<u>CDC's DES Update Presents</u>
What Do Animal Research Findings Reveal About Future DES Health Effects?
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***This transcript has been edited for clarity. The views expressed in this transcript do not reflect the views of CDC.**

TELECONFERENCE TRANSCRIPT

Dr. Forsythe — Thank you. Good evening everyone and welcome. My name is Dr. Ann Forsythe. I'm a Health Communication Specialist at the CDC in Atlanta and I'll be your moderator for tonight's call.

I'd like to thank everyone for joining us in the second in a series of CDC's DES update conferences. Tonight's presentation and question and answer period will highlight current animal research findings and updates for individuals exposed to DES, but before we begin, there's some information I'd like to share with everyone.

CDC has additional DES materials for the public such as current DES research information; the history of DES; DES health effects; and fact sheets, resources, and materials for healthcare providers. The information is available through the CDC Web site where you can download and print all materials directly from the site.

CDC also has established a toll-free number where you can call to ask questions, locate DES organizations, and order materials for yourself or to share with others. The number for CDC's DES update is 1-888-232-6789 and the Web site address is www.cdc.gov/des. At the conclusion of this teleconference I will repeat the number and Web site address so make sure you have a pen or a pencil available. Also, the teleconference transcript of this call will be posted on CDC's Web site.

I'd like to remind everyone that we'll have a question and answer period after the presentation, so please feel free to jot down questions while you're listening.

Before we begin, I'd like to introduce our presenter tonight. We're very pleased to have with us Dr. John McLachlan. He's the director for the Center for Bioenvironmental Research at Tulane and Xavier Universities. John received his B.A. degree in liberal arts from the Johns Hopkins

University and his doctoral degree in pharmacology from George Washington University.

Before coming to Tulane and Xavier in 1995, he spent the previous two decades at the National Institute of Environmental Health Sciences, a large and comprehensive center for research on the effects of environmental factors on human health.

Dr. McLachlan's scientific findings and thoughts have been published in over 150 journal articles, 50 book chapters, and five edited books. His primary research on environmental chemicals that mimic the female hormone estrogen has established a new field of research called environmental signaling or endocrine disruption. Dr. McLachlan's Environmental Endocrinology Laboratory utilizes cutting-edge techniques to study environmental signaling. The major area of concentration for the lab's work is environmental estrogens, natural and synthetic chemicals that interact with the estrogen receptor.

Again, we'd like to thank you very much, John, for being with us tonight and now I'll turn it over to you.

Dr. McLachlan Thank you, Ann. Welcome, everyone. I have been asked to speak about what we know from animal research that can be of importance to people exposed to Diethylstilbestrol. I started doing animal research on DES in 1972. At the time we were all blindly searching for ways to evaluate the findings that were coming out -- almost on a monthly basis -- from humans exposed to DES. It has been an interest and a passion of mine for almost 30 years now.

What I can tell you in this very brief introduction is that many of the biological changes that are induced by or associated with DES and in utero exposure to DES turn out to be very similar across species.

After many years of working on these problems and debating and discussing these issues with colleagues, it seems most of us are more surprised to see just how similar species' responses to DES are; the similarities rather than the differences are striking.

We, and many others, have done research looking at the effects in the reproductive systems of male and female offspring of mice treated, both neonatally and prenatally, with DES.

Other laboratories have looked at rats, hamsters, and different strains of mice. There have also been some studies in non-human primates, such as monkeys and chimps.

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.

It's important to me as a researcher, to all of us as researchers, to understand mechanisms and to make predictions about what might happen in the future. But we must also try to come up with a plausible mechanism for how DES could have been associated with the kinds of changes, including neoplasia, seen in the cervix and vagina of both mice and humans. This molecular biology, which includes a process called gene imprinting, has become very exciting to a lot of different laboratories around the world.

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, and I think the use of these different models have been very powerful in trying to elucidate both mechanisms and effects.

I appreciate you taking your time to call in and I hope I have a few answers for some of your questions. I don't anticipate being able to answer all of them; I have my PowerBook here hooked up to the Internet and I'll try to keep up with your questions either in my head or on my computer. If I don't know something, I'm sure among the group out there we'll be able to figure out an answer.

So with no further ado, Ann, I'll turn it back over to you.

Dr. Forsythe — Thank you, John, very much.

Caller 1 — Doctor, I just finally found out what I was given 32 years ago and it's Delalutin. Now is that part of DES?

Dr. McLachlan Delalutin I think is actually a progestenic agent, progesterone, but I'm not absolutely positive. I will look that up and get back with an answer as we go through the other questions. Do you have anything else?

Caller 1 I wanted you to know the fact that I was given that in the first trimester.

Dr. McLachlan … the … preparation but my remembrance is it's more like progesterone than it is like DES, but I think we can find that out.

