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Alzheimer's Talks Transcript

Alzheimer's Disease and Women: SeXX Does Matter
with Dr. Jill Goldstein
Friday, May 17, 2013

George Vradenburg: Welcome to Alzheimer's Talks and thank you all for joining us today for what should be a very very interesting discussion.

My name is George Vradenburg and I'm the Co-Founder and Chairman of USAgainstAlzheimer's an enraged and engaged set of families that have been affected by the disease that now has created networks of Alzheimer's serving organizations, industry members as well as sitting on advisory councils to the government on the subject of Alzheimer's. So we welcome you here today. Today's call is presented by WomenAgainstAlzheimer's, a new national network of women that harnesses the power and creative energy of women to create a new approach to finding a cure.

Women are the disproportionate victims of this disease both as patients and caregivers and their voice will be a powerful one in bringing a greater attention to this disease in the halls of Congress and the Administration and with Industry. Together we're all building a movement to hold our nation to the bold and aggressive plan to prevent and treat Alzheimer's disease by 2025.

Today's call is a discussion with Dr. Jill Goldstein on the growing impact of Alzheimer's on women. Did you know that women are two times more likely to die from Alzheimer's disease? Two times more likely to have Alzheimer's disease? We need to better understand this gender disparity and how the research on sex-based differences might lead us to a cure.

Also on the call today is Meryl Comer who near the end of the hour, will provide us a description of the new WomenAgainstAlzheimer's and an exciting challenge that she is running from her foundation, Geoffrey Beene Foundation Alzheimer's Initiative, on sex-based differences between men and women with respect to Alzheimer's.

Today our guest is Dr. Jill Goldstein, Professor of Psychiatry in Medicine at Harvard Medical School and Director of Research of the Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital in Boston. Dr. Goldstein also serves as Director of Research on Gender Neurobiology and Women's Mental Health in the Department of Psychiatry at Brigham and Women's Hospital.

As always if you have a question during the call, please, please press star 3 on your phone. By pressing star 3, you'll be place into a question queue and we will get to you after Dr. Goldstein finishes her remarks. Please have your question ready to share briefly with a member of our staff. We'll try to get to you on the air as soon as possible when we open up for questions. If you

go into the question queue, you're still on the call, you're not going to miss anything and miss any remarks from Dr. Goldstein. So please feel free to press star 3 at anytime to put your question in a question queue so that you can go on the air and ask Dr. Goldstein directly.

Dr. Goldstein, thank you for being with us today. And we express our sympathies for all those affected by the explosions up at the Boston Marathon but, glad to have you with us and glad to talk about this very vital and important topic.

Dr. Jill Goldstein: Well, thank you for that lovely introduction, and for recognizing Boston Strong. I'm thrilled to be here today and to talk to you about a topic (sex differences in disorders of the brain) that is near and dear to my heart; and I am absolutely thrilled it has become a focus for USAgainstAlzheimer's and now the new WomenAgainstAlzheimer's group within that.

As we just heard, there is a substantial sex difference in the risk and frequencies actually of all the dementias, including Alzheimer's disease but also even mild cognitive impairment. Women have about 1.5 to 2 fold higher risk than men and it is not just because women live longer, which was the line about this previously. Alzheimer's afflicts, as many of you likely know, about 5 1/2 million Americans. But I don't know whether you knew that 2/3 of them, that is 3.3 million are your grandmothers, your mothers, your sisters, your daughters, your aunts and nieces afflicted with this illness. So that makes this illness a major medical concern for women, and frankly also for men, not only in terms of understanding the biology of this but for men who depend on these women.

This sex difference in Alzheimer's disease, which is essentially a disorder of memory, is actually a curious fact given that healthy women have better verbal memory performance, better verbal memory, than healthy men, and that is true throughout life. It attenuates after menopause, but it's even present in the healthy brain after menopause. So this is very curious: how is it that women can actually have a little leg up on the verbal memory front but have a higher risk for Alzheimer's disease and memory decline. There's been very little systematic focus on understanding it.

