely that it's an explanation for what your son has experienced. I also see, as Dr. Messing has just mentioned, that this is not an uncommon condition. So again, it could be a coincidence.
- Moderator Thank you. Our next question comes from a caller in New York City. Please go ahead.
- W I'd like to know whether there are any third-generation studies. I'm a DES mother, and I would like to know. I realize the sons are very young, but I want to know if any studies are being done.

L. Titus Ernstoff Actually, we are not doing any studies, I'm sorry to say, of the DES grandsons. One reason for that, and this is a disappointment on the part of the researchers and for all of you, is that we didn't have extremely good participation in the sons cohort, and we were worried about potentially biased results if we studied the next generation.

Another reason is that, based on the animal studies, we have more reason to expect problems in the granddaughters than in the grandsons. So, currently we're studying the DES granddaughters – these are the women whose grandmothers took DES while pregnant. I'd like to be able to say that we would also, at some point, undertake a study of the grandsons, but I'm not sure that's going to happen.

Yet another reason we aren't studying the grandsons is that we've not seen anything of huge concern in the sons. The genitourinary abnormalities are obviously not a happy outcome, but they don't seem to impact fertility or reproductive outcomes, and they're not that much more prevalent in the DES exposed sons than in unexposed men.

Moderator Thank you. Our next question comes from a caller in Fort Lauderdale. Please go ahead.

M Thank you. In the discussion on the CDC Web site talks, for the most part, about epididymal cysts in sons, which seems 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 exam, that should be looked out for and regular, routine, preventative in otherwise healthy individuals?

E. 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.

An associated matter is that because of that association and the allusion to an increased risk of testicular cancer in men, even if there are no abnormalities of the genitalia, it may be justified to do testicular self-exam, and that's certainly advocated to all young men anyway. This can be instructed; both the National Cancer Institute and the American Cancer Society have Web sites as to how to do this. It's quite an easy thing to do in the shower, to feel the testicles and make sure there are no lumps on it, and it should be done occasionally.

The second is the issue dealing with prostate disease, that of course is a complete unknown. As you probably know from the discussion here, both screening and testing for prostate cancer, while certainly popular in the United States, is still a debatable issue as to whether it really winds up saving lives or not. I happen to believe that it does, but I certainly acknowledge that it's controversial. It probably would make sense for certainly men who have DES exposure to consider doing that. Whether the entire society should or not is another thing, although we have no data to say that. Screening for prostate cancer involves an annual rectal exam and a blood test, and since currently there is no blatant sign of increased prostate cancer risk with DES exposure. I think waiting until one is 50 years of age to do that would be justified.

In terms of benign prostate disease, these usually cause symptoms of obstructed urination where the urinary stream is less forceful. You don't empty your bladder as well and so you have to void more frequently. Clearly, if you have those symptoms you should discuss it with your doctor. I'll stop there.

Moderator Thank you. Our next question comes from a caller in Massapequa Park. Please go ahead.

W My question concerns epididymal cysts. Is that a pre-malignant condition, and does the testicle have to be removed along with the cyst?

E. Messing I think I'll answer that. The answer is no, and indeed it's not clear the cyst has to be removed either. Unless it is causing symptoms, meaning discomfort, or adversely affecting fertility, which is a harder thing to prove and certainly could not be shown in the studies that were discussed earlier, treating the testicular cyst is unnecessary. On rare occasions the cysts, rather than being small, a few millimeters in size, say a third of an inch in diameter or smaller, can become quite large, and then they are symptomatic and require removal just for comfort's sake.

There are absolutely no data to indicate that either in DES exposed or unexposed individuals these kinds of cysts result in malignant degeneration or cancer. So they don't provide a marked or any increased risk that is known right now. The epididymis lies in the back part of the testicle. It's a longitudinal streak of tissue that is attached to the vas duct, and in learning testicular self-exam most men learn to feel the epididymis. But it does not require treatment of any sort of if fertility or other symptoms, discomfort, aren't part of the picture.

Moderator Thank you.

Moderator Thank you. Our next question comes from a caller in Inverness. Please go ahead.

W Good evening. It's Enverness, Florida, and I'm a DES mother, and I'm actually calling with great concern regarding my son. He's 42 years old, and in April he started having trouble with his urinary flow and some hematuria, and he went to a urologist and he had a PSA of 3.6, and his repeat one in June was 3.8, and they gave him Trimethaprim for 30 days. He had another PSA, which was 3.4, and the last one he had in July was 3.8 again. Now, they did find that he had the varicocele vein and urethral stenosis, and they did a biopsy in August, which was negative for cancer.