Caller 1 Because I wanted to know how that would effect … My son now is 32, if there were any side effects along the way for him, and possibly he's thinking of starting a family and he wanted to know if that would have any effects on his offspring?

Dr. McLachlan Does anyone have any idea about that?

Dr. Forsythe No, John, I don't. I think what we can do is research that a little bit.

Dr. McLachlan I'm going to try to research it as we're talking.

Dr. Forsythe Okay. That's great. Thank you, John.

(Added note: Delalutin is a name for hydroxyprogesterone, a female sex hormone--progestin. Progestins have been used to treat menstrual or uterine disorders and to prevent miscarriage.)

Caller 2 Dr. McLachlan, my mother took 250 milligrams of DES prior to her getting pregnant and during her pregnancy with me, and I have had a series of chronic health conditions that have developed over the years, including partial hypopituitarism or empty cella syndrome, diabetes insipidus, hypothyroidism. I never menstruated or ovulated. I had a hysterectomy because of pre-cancerous cells and I've developed polycystic disease in my breasts. I guess my question to you is I don't know if any of that is replicated in animals, if you have seen any of this in your research?

Dr. McLachlan We have seen some of those things in animals. One of the things that we have noticed and published is a fairly high prevalence of endometrial cancer in mice that were treated neonatally with DES in a dose-related way. As far as I know, there haven't been case reports of this in women exposed prenatally to DES, and I'm not sure whether that's a question of age or whether what we saw in mice won't happen in humans. Mice don't

menstruate so the cells that are there stay there. That might be a biological difference that doesn't show up.

In terms of diabetes, as far as I know, the animal studies have never shown effects related to insulin …

Caller 2 This is diabetes insipidus.

Dr. McLachlan Yes. That's something we have not seen in animals, nor do I know of any studies that have shown that.

Caller 2 What about the impact? Do mice have, I would assume, a pituitary? Has there been any impact on the overall endocrine systems?

Dr. McLachlan Before we started doing studies with DES in mice, there was a long history of research using estrogenic or androgenic hormones during development of experimental animals like mice and rats, in which we certainly got profound effects on the pituitary. What we know from experimental laboratory animals doesn't seem to transmit as easily to what we know in humans and other primates. The regulation for the pituitary and control of hormone secretion seems to be somewhat different in terms of feedback.

In mice there have been very stereotypical changes in sexual behavior, literal feminization or masculinization of the brain with hormones early in life; that has never been seen in monkeys or humans. It certainly is something that we spent a lot of time looking into -- working with various colleagues and primate centers -- but from what I've seen of comprehensive literature searches of results in DES-exposed men or women, there is nothing to suggest the hypothalamus or pituitary has been affected. It doesn't mean it hasn't been and doesn't mean that there isn't some relationship to your mother's exposure and you, but the animal studies have not borne that out and it may just be that we looked the wrong way.

Caller 2 Okay. Thank you.

Caller 3 Doctor, at the beginning of the program you mentioned that DES interacts with estrogen receptors. Can it change whether it's positive or negative?

Dr. McLachlan I'm not sure what you meant by changing from positive and negative?

Caller 3 The estrogen receptor that is examined at the time of breast cancer.

Dr. McLachlan I see what you mean. The molecule called an estrogen receptor recognizes all different kinds of estrogens, and then tells the cell or the organ or the breast or the uterus to act as if it's seeing estrogen. DES interacts, that is, binds with the estrogen receptor and that's the way it exerts its estrogenic effect.

What you're talking about, I think, is the fact that in some cases with gynecological effects or breast disease there are receptor positive or receptor negative cells, or there are low receptor kinds of situations. Is that what you were referring to?

Caller 3 Because I've had cancer and I thought it came from the estrogen, but the estrogen receptor was negative.

Dr. McLachlan It could be. It is entirely possible that you can have an estrogen-associated disease or disorder that shows up with a low-level or absent estrogen receptor. It doesn't mean that the estrogen couldn't have played a physiological role through its receptor. It is possible with breast and gynecological cancers that you can lose some of the markers of a normal cell, including the estrogen receptor or the progesterone receptor.

Caller 3 Yes. I was given DES in 1955. We lost that daughter when she was 34, and I have had breast cancer so there's been a long history here.

Dr. McLachlan The latest paper that I've seen from Dr. Herbst's group in Chicago, who has been following breast disease in mothers who were treated with DES, is that there doesn't seem to be any difference in the prevalence of breast disease in women who were treated or not treated with DES before the age of 50.

After the age of 50, there seems to be greater prevalence of disease. However, it's not statistically significant. It's the kind of situation where you might end up an article by saying something like, "we don't know if this is real, but it leads us to suggest that there be more follow-up and more research, and that mothers who were given DES when they are over 50 should probably be followed more closely for breast disease."