So what I'm going to talk to you about today is how Alzheimer's disease disproportionately affects more women than men, with more severe pathology in women, and I want to leave you with the notion that the development of successful treatment for Alzheimer's disease will necessitate incorporating a sex-dependent knowledge of the brain regions associated with memory function and sex-dependent knowledge of the illness itself. Now the literature on sex differences in Alzheimer's falls into four camps. There are hormonal effects, that is gonadal hormone effects (estrogens, testosterone and progesterone) on the brain, but also on their risk for Alzheimer's. And most of that has been via looking at hormone replacement therapies. So we'll talk about that a little bit. Then there is some research but very little on sex differences in Alzheimer's pathology per se (the so called plaques and tangles), and we'll talk about that a little bit. There are sex differences in genes associated with Alzheimer's; and then lastly, which doesn't get very much attention at all, are the fact that there are sex differences in other medical conditions that are associated with the risk for Alzheimer's disease, such as depression, which has a two fold risk in women, cardiovascular disease and associated syndromes like obesity and diabetes. So we're going to get a little bit into that as well.

Now, what is the impact of hormones on memory function? So there's a long-ish, I will say, history to the study of this and that's been both in human clinical studies as well as in animal studies, with the primary foci being on the impact of hormone treatments in women after menopause on the risk for Alzheimer's, or on the attenuation of cognitive decline, or on the impact of hormones on specific brain regions that are responsible for our memory and memory circuitry in the brain. So these hormones have implications for risk for Alzheimer's, but they again have specific effects on brain regions and memory functions. They can have what are called, neuroprotective effects, that is protecting the brain from injury or demise. Or they can have what is called neuromodulatory effects, that is, these hormones have direct actions on our nerves in the brain. Or, these hormones can regulate blood flow or blood vessel function in the brain, which also has implications for our nerve function. So there is the brain-cardiovascular, brain-nerve interface. That's very important in understanding risk for Alzheimer's, and these gonadal hormones can regulate all of these systems.

With regards to Alzheimer's risk, there has been some inconsistency in the literature, with on the one hand, naturalistic studies have supported the positive role of estradiol. (And I'm going to use this word instead of estrogen, I'm going to say estradiol, because estrogen is actually a plural word. It's estrogens, and there are a few types of estrogens, but estradiol is the one that has the greatest effect in the brain. So that's very important, we're going to tuck that little fact away for a moment, because what goes into these hormone treatments actually matters for what gets in the brain, and what the actions are in the brain to help enhance cognitive, specifically memory function. There's been a positive role of estradiol in enhancing cognitive performance, like memory, and lowering the risk for Alzheimer's per se. In contrast, some of these same hormone replacement studies, like the Women's Health Initiative clinical trial, resulted in deleterious outcomes to the brain and Alzheimer's onset. The reasons for these inconsistencies, were, in part, methods of study, and they included the following: the timing of the hormone treatment administration, that is how long after menopause was hormone treatment introduced or was it introduced within the perimenopausal transition. It had to do with, as I just mentioned before, different hormone treatment formulations. What was the type of estrogens put into the hormone, and how did it vary with the amount and the type of progesterone? And finally, the duration of the treatment. So the results of the Women's Health Initiative trial, for example in the last 10 years of work investigating what went wrong, found that when given early, that is during or just after the menopausal transition, outcomes were generally good; they enhance cognitive functions, they enhance brain function, you had better cardiovascular result. But when given later, say after age 60, outcomes were more deleterious in terms particularly looking at cardiovascular and stroke, but it was also true for the brain and for Alzheimer's risk.

Now, this early period of aging that is around the perimenopausal to menopausal transition turns out to be a very important new target for Alzheimer's therapeutics. So understanding the hormonal regulation of the aging of brain regions during this period, implicated in memory function will be critical, I believe, to the development of sex dependent therapeutics for Alzheimer's. In fact, there is evidence from animal studies that supports this and supports the importance of understanding what I will now call the hormonal regulation of the brain, and how it differs for men and women. This is not just a women's disease, as we all know, this also affects men. So some of the same processes, we believe, affect men; it just does it differently in the male

brain than it does in the female brain. It's very important to understand that. This is about men and women, even when you study women alone and looking at gonadal hormone regulation of the circuitry, men and women share many of these hormones, they just have different amounts (and types) of them. So our brains act differently to even get to the same outcome point and we need to understand that to develop the sex-dependent therapeutic.

This has not only been shown in animal studies, but it's been shown in human clinical studies. Validating what's been seen in animals with a human clinical study (as reflected in brain imaging studies where you take someone, put them into an MRI scanner, and look at brain activity, we've shown (and others have shown) how hormones regulate memory circuitry, how they do it differently at different points in the menstrual cycle, how they do it differently as the brain ages. So one substantial arena of work is hormonal regulation of the memory circuitry as the brain ages, and enhancing and rethinking the development of what goes into these hormone treatments, which, although are administered orally in the periphery, have important implications for the brain.