My question is kind of a two-part question since I'm trying to get some knowledge and help for him. How reliable is the PSA test, and the second part is the urologist in the state he lives knows absolutely nothing about DES exposure and would not bother to look at the information, the booklet I had provided to him because I took DES from 1958 to 1964, and it has affected my daughter as well. The son I'm speaking of, my only son, is also sterile, so he probably would have been a good one for somebody to investigate. But my question is how reliable is the PSA, and can you tell me anyone in the state where he lives that could help us determine if he has an epididymal cyst or why his PSA is going to stay at 3.8?

E. Messing Well, I'm not sure I can answer any of the questions definitively. I can tell you a little bit about the PSA test. PSA stands for prostate specific antigen. It's a chemical that's needed for reproduction. It is secreted in the semen, and it prevents sperm cells from glumping together so that each one is independent, which is what's needed to fertilize an egg in a woman. So the only reason you're alive now is because your father's PSA was working. That's not meant to be a joke, but that's its purpose.

W Right.

E. Messing PSA does leak into the blood stream at a certain amount in all men, and when that happens it can be measured. There are data to indicate that prostate cancer results in a higher PSA blood test per given volume of prostate tissue than normal prostate tissue does. That is probably correct.

The problem is that many men fall in a shade of gray range. For the average 42 year old, a PSA in the mid three range is clearly elevated compared to what most other men have. I think it would be an area of concern. On the other hand, based on your son's symptoms, the fact that his urethra is partially blocked, he has predisposing factors to get a prostate infection. The doctors there treated him with antibiotics, and I think his symptoms were typical of someone with an infection, and prostatitis, infection of the prostate, can also elevate the PSA. So it's quite possible that with time and with antibiotics and with treating his stenotic urethra, his PSA will eventually come down as his prostate simmers down.

On the other hand, he certainly needs to continue to be followed because it is possible that the biopsy failed to find cancer that is already there, and I think that if his PSA doesn't go down further with further treatment that he may require a repeat biopsy. Whether this is in any way related to his sub-fertility, to his other probably DES exposure related conditions, the epididymal cyst and the urethral stenosis, we don't have enough data on it. Certainly, a prostate infection can well be related to urethral stenosis, so that connection may exist. I hope that helps some.

Moderator Thank you, sir. Our next question comes from a caller in Calgary. Please go ahead.

M Hi. Given Dr. Titus-Ernstoff's psychosexual study did not include gender identity and given the large amount of studies which indicate that proper testosterone levels are very important to the masculinization in men ... and that many university lecturers discuss the relationship between prenatal hormone levels and gender identity, i.e., Harvard Medical School, University of South Florida, etc., and even the Merck Manual states biological factors such as gender complement and the prenatal hormone largely determine gender identity, does the CDC have any plans to acknowledge any of these studies and university lecturers and their continuing research on DES exposure to genetic males?

L. Titus Ernstoff I actually can't speak for the CDC. I can tell you that it's very difficult to study uncommon outcomes in men or women, because when an outcome is rare, there's limited statistical power to look at an association with DES exposure. In our study, we had a hard time evaluating homosexual orientation, even though it's not that rare. To look at something more subtle, like gender identity, or more rare, like transsexuality, would be almost impossible in our study. I don't know of any study that's larger than ours, or even close to ours in size, so I'm afraid that these questions, while they're important, may never be completely answered.

Moderator Thank you. Our last question comes from the line of a caller in Peaport.

W Great. I'm a DES mother, and my son is 44 years old, and he married a DES girl, and they have no children, could not have children. Her mother had to have a hysterectomy. I had a hysterectomy, and my daughter-in-law had a hysterectomy. Are there any others who married each other?

L. Titus Ernstoff That's not something that we have studied. I don't know whether anyone else has. It's probably ...

W I mean, it's one in a million where they both married.

L. Titus Ernstoff Right. Yes. It's probably pretty uncommon, so unfortunately ...

- W They've been married 15 years.
- L. Titus Ernstoff Yes. I can't really answer your question. We don't really know how often that's happened.
- W There was not another study, but I had to fill out about them, and I never did find out anything about it, you know, if there were others who married each other.
- L. Titus Ernstoff Yes. I'm really sorry. I can ask around and try to find out about that because I do know a lot of people who work in the area of DES, but I don't think anyone has kept track of that information.
- Moderator Thank you. Dr. Forsythe, I'd like to turn the conference back over to you.
- A. Forsythe Thank you, John. Thank you, Linda, and thank you, Ed, and all of the participants for a very informative teleconference. I'd also like to remind everyone that information is available at the Web site, and again, that Web address is www.cdc.gov/des or by calling our toll-free number. That's (888) 232-6789. Again, thank you, everyone, and have a good night.
- Moderator Ladies and gentlemen, that does conclude our teleconference for this evening. We thank you for your participation and for using AT&T Executive Teleconference Service. You may now disconnect.