Caller 3 Yes. We know that now, but we didn't then.

Dr. McLachlan Yes.

Caller 3 Thank you.

Caller 4 I'm really not sure whether or not my mother was given DES. I was six when she died of breast cancer, and I was also given several injections of a synthetic hormone when I was pregnant with my second son early in 1970, and shortly thereafter I developed vaginal adenosis. My gynecologist thought that I might possibly have been exposed, not only when my mother was carrying me, but also when I was pregnant with my son. My question is now that I've reached menopause and its hell, I'm wondering if there are any possible effects that DES has on menopause?

Dr. McLachlan There are none reported that I'm aware of. As far as I understand it, menopause is hell no matter what you had prenatally or postnatally. I don't mean to be funny, but my partner in life is just going through menopause and she's not happy. She's not had any hormones in utero or postmenopausal either.

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. It's exactly the same functional change as humans have at menopause, but it doesn't have all of the corollary hormonal issues. We were able 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.

I think there have been very preliminary studies looking at age of onset of menopause and have not seen a statistically significant difference. I don't know if those have been published, and I don't think there have been enough people to really make any statement about that.

Caller 4 Okay.

Dr. McLachlan You also inquired as to whether your adenosis could have come from when you were premature with your son or whether it was possibly something your mother took. As far as I'm aware, adenosis has been

shown to come pretty much exclusively from the prenatal treatment with DES, rather from taking a hormone in adulthood.

Caller 4 Okay. It just seemed so odd that it occurred right after I gave birth to this second son.

Dr. McLachlan You also had other kinds of hormones. You had progesterone and a bunch of other things that went along with your pregnancy that may have forced the expression of some of these cells that were lying dormant for many years.

Caller 4 Right.

Dr. McLachlan I wish I had better answers for all these questions. They're breaking my heart.

Caller 4 This is wonderful to be able to ask questions to someone who really cares. One other question I have is what do you think about using estrogen patches and progesterone suppositories during menopause if a person has been exposed to DES? Because I swore I would not use anything, but I have broken down.

Dr. McLachlan Right. Again, I am an animal researcher so I want to make sure that everyone understands that I'm not a physician, and so I'm not really licensed to give medical advice. I can give you some advice, however, because I've studied hormones for three decades. In fact, when I give lectures here I say that there's an advantage and a disadvantage to the fact that I'm not a physician. The disadvantage is that I don't prescribe estrogens or other drugs, but the advantage is that I don't prescribe estrogens or other drugs.

Caller 4 Right.

Dr. McLachlan I would be careful. I would suggest caution even if you weren't DES exposed, and being DES exposed I would even be more cautious. I would recommend more caution. I hate to say that.

Caller 4 That's my sense.

Dr. McLachlan I say that especially in terms of the latest published findings -- both a nurses' study and the Women's Health Initiative -- in which postmenopausal estrogens have not had the level of benefit in terms of

cardiovascular health and others areas that many people over the last ten years have thought they did. So my advice would be to be as careful as you can be and that's all I can say. I know that it's terrible going through those changes.

Caller 4 Thank you so much.

Caller 5 Doctor, I took DES 38 years ago when I was carrying my son, and I was just wondering how would he be affected? He seems to be, thank God, okay, but he is a smoker and what should he look for?

Dr. McLachlan There haven't been many studies on this in the last decade or so, but in the 1970s and 1980s there were a great many animal studies of males whose pregnant mothers were given DES. Based on those results and on things seen in humans, it seems your son would have already encountered these complications. One of the most traumatic things we've seen, and this was actually fairly frequent, was a condition called cryptorchidism. This is when the person's testicles failed to descend, and either one or both testicles remained up in the abdominal cavity close to where his kidneys would be, part way down, or just above the scrotal sac. That's something he could find, but he would know whether his testicles had descended or not.

Caller 5 He does go for physicals. They would know that by now.

Dr. McLachlan Yes, they would know that. In animals there has been a slight increase in testicular cancer. It might be worth him telling his urologist or doctor that he was DES exposed and to keep a closer eye on that.

Caller 5 Testicle cancer?

Dr. McLachlan Yes. There have only been some cases seen in animal studies so I wouldn't say that it's something to worry about. But it's always safer to tell your doctor all of the things that have happened that might make you more susceptible to a disease. I think that would be worth mentioning.

Caller 5 I do tell him. I always say please mention to your doctor that I did take DES, and he seems to say yes, and I hope he does. So that's really what he should be looking for then. That's about it.

Dr. McLachlan Yes, but I think most men that age should be doing the same thing anyhow.

Caller 5 Okay. I just have another couple of questions. I did stop menstruating when I was 38, and I did give birth to him when I was about 35 so I always felt that it was the DES. Is this why it's so difficult for me to lose weight? What should I be looking for in myself? I do go for my Pap test, my breast exam, and my mammography every year; I'm very careful with that. Is there any way it would have affected me at this late date? I'm 75.