Secondly, what are the sex differences in Alzheimer's pathology and Alzheimer's related genes? There's much less work that has focused on other potential pathways for understanding sex differences in Alzheimer's, such as with the pathology per se (the plaques and tangles), or genes. With respect to Alzheimer's disease pathology, studies have demonstrated that women are at high risk for Alzheimer's pathology and greater severity of pathology after onset. Now as many as you may know, there are abnormal clumps of proteins called amyloid plaques, the beta amyloid protein, Abeta, and tangled bundles of nerve fibers called neurofibrillary tangles, associated with a protein called tau. This classic definition of Alzheimer's (the plaques and tangles) accumulate in key regions responsible for memory function. So they're not necessarily so dense all over the brain, they really love those memory areas. And in addition within these brain regions, there is a loss of connections between nerve cells in these regions.

We need to understand how these memory brain regions develop in sex-specific ways, age in sex-specific ways, and we believe it will be critical to capitalize on our knowledge of this to help us develop new sex-dependent treatments for Alzheimer's. Women have been found, as I said, to exhibit greater Alzheimer's pathology, that's greater particularly with the plaques but also with tangles in these brain regions; and it's been shown this is associated with worse cognitive deficits in women than in men who have Alzheimer's. In animal studies, estradiol has been found to reduce the formation of these pathologies, and testosterone has also been found to have an effect on this as well. Some studies actually reported increased tau or increase of the tangle-like aspect of the pathology in men rather than women; others have founded it in women. But, these studies are so few and far between, there is really very little work in this arena, and more in animals than humans on this. But we need to understand how a gonadal hormone regulates this pathology different in the male and female brain. When I say gonadal hormones it's the estrogens, progesterone, testosterone. Lower testosterone has even been found in the male brain with Alzheimer's. So gonadal hormone regulation of this circuitry is very important for both sexes.

With respect to genes, most of the work on sex differences in genes related to Alzheimer's has to do with the ApoE, or Apolipoprotein E, gene that many of you have heard about. There are three

flavors of this gene, there's an e2 form, e3 form, e4 called allelic variants. Sex differences in genetic risk differed depending on the form of the genes. There have been significant differences if you looked at the e4 flavor, which by the way is the variant of the gene that's most highly related to Alzheimer's risk. But there have been no sex differences reported for the e2 and e3 forms. So there's a sex difference in gene expression. Now one of the explanations of this was also the fact that gonadal hormones, like estradiol, actually can turn these genes on and off. These gonadal hormones, the estradiol for example, work through receptors in the brain; and these receptors actually sit right next to these genes and can turn them on and off. And estradiol, for example, actually comes in two flavors, its receptors, alpha and beta; and these two receptors in the brain do different things, which again complicates the picture even further. So the expression of this ApoE Gene abnormality can depend on the type of estrogen receptor to which let's say the hormone treatment is directed. I know you may not be able to remember all these facts but the picture I just want to paint for you is that the work is complicated and understanding the importance of mapping out the complexity of these issues related to sex differences in the brain, given that even estradiol does not have one effect in the brain. So the effect of hormonal treatment and its impact on the brain will depend perhaps on the components of the estrogens in the drug whether it's a little more alpha or beta-associated and they can have different effects on nerves and nerve function.

Work on sex differences and genetic abnormalities is ongoing, really only in a few labs. There's work here at the Brigham, but this is an arena that really deserves more systematic focus.