Dr. McLachlan You sound like you're pretty healthy and happy. There are a lot of things that DES did that was bad for all of us, but I don't think weight gain can be blamed on DES.

Caller 5 Okay.

Dr. McLachlan It could be, but I haven't seen it.

Caller 5 Okay. My son does smoke. Having been exposed to DES, would that have even a greater risk, a smoker?

Dr. McLachlan I have no evidence that that's the case. There have been some studies done mostly in Boston and New York, where rats that were treated prenatally with DES were more susceptible to cancer when also given a chemical that caused cancer later in life.

In other words, if the rat was exposed to DES prenatally it was likely to get a cancer of, -- in this case, the liver -- if the experimenter treated that rat with a chemical that was going to cause cancer anyhow; there was more cancer and sooner. This is nothing concrete, however. It's just a hint from a few animal studies. I think that if you can get your son to be afraid of smoking through this that would be good for his health in any event.

Caller 5 One more question and then that's it. I do have cysts on my liver. Would that be from the DES?

Dr. McLachlan I don't think so. I've never heard of anything like that and we never saw it in animals.

Caller 5 Okay, good enough. Doctor, I appreciate your time and thank you very, very much.

Dr. McLachlan It's a pleasure.

Caller 6 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?

Dr. McLachlan I'll go ahead and answer it just the way you asked it. 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 lesser extend 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.

I don't know of any studies as yet that have looked at the next generation, which would be an important set of studies to do.

Caller 6 You mean the fourth?

Dr. McLachlan Yes. It depends how we number the generations, but what I'm talking about would be the sons and daughters of daughters or sons whose mothers were given DES.

Caller 6 I see.

Dr. McLachlan So if you were a mother who took DES, we're talking about your grandchildren when we say second generation.

Caller 6 I thought that was third generation.

Dr. McLachlan It could be third.

Caller 6 Okay, and what about our great grandchildren?

Dr. McLachlan Yes. That has some important genetic ideas, but it hasn't even been done in animals yet; those studies would be extraordinarily expensive to do. I don't know of evidence other than anecdotal, as doctor's say, that reports of a cluster of granddaughters or grandsons who have DES-related changes or abnormalities in any way. I haven't seen any publications in this regard.

Caller 6 Okay. You did say there were some feminine changes and some male defects.

Dr. McLachlan Right.

Caller 6 Would you say that's a very slight risk among the grandchildren?

Dr. McLachlan I would say there is a slight to less than slight risk for the grandchildren. Physicians discovered that DES taken by a mother would cause cancer in her daughter only because the cancers found were so rare; they were almost always associated with women over 60, and even still they were very rare in older women. A group of patients between the ages of 14 and 24 coming into one practice in Boston with these cancers within months -- that's what rang all the bells.

Caller 6 Were those the clear cell carcinoma?

Dr. McLachlan Those were the clear cell cancers that came into Herbst's office when he was at Massachusetts General Hospital. It's going to be much more difficult to find subtle changes in grandchildren unless they are, again, some kind of obvious marker. But as I said effects in the mice grandsons and granddaughters are much less prevalent than in the sons and daughters.

The sons and daughters have a great deal of trouble with their fertility, suggesting that the changes in their reproductive systems, in some cases cancerous changes, lead them to have dysfunction in their reproduction function. This was not seen at all in the granddaughters or grandsons, suggesting not only that these other defects occur at less frequency, but also that their effect on function is probably much lower too.

Caller 6 So you're saying it's less in the mice sons and daughters?

Dr. McLachlan It's less in the grandsons and granddaughters.

Caller 6 I see.

Dr. McLachlan Effects decrease as you go down generationally.

Caller 6 Okay, of course. Thank you very much.

Caller 7 Is there any data relating DES to the immune system disorders? I was given DES 42 years ago, and then 11 years after that I was diagnosed with rheumatoid arthritis and my daughter was diagnosed with chronic fatigue syndrome at 31, and she also has hypothyroidism. Since they're both immune system related, I'm wondering if you have any data on that?

Dr. McLachlan There was a whole series of papers on this subject. There were some in the United States, a few of which I was actually an author on; other more comprehensive papers were published in Sweden and other Nordic countries.

I know some of these effects were looked at in a couple of studies in DES-exposed daughters, but they were not clear-cut. There were a series of animal studies, and I'm talking 15 or 20 publications in the mid-1970s to mid-1980s, and then a paper or two on humans that couldn't find anything concrete and that's pretty much been it.