Finally, there are sex differences on Alzheimer's risk that may be due to associations with other medical conditions, as I said. Medical conditions that have independent associations with the risks for Alzheimer's include: depression, cardiovascular disease, obesity, diabetes; all of these medical disorders also show sex differences in their onset and course. So we believe that some of the causes, the pathophysiologies of sex differences in these illnesses, may be shared with sex differences in Alzheimer's disease. Our team has taken a developmental approach to thinking about sex differences in brain aging, that is we are mapping out sex-dependent and sex-specific developmental pathways that result in sex differences in memory decline in one's 50s. We believe this developmental approach lays the vulnerability for why we see sex differences in early cognitive decline in Alzheimer's in women. And we believe that by understanding sex differences in the *development and course* over the life-span looking at sex-specific changes in memory circuitry regions will be shared with understanding sex differences and risk for Alzheimer's in *the aging* of the memory circuitry. We're looking at hormone regulation of this circuitry but it's not only gonadal hormones, it's thyroid produced by the pituitary or hormones produced by the adrenal gland like the stress hormones. These things interact with our gonadal hormones to produce changes in the brain in memory circuitry. We're also looking at sex differences in the direct effects of genes and also metabolic pathways, like insulin and glucose, which are very important for memory function. And finally we look at the so called inflammatory pathways - those are referring to our immune response in the brain. All of these pathways are important for teasing apart the causes of sex differences on Alzheimer's risk. They're sex-dependent and some of them are even sex-specific (that means in one sex and not the other); most are sex-dependent (when the effect may be different in one sex from the other, even though the cause may be similar).

In conclusion it is critical to systematically map the neurobiology for understanding sex differences in Alzheimer's disease in order to develop sex-dependent therapeutics and prevention strategies for Alzheimer's and mild cognitive impairment. We believe taking a developmental, a life span perspective, to studying aging of the brain is actually a very optimistic approach for Alzheimer's, since we believe it will help us develop strategies for early intervention. Even a delay in onset of Alzheimer's disease by 5 years can have a substantial impact on the frequency or the prevalence of Alzheimer's disease and health care outcome, estimated by one group as up to 50% reduction in one generation. We believe that the development of innovative sex-dependent therapeutics, in particular the hormonal regulation of brain circuits, is critical to realizing the dream of personalized medicine. The hormonal regulation of genes actually has revolutionized the treatment of breast cancer in women. We can do this in the brain. We have ideas about how to do this because for personalized medicine, what can be more personal than one's sex? Thank you.

Vradenburg: Thank you very very much Dr. Goldstein. We joked with Dr. Goldstein before you all got on that if you ask at a cocktail party or said to someone are the brains of men and women different, everyone of course would say yes men are from Mars women from Venus and now the scientific community is finally coming around to the proposition so that I think is terrific.

I'm going to ask a question and then we've got a few coming online, but to all of you if you do have a question of Dr. Goldstein, please press star 3 on your phone and you will be put into a question queue and then we will get to your question in just a few moments.

Dr. Goldstein, you know we've seen the failures in phase 3, the final stages of potential new medicine and treatments for Alzheimer's, at an alarming rate. There simply has been nothing that has really gone through the entire scientific pipeline and proven to be effect against this disease now for many, many years when we first developed symptomatic treatments but nothing that actually modifies the course of the disease and we frequently hear that there are a thousand or 2000 people participating in these trials. There's usually and typically no description of how many of those are men and how many are women and I guess my question is, are these trials designed in a manner that has sufficient size and scope and testing processes to discern a different effect of a potential drug on men and on women?

Goldstein: It's a fantastic question and I promise I didn't prompt him on this question. It's a perfect question and I'll tell you why. This is not only true for Alzheimer's. It's really true for research and treatment in neuroscience in general: sex differences in the brain has not had the attention from the pharmaceutical industry nor even from neuroscience. There's really a small group of people (we work with a number of them in the neuroscience or the basic neuroscience world who have been looking at these issues for many years) and even though the data are out there about sex differences in the brain, it has not been a focus of clinical neuroscience and certainly not of industry. In fact, the biology of this and the mechanisms of this are many times only worked out on male mice or male rats or male animals in general. Even when the disease has a preponderance of women. There's a politics to this but also the science of this. I'm a 60's child and we weren't allowed for many years to really talk about sex differences in the brain for the fear of the political distortion of the science. I think we're at a time now where we can not only talk about this but it's absolutely essential to become part and parcel of how we think about

the development of therapeutics and also the design of our study. The study of sex differences is not just about seeing if your data differs by sex. This is the majority of work in this arena. But sex and gender are complicated variables, and studies are not being designed this way. I would not be so arrogant to say if we had designed our studies to look at sex differences, we'd have better therapeutics and that's the answer, but I do believe it actually would contribute an enormous amount to enhancing the efficacy of many drugs that are out there now.

Vradenburg: Well I appreciate that because the implications are that as you look at a thousand people and try a treatment and you see that it has modest or minimal or no impacts statistically, it could be having a positive impact on men or on women but it's masked because you are not seeing the same effects in the other gender. As a consequence we may be fooling ourselves into thinking that these drugs don't work but in fact they may work for sub-populations.

Goldstein: Exactly, and they may work better perhaps with particular hormonal enhancements of them. Those are things we are beginning to actually look at. The hormonal enhancements of some of these drugs may perhaps act differently in men and women to attenuate disability and really enhance efficacy of these treatments. We believe that this is a very important new direction that we are really hoping we can partner with pharmaceuticals on this.

Vradenburg: Great. So, we have a number of questions in queue and I'll start going through them. There's a question here from Cheri Jennings in Richmond, Virginia. Cheri, we will put you on live and you now can ask your questions of Dr. Goldstein.

Question: Good afternoon. Thanks for taking my question. Early on you were talking about the four camps and you spoke about hormone regulation and brain functions and so my question is, is anyone taking a look at the differences in using bioidentical hormone replacement therapy versus traditional hormone replacement therapy?

Goldstein: You mean, like the phytoestrogens and things like that.

Question: the phyto ones.

Goldstein: Phyto ones. There's a little bit of work in that arena. There is not a lot of work. There are a couple of studies that have looked at this but not with positive outcomes. As I said, it's very complicated; how do you design these studies? Who do you look at? Just like with the hormone trials where they started with women 65 and older and had deleterious outcomes, the design of the phytoestrogens need to also take this into account. I don't want to say there wouldn't be an effect, it's just they have not been studied in this systematic way.

Vradenburg: Thank you, Cheri for your question. Next question is from Marilyn Flint in Bellingham, Washington. Marilyn.

Question: Hello. I would like to know if there's any research being done on the effect of genetically modified foods on the brain because the gene they put into the corn or soy is designed to split open the bodies of the insects it must have an impact on the brain. Thank you.

Goldstein: Well, I have to admit I don't know the answer to that. It's not my arena. You're asking me whether you think it has an effect on Alzheimer's or whether it has an effect on other aspects of the brain. I really could not answer that.

Vradenburg: Okay. Next question from Jim Mortimer. Jim, please ask your question of Dr. Goldstein.

Question: Okay. This is Jim Mortimer in Tampa. I have a question for Dr. Goldstein. At the beginning you mentioned that the incidence of MCI was higher in women than it is in men. However the two largest studies, the Rochester study shows just the opposite that men have a higher risk of MCI than women. This is particularly true up to about age 85. After age 85, it becomes a bit more iffy and I just wondering if you have any comment on this?

Goldstein: Yes. So I think when something has not been systematically addressed there's going to be literature out there, just like the tau pathology I said, some studies show higher in men, some studies show higher in women, because a number of these studies have not been designed to ask the question about sex differences. So depending on the type of sample, the age of the sample, the stage and so on and so forth, you're going to have different results for these different outcome.

Question: These are the 3 largest best instant studies of Alzheimer's disease that we have in MCI and they really are very large and they're very strong the findings are quite strong especially for male predominance of MCI in the Rochester cohort. It was just published I believe in 2012 by the Mayo clinic group.

Goldstein: Yes I don't know what the age of the sample was, for example. Just because the study is large, does not mean that it has been designed in such a way to look at the sex effect. So, the sex effect may differ depending on the characteristics of who was recruited into that sample and how they were recruited. So, I would actually need to go back and actually look at the method, look at the sampling, look at who is in the trial and the age, particularly, the age effects, their medical histories, things like that.

Vradenburg: I'd like to ask Jim, do you know whether there is a different MCI risk in men and women at different ages?

Question: We don't know that for sure because then the numbers become smaller but if you look at the age specific instance of amnestic MCI, the type that usually moves on to Alzheimer's disease, the big differences are seen at earlier ages so that in ages say 70 to 80 men seem to predominate. Now, there may be something going on in very late life, which is different from that.

Goldstein: So, again the age of the group that's been studied is absolutely critical. So, prior to menopause for example, men have a much higher rate of cardiovascular disease, we use to think that it was just a male disease but in fact it is the number one killer of women in the U.S. and after menopause the rates for women actually become similar. So, if you look across the whole span you might see that men have higher rates of cardiovascular and all the treatments that were

being developed were really focused on it as a male disease, even the symptoms. We now know that the vasculature is different in the male and female brain. The same can be said for Alzheimer's depending on, for example, if these were 70 year olds. I don't have the study in front of me right now. Happy to go through it and respond to you if you would like to e-mail me and I can think about it with you.