In terms of the animal studies, this research looked at the effects of DES prenatally or neonatally on the immune system of mice and showed that, in fact, there were many surprising changes that persisted into adulthood. There's clearly a long-term effect on the immune system following prenatal exposure to DES. Whether or not that would also have an effect on a directly exposed mother I do not know but estrogens are very powerful hormones and the levels of DES that were given, depending on where you were, could be pretty great.

Caller 7 And I guess what was to my daughters' benefit is that my problems didn't start until the beginning of the fourth month, which meant it was introduced later.

Dr. McLachlan Yes, that's better.

Caller 7 And I think that may have helped a little bit.

Dr. McLachlan It helps a lot.

Caller 7 But I am wondering about studies that perhaps have related chronic fatigue syndrome to DES because my daughter is on disability now.

Dr. McLachlan It wouldn't surprise me, but there's no data in animals or humans relating to chronic fatigue-like syndromes. All I know is that there were this series of publications in animals looking at immune system function. At the time these studies were being done it was surprising that after a fairly short treatment with DES early in the development of the organism, the immune effects persisted well into adult life, such that they couldn't handle secondary challenges with antigens and other sorts of immune stimulants.

Although there's nothing in the human literature, based on what we know from the animal studies, a relationship to chronic fatigue syndrome would not be surprising.

Caller 7 So actually there haven't been any studies lately?

Dr. McLachlan No. I don't think there have been animal studies or human studies in 15 years and I have no idea why.

Caller 7 Yes. Most of your studies are looking at molecular changes more in relation to cancers.

Dr. McLachlan Yes, and reproductive function. My interests are very much around male and female reproductive organs and the effects of estrogens. We've been mostly in the molecular biology lab the last ten years trying to find things that we could pick up as molecular markers in humans that might be predictive from our animal studies, but somebody could have been studying the immune system. I'll look around for that. I'll write that down with Delalutin and see. I'll follow up and then put the information back through the CDC system. Okay?

(Added note: for a list of human studies about DES and possible immunological effects please see http://www.cdc.gov/des/consumers/resources/bibli_immuno.html)

Caller 7 I thank you.

Moderator Our next question is from Seattle, Washington. Please go ahead.

Caller 8

Dr. McLachlan, I appreciate this program very much. I'm getting close to menopause. I'm now getting ready to turn 49 and I found out that I was exposed in 1972. As a matter of fact, I had pre-cancerous cell growth, and cryo surgery was the ticket back then. Then they linked it to the DES, then subsequent infertility problems, and a couple of ectopic pregnancies so I didn't have children.

It's kind of been a juggling act with lowered immune system and allergies and all sorts of stuff, but I've been very healthy, knock on wood, for quite a long time and I've kept myself in really, really good shape. Suddenly I'm starting to have some health problems now that I'm getting a little older and I'm very physically active. One of the things that I'm having, which may or may not have sprung out from the DES exposure, is rather serious endometriosis pain. I'm a pretty small person and very athletic and it's getting to be very painful, but my monthly cycles are very light and very regular.

My doctor is telling me to have a complete hysterectomy, and then she is very much pushing hormone replacement therapy for me. I, of course, with all the DES literature would prefer not to, but here I am. I'm still having monthly cycles regularly and things are really doing pretty well except for the pain, and the risk of doing a surgery to remove the endometriosis after numerous other surgeries is just to risky I guess. If they're going to go in at this point, they want to go in and just take everything out and be done with it.

So my question really is, with the animal testing that you've done, have you done any tests with synthetic estrogens that are plant derived, such as soy, for example? Because there's a school of thought out there that if you're DES exposed you want to avoid anything that in any way, shape, or form resembles estrogen. It's just not a good idea.

I might add that my mom died of inflammatory breast carcinoma so there's always that other issue of breast cancer and being careful about that. But on the one hand I'm thinking this is plant derived. What harm can it do? And on the other hand I'm worried about the whole DES connection. I'm wondering if in any of your studies you did any studies with mice that were exposed to DES and then using soy, for example, and see if there were any changes as a result.

Dr. McLachlan That's a very complex set of issues. I'll answer your last question first. There have been two groups, I believe, that have studied early DES exposure followed by consumption of some specific phytoestrogens, primarily genistein, which is in soy. There seemed to be an increased risk in some endocrine disease; I think related to the mammary gland. I can't recall if it was mammary gland cancer, but there was some relationship. But they gave very, very high doses of genistein.

Here's where I come down on this. We do a lot of work on environmental factors that are estrogenic. Some of them are synthetic chemicals that are pollutants, others are made by fungi, and others are made by plants. Soy has at least two weak estrogens, but it also has a very good anti-estrogen called glyseone that is almost as effective as Tamoxifen. We just published a paper in a clinical journal on that last year. My hunch -- and there's not really much more than hunches around right at the moment -- is that soy containing a mixture of chemicals that have been sort of worked out over 400 million years of evolution is probably the best way to go rather than taking extracts or tablets or genistein alone. It may be that the balance of estrogens and anti-estrogens together might be beneficial. Epidemiologically it's been shown that women who are on soy diets or eat lots of soy have less risk for breast cancer.

When it comes to endometriosis, that's a really tough one. We do a lot of studies in the clinic on uterine fibroids and endometriosis. These are both called benign uterine diseases and they're only benign to the pathologist that makes the diagnosis, meaning they're not malignant. They're not benign to the woman that has them.

Caller 8 Right.

Dr. McLachlan In terms of getting a hysterectomy, or going on hormones, as I said to one of our earlier colleagues, my sense is that there should be another way. Have you tried progesterone treatment for your endometriosis? Have you seen a gynecological or a reproductive endocrinologist?

Caller 8 I've considered that, but having gone through the myriad of hormone injections when I was trying to have children, I was in my thirties, the problems, actually the endometriosis really kicked in after that whole series ended. I had a couple of laparoscopies, and every time they go in to remove something it leaves something behind in terms of scar tissue. So I thought about trying that, but then I decided that I'd just rather not add anything else to the stew, so to speak, just keep it as clean as I can.

What I'm probably going to end up doing is just taking ibuprofen when it's bad and riding it out as long as I possibly can and watching the research. I think your advice about just eating a really good diet that's low in extra chemicals, which the body can translate to estrogen, organic foods and good soy maybe the ticket until eventually when I bite the bullet and have the hysterectomy. It's just very painful, but to answer your question directly, I'm afraid to go on anymore.

Dr. McLachlan I understand.

Caller 8 Yes.

Dr. McLachlan Here's another thing I can do. A former colleague of mine, Dr. Arthur Haney is a reproductive endocrinologist at Duke University. He has really studied this a lot, though he's not as active in this area as he used to be when he and I were working together. He has done a lot of work on hormone treatment and therapy in women who were exposed prenatally to DES. He was actually the doctor who did some of the most elegant studies on the T-shaped uterus back many years ago. I will contact him and see if there is any new information regarding this topic. Okay?

Caller 8 Okay. I do appreciate that. Thanks.

Caller 9 Dr. McLachlan, it's Scott Kerlin from the DES Sons Network. Good to make a connection with you here. I appreciate your presentation on many different levels, but I'll try to be fairly specific on my own topic question. Our network in the past year did a poll to try to find out what were the leading concerns of DES sons and, as you've pointed out and other's have, there's a lot less research that has documented the effects on DES sons than on daughters.

We learned quite a bit though from network members that: endocrine system problems, gender identity problems, and mental health problems seem to be among the top three areas, closely followed by cancer. I wonder if you could just briefly comment from your own long-term research about two somewhat questionable or controversial topics; one being feminization in males, and the other being various endocrine disorders in males, particularly hypogonadism, and whether you've seen linkages in your research over the years in animal research that might point to a significant predominance of hypogonadatropic hypogonadism, I guess is what it would be called.

Dr. McLachlan Right. Hypogonadatropic hypogonadism, is a low level of pituitary hormone telling the testicle, the gonad, to make testosterone and sperm. It is something that has been seen occupationally in men who have acute exposure to DES. So if an adult male takes estrogen or is exposed to estrogen, the obvious results will be gynecomastia (enlarged breasts),, and hypogonadotropic hypogonadism, (small testicles, low libido).

I haven't seen the same kind of thing reported from prenatal exposure to DES. Mice that get treated with DES prenatally have a smaller than normal testicular size and a lower than normal sperm count that's dose related. Testosterone levels in these mice are pretty much normal, although estrogen levels are higher than normal. I don't know of any comparable studies that have been done in humans, but you might know.

Caller 9 I've been looking hard.

Dr. McLachlan The other issue you mentioned was feminization. All mammals – mice, rats, and humans – as fetuses start out as bisexed beings. We have a gonad that's going to be either a testis or an ovary, depending on the genetics. Once that happens that little organ secretes some things that do one of two things.

In the case of a genetic male, the testis will start making testosterone, which keeps the male reproductive system intact during fetal life. They also make another protein called Mullerian inhibiting substance, which is specifically set to wipe out the female reproductive system that the fetus has at this time.

If there is no genetically determined male gonad that makes androgen to keep the male tract alive, and then makes this other inhibitor to kill the female tract, invariably you end up with a female. There are genetic disorders or genetic syndromes where those things can change resulting in a genetic male that may have a complete functioning cervix or uterus. This could happen, it seems in mice or humans exposed to DES, though it hasn't been shown clearly in many human cases. In a mouse whose mother is given DES, you feminize the reproductive system such that a genetically born male, has testis, is usually not making as many sperm as normal, has slightly lower androgen levels, and has higher estrogen levels. That male mouse will have a prostate seminal vesicle, all the other plumbing to get the sperm from the gonad out, but it will also literally have a functioning set of fallopian tubes, uterus, cervix, and an upper portion of the vagina.