Question: Okay. Thank you.

Vradenburg: I think the bottom line in that particular comment is there still is a sex based difference or a gender based difference and depending on the stages of disease or the rate of progression. It can vary depending on who's got the higher incidence but there still are differences and we still don't understand the reasons for those differences yet.

Goldstein: Yes. It's a very important issue which again I underscore because if a trial is large or a trial has equal numbers of men and women does not mean that it has been designed to study sex differences and you can end up with different results depending on who it is you have in your sample. Who are those women? What other characteristics do they have that actually affect the biology of sex differences in the brain? Those are the kinds of things that have not been addressed systematically but need to in order to develop more successful therapeutics.

Vradenburg: Our next question is from Sandra Brenton. Sandra, would ask your question please?

Question: Yes. Thank you doctor and thank you so much for this information. I was wondering what kind of clinical trials are currently being done that have been narrowed down specifically the sex differences and also differences between woman who have had hormone replacement versus woman who have not?

Goldstein: Yes. Let me just say, there are no clinical trials that have been specifically designed to study sex differences. I'll repeat that. There are no clinical trials that have been specifically designed to study these sex differences. Those of us who have studied sex differences in the brain have been doing this for a while but this information has not been translated into the development of sex-dependent therapeutics.

Now, what there is out there are a couple of wonderful hormone replacement in women studies in which they are looking at some of these issues that I talked about today around what happens when you give the treatment early. What happens when you change the type of hormone within the hormone treatment. What kind of estrogen is in there? What kind of progesterone is in there? There are trials, the Kronos trial or KEEPS trial as it's called. You can look on clinicaltrials.gov and one has the acronym ELITE, and they are looking at this early perimenopausal to menopausal transition and the impact of hormone treatment on the risk for Alzheimer's and also cognitive functioning, memory functioning. So, those are the current ones that are ongoing and that hopefully will be giving us answers soon. I believe one is ending this year and one is ending next year.

Question: Have, have they actually shown a difference between women who have had this type of replacement therapy versus woman who have not?

Goldstein: You mean if you started early?

Question: Yes.

Goldstein: Yes. There has been, after the Women's Health Initiative, over the last it's been almost 10 years, they looked at why there were deleterious outcomes and what they found is if they looked at the women that started treatment around the perimenopausal or right after menopause than those women actually did better and had better outcomes than ones that started at 65. So, this raised the issue of what they called the critical window or sensitive periods in the brain that could respond to these estrogen/progesterone treatments. And we know that as the brain ages, these receptors that I told you about these estrogen receptors in the brain, they sometimes lose sensitivity to the signal, the estrogen and progesterone signal. So starting them late was worse. Starting them earlier was better.

Question: Can you give me an age bracket as to how early?

Goldstein: There's a real range to those who are perimenopausal to menopausal. So, it's actually less focused on age per se and more on your perimenopausal to menopausal transition.

Question: All right. Thank you so much.

Vradenburg: Did that study also indicate a difference depending on the duration of the use of hormone replacement therapy?

Goldstein: Yes. There was a range from 5 up to about even 10 years.

Vradenburg: So for these purposes taking them more than 10 years increases your risk?

Goldstein: I don't think they have actually studied that if you start early. But I think the answers will come from the KEEPS study, the principal investigators are coming out of the University of Wisconsin Dr. Sanjay Asthana, for those of you who are interested in participating in that Keeps trial. I think the answers will come from those two trials about how long and so on and so forth. So far clinically they're saying 3 to 5 years. For the longer duration, I think the data are still out on that, so they're not making clinical recommendations on that at this time unless it's by your individual physician.
Vradenburg: Okay. Thank you.

Goldstein: It also depends on other risk factors that you may have.

Vradenburg: We have a question from Monica Mallampalli from the Society for Women's Health Research. Monica, would you ask your question?

Question: Yes. Hi, Dr. Goldstein. That was a wonderful presentation. I'm calling from the Society for Women's Health Research and first I just want to make a quick comment. The society actually hosted an interdisciplinary roundtable in 2011 to address the same issue on sex and gender differences in Alzheimer's disease and our panel, or actually the roundtable participants, had come up with several research recommendations for both basic Science research and also clinical recommendations and some of those actually resonated with what you have talked about today. So I'm very happy about that.

And I also have just a couple of quick questions that came out of our discussions. One was, the role or adrenal steroids on Alzheimer's. I mean, has anybody been looking at the effect of other steroids on estrogen and testosterone receptors in Alzheimer's. And also the second question is, you know the sudden decline in estrogen after menopause with testosterone there's a gradual decline in men and again, is this being addressed in looking at onset of Alzheimer's and progression and, again just to wrap it up real quick, these recommendations that came out of the roundtable actually have been published. They were published in 2012 in Journal of Women's Health Research. Thank you.

Goldstein: Thank you for that response. I'll say a couple of things in trying to remember the set of questions that you ask.

I'll address the adrenal one first, so when we look at sex differences in brain and changes in memory, we look at the interaction between the gonadal and the adrenal. In fact, the adrenal gland actually can produce a weak androgen, and that androgen can actually be converted to estradiol in the brain. So for those of you who don't know, the ovaries of course produce estrogen of course, but also the brain can produce its own source of these gonadal hormones, which is probably not known by many people. But also the adrenal cortex can help produce some of these gonadal hormones, weak androgens which then get converted into estradiol in the brain. So, the adrenal cortex may play a very important role as the ovaries decline. That's actually something we're studying in our current study of the aging of the circuitry around perimenopause to menopause and the sex difference in that.

As far as testosterone is concerned I think this is an absolutely critical realm and an important realm for study. There's been very little work on this. There was a post-mortem study that looked at male brains with Alzheimers and low testosterone, but there really hasn't been a systematic look at the role of testosterone and the changing of that over time and the risk for Alzheimer's in men. Testosterone is also very important in the regulation of a number of the pathways that I listed that have to do with risk for Alzheimer's and changes in memory. So for example, testosterone has anti-inflammatory effects in the brain. And so it is a very important hormone when thinking about immune pathways, immune responses, to stresses that affect nerves in the brain and changes in aging of those nerves. That's just one piece, but there's really important animal work out there that has not been translated to humans.

Vradenburg: I think our last question here is from Bruce Holroyd in Rochester, New York. Mr. Holroyd, please ask your question.

Question: Thank you very much. My question is this, my wife had thyroid cancer approximately 20 years ago and had her thyroid completely removed and has since been on Synthroid and will be for the rest of her life. Her mother died of Alzheimer's disease. Does the cancer of the thyroid and being on Synthroid and her mother dying of Alzheimer's increase my wife's chance of coming down with Alzheimer's more than what would be expected?

Goldstein: There has been a little to no work on the thyroid. I mean, there has been work looking at memory functioning and the role of thyroid but there's no work that has looked at whether thyroid cancer and the treatment of it places you at risk for Alzheimer's. The fact that your wife has a first-degree relative may be more relevant than the thyroid cancer. There are other elements that are involved with the treatment of cancer that may change her risk but the fact that she's on Synthroid should not, if that's what your concerned about that.

Question: Yes.

Goldstein: That's not in and of itself a risk factor if it normalizes her thyroid levels. Many women, not with the cancer but many women are hypothyroid and they're on Synthroid in this country. So, I would talk to your physician or have your wife talk to her physician about that. There are no data out there to give you the answer to that. So that would be a personal medical discussion.

Question: Okay. Thank you.

Vradenburg: Thank you very much Mr. Holroyd and thank you Jill.

We're going to turn some attention here for a few minutes to Meryl Comer. Meryl Comer is on the board of USAgainstAlzheimer's Network and she is the President of the Geoffrey Beene Foundation Alzheimer's Initiative and one of the leaders in this new movement called WomenAgainstAlzheimer's. Meryl is an Emmy award winning and 30-year veteran reporter, producer and talk show host. She's been the at-home caregiver for the last 18 years for her husband who had early-onset Alzheimer's disease and is now in his late stages. She's currently writing a book called Slow Dancing with a Stranger with 100% of the proceeds going directly to support Alzheimer's research.

Meryl's going to share with us a little bit about the new WomenAgainstAlzheimer's network as well as report on an exciting research award for hypotheses about the origins of sex-based differences in Alzheimer's disease called the Geoffrey Beene Global Neuro Discovery Challenge. Meryl…

Meryl Comer: Thank you, George and thank you Jill for both being visionary and your focus on women's health issues long before it was fashionable.

We are very excited WomenAgainstAlzheimer's is hosting its Inaugural Founder Summit. It begins this Sunday. It is a response to the fact that advocacy around Alzheimer's has lacked the energy that has been so familiar both in cancer and HIV/Aids because the natural advocate, the caregiver, is really too worn out to protest. So, it's going to take women to find the voice and

those of us who are caregivers just sort of flip the pain and act up politically and say Alzheimer's is unacceptable for our future and we're going to change things. And that's why I'm so excited about this group and the women have responded from around the country. We have, I think nearly 40 women founders nationwide. These are women who are leaders in their states and local communities in advocacy, business, science, media, and other fields and they are saying times up. We are throwing this as coming out party. For so many years we have protected our loved one's dignity by hiding them away and not talking about this disease, and that has to change if we are going to get Congress to respond, get us more money for research. So, that's the energy of WomenAgainstAlzheimer's. And for those of you on the line we'd love to have you join us. If you're interested just press 1 on your phone and someone will be in touch with you or go to WomenAgainstAlzheimers.org. We have a busy line-up. We are going to be on Capitol Hill this week and we are going to be talking with Barbra Mikulski, Debbie Stabenow, we will even hear from House Minority Leader Nancy Pelosi and we will be on the Hill lobbying for more money for Alzheimer's research funding. Right now, we spend $215 Billion annually on care and less than 1% on research for a problem that is growing exponentially as the baby boomers age. The nice thing about WomenAgainstAlzheimer's is we have an agenda and it's research focused.

The Geoffrey Beene Foundation Alzheimer's Initiative, in support of WomenAgainstAlzheimer's, is launching the first of it's kind because as Jill said no one has really paid attention to the sex based differences in presymptomatic, early symptomatic and the late stages of Alzheimer's and as we say the gender research benefits both women and men. As we have seen in cardiovascular disease, it was just transformational and we want to know if the same is true for Alzheimer's. Now, we'd like to say that this challenge by the way, has been vetted by the NIA, they were our technical advisers. We have support from the Society of Women's Research. We have looked at the Foundation for NIH. We have the Institute of Medicine on Board and I'm proud to say that all these organizations are lead by women as well and I think we're getting the sentiment that it's time we speak up. We like to incentivize people to look and participate. So the challenge will offer $100,000 in research awards for the best proposal and we are really encouraging the next generation scientists, the mathematician and we want others to collaborate to sort of break the impasse on Alzheimer's research in the space. We're also saying that we don't want this to take years. One of the goals is to accelerate the process of research. So, we're saying go look inside the big data on Alzheimer's in ADNI and some of these big public data bases that are open online to the public, it's a huge investment. Let's go mine that data and when you think about it, what is big data. It's really those of us who have stepped forward and offered our data for science and I must tell you this comes at a very critical time because Reisa Sperling who again is with Harvard Medical School and Brigham and a colleague of Jill's, we need to understand the interaction of gender, genetic risk factors and the biological markers, because upcoming beginning November we are going to be entering the A4 Prevention Trials and we need asymptomatic people to be stepping up but all of this plays into the issue.

One of the other exciting things is in less than 3 weeks since our launch at the Society for Women's Health Research event, we have 370 teams already opening up project rooms on the challenge site. So, those of you who know young scientists or mentors who are online who have young scientists please let them know just go to http://www.geoffreybeenechallenge.org and you will be able to sign up and engage. And once again, most importantly for the women on the line, please join with us. It's time that women spoke up. We can't take it any more this is

unacceptable for our future, and we don't want to be a burden to our children. So, thank you again to George and Trish Vradenburg for their leadership and underwriting an opportunity for women to organize this way. So, thank you George and Trish for everything you do.

Vradenburg: Thank you Meryl for sharing with us a little bit about your efforts in this field which have been extraordinary over the years, on this new WomenAgainstAlzheimer's initiative and the Geoffrey Beene Challenge really sort of breaks the mold in terms of focus on the gender based or sex based difference in this question. As a reminder, if you'd like to receive more information about WomenAgainstAlzheimer's or about the Geoffrey Beene Challenge, including how to sign up for either, please press 1 now and someone will be in touch with you.

We're at 2 o'clock. Thank you again for participating in Alzheimer's Talks. In about a week we'll have a copy of the recording and the transcript on our website for you to share with your friends. As always please stay on the line, if you would like to leave us