The penis of this mouse is also feminized to the extent that there is a higher prevalence of a condition called hypospadias, which is a congenital defect wherein the penis doesn't totally close in the right way. There is an opening that might be along the shaft of the penis or is often at the end of the penis where there's almost another kind of -- I hate to use the term because it's not scientific -- quasi-vaginal like orifice. It means that estrogen has prevented the total masculinization of what could just as easily end up being the clitoral structure and vaginal structure.

Caller 9 Right.

Dr. McLachlan We also know that femininization can even happen inside a cell, and from a molecular level there's a kind of feminization that we and others have shown in mice.

Coming back to one of the earlier questions about hormonal changes in the brain and how this might relate to gender identity. That's been a really tough one for a lot of people. In the mouse and rat you can certainly do prenatal or neonatal treatment with estrogens or androgens to feminize or masculinize behavior. But in humans it's very controversial and unknown as to whether this can happen at all. It seems as if the network is hardwired in a different way. Having said that, I'm not sure if anybody is really dealing directly with this.

Caller 9 I will let go at this point so everyone else can ask their questions, but one of the documents that we have actually posted to our Sons Network home page is from the National Toxicology Program fact sheet on DES. I was intrigued when I read the list of symptoms from physical exposure taken by adults. It says right in the text, not only can it cause male impotence, but it can cause transsexual changes, and it indicates it can cause gynecomastia.

Dr. McLachlan This is in adults though, right?

Caller 9 I think so as best as I can tell. My understanding was that if one time DES was used for male to female transsexuals who were transitioning.

Dr. McLachlan It is actually.

Caller 9 Is it? Okay.

Dr. McLachlan Yes.

Caller 9 But the prenatal exposure and transsexual effects, that has never been clear to me exactly how that works.

Dr. McLachlan Yes. We are talking about, in both humans and mice, a feminization of structures. An example in terms of the genital tract is that with undescended testicles the male gonads stay right where they were when they were both male and female. But again, even though animal studies suggest that you can feminize male rats or mice with developmental exposure to estrogens or androgens, this is not clearly the same case, and I think is pretty much considered impossible, with humans. I don't think that has really been tested in all of the kinds of subtlety that would be required when one considers the complexity of an issue like gender identity.

Caller 9 Yes, that would concur. Thank you so much.

Caller 10 Dr. McLachlan, I was diagnosed DES exposed back in July of 1977, and that was following being on birth control pills, Ortho-Novum 150, from approximately December of 1974 until July of 1977. The doctor who diagnosed me told me that I had cervical ridges and he also referred to the adenocarcinoma risk, and I had colposcopies done. I was never able to officially confirm the exposure. The hospital didn't keep the records. The doctor, it appears that he had retired because this was 20 years later when I was trying to confirm. What I want to know is how accurate do you feel that the diagnosis was made on the cervical ridges?

I did some reading, and I understand that sometimes these changes can occur without the DES exposure, but it seems that it would be more likely to happen with the DES exposure as opposed to not the DES exposure.

Dr. McLachlan The answer to your question is yes. It's not in itself diagnostic just from the reason you said. Did they do an iodine stain on your cervix looking for adenosis?

Caller 10 He said that there was adenosis and I do remember the stain. I even remember one of the exams had a nurse in training, but he was bringing her in because he wanted her to see the cervix so that she could know what DES exposure looked like.

Dr. McLachlan Then the only other thing I would ask is did they do a hysterosalpingogram and did you have what was called a t-shaped uterus?

Caller 10 No, that was not done.

Dr. McLachlan The gynecologists that I've worked with over the years would say that with those three things, especially the t-shaped uterus almost by itself, are just not seen in somebody who isn't DES exposed. If you have had adenosis and the cervical ridges that sounds to me like what you see with DES.

Caller 10 Okay. So it would be more likely to be DES exposure as not to be.

Dr. McLachlan It's more than likely to be than not to be. Yes. That won't stand up in a court of law though.

Caller 10 I understand, but I want to thank you because it kind of gives me the peace of mind that I need to move on. Is there time to ask one more question? I don't want to take away from anybody else's time?

Dr. McLachlan It's not up to me, but yes, go ahead.

Caller 10 Okay. Adenomyosis, I have that problem now too. Any thoughts on that with DES exposure, plus I have never been pregnant and never had an abortion, and I've been told that the adenomyosis is usually associated with that.

Dr. McLachlan Adenomyosis is the group of glands down into the muscle wall of the uterus that sometimes come out the other side. With our DES-exposed mice, we saw high prevalence of adenomyosis in the uterus and a similar condition in fallopian tubes of the female offspring. I am not aware of any evidence of that in humans, but I think that's because the uterus has not gotten nearly the level of attention that the cervix and vagina did, nor the level of attention I think it should get.

Caller 10 Okay, so mice yes, and not studied yet enough in humans.

Dr. McLachlan Right.

Caller 10 Okay. Thank you much.

Dr. McLachlan — Adenomyosis was seen as a very unusual condition, and it was seen in a lot of the mice that were exposed prenatally.

Caller 10 — I'm afraid a lot of my questions have been addressed now, but I guess the one thing I am personally concerned about is I am in full menopause at age 47 in a family where the women generally don't go into menopause into they're in their mid-50s. I realized that you said that mice don't actually have menopause, but has there been a looking at unusual cancers or unusual things happening with menopause?

I guess the reason I worry is this first came up when we started entering puberty, which was a hormonal change in our bodies and it kind of flagged the cancer, the clear cell coming up. Then our next wave of problems seem to be with pregnancy, whether we were able to get pregnant or not get pregnant. I'm now concerned that menopause is our next big hormonal change in our life, and there doesn't seem to be too much research going into that or too much information being circulated. Since it started being used in the population in about 1949 in a pretty good amount, I would think there would be enough women now that are in menopause where there would be an ample study sample to start looking at any menopause-related issues.

Dr. McLachlan — I agree completely. As I've said, even though mice don't have a menopause per se, they do have reproductive aging and reproductive essence. The daughters of the mothers who got a little bit of DES quit reproducing and their ovaries ceased functioning a little bit earlier than animals that didn't get any DES, and the more DES we gave to the mothers the sooner the functioning ceased. Their follicles were devoid of germ cells earlier.

I agree with you completely, and I have said this in print and at congressional hearings and things. I think that, just as you said, the big hormonal hallmarks in a woman's life are puberty, pregnancy, and menopause. I think that there should be more research looking at what may or may not happen.

Some of the diseases in female animals, like uterine cancer and other dysfunctions, are usually seen later in life. They're not something you see early in life. I agree with you, but I'm not quite sure of the best political route to make this something to which more attention is paid.

Caller 10 Then secondly, in relationship to the immune system issues, would it be possible to make that information available on the CDC Web site? Since these studies are so old, many current doctors may not be aware of the studies that took place 15 years ago?

Secondly, I'm on a DES action mailing list, and we're seeing a lot of this happening. The immune system is really flaring up when we're turning 30, 35, and 40 and there weren't too many of us that age when these studies were performed. We were all, not all, but the greatest bulk of the population was probably under 35 at the time. It seems like it's having some sort of delaying action before the immune system issues are kicking in.

Dr. McLachlan Right. I agree with everything you just said and I'll try to get as much information as I can to the CDC. I'm sure they will be happy to post it. You're exactly right about these issues of age. It's interesting how, science, like everything else, tends to follow fads and that DES is yesterday's news. This seems to be the case not just in the United States, but in the whole world, I lecture medical students every year at Tulane, and I have to go through DES and thalidomide with these kids each year. These are second-year medical students and they've never heard of it..

Caller 10 Right.

Dr. McLachlan I agree with your concerns. I think it would be one of the ultimate tragedies -- in the scheme of this whole tragic event – to fail to follow up with women as they enter menopause and for the next 20 years after all that we've learned and after these women have formed groups, raised research dollars, and put themselves out there to be followed.

Caller 10 Right. One last thing, my fellow women sufferers, the few women that have not been certain if they were DES exposed and their doctors are no longer living, a good gynecological oncologist with a background on DES doing a colposcopy can do a fairly good job of determining whether or not you've had it. It may not hold up in a court of law, but at least it gives you an idea of whether or not you should be treating yourself as a DES-exposed woman.

I had the good fortune of being diagnosed by one of Dr. Herbst's students, Dr. Azizi, and he was actually able to tell me in what week my mother started taking the DES so the colposcopies are that good. This was 20 years ago so I can't even imagine how good they might be now, but

colposcopy is pretty effective at diagnosing the changes to the vaginal area.

Dr. McLachlan — Yes. I think colposcopy and hysterosalpingogram, which is even less invasive, are two good tools to resolve that anxiety.

Caller 10 — Right, and if it's an issue then you know to watch your health. Thank you very much, Doctor. We appreciate it. You answered a lot of my questions tonight.

Dr. McLachlan — Thanks for being so patient and sticking around to be the last questioner.

Caller 10 — I was so glad I got in.

Dr. Forsythe — Great. Thank you, everyone, for a very informative call. I would also like to thank you, John, for your presentation and all of our partners involved in CDC's DES update.

Again, I'd like to share with everyone the toll-free number and the Web site address. The toll free number is 1-888-232-6789 and the Web site address is www.cdc.gov/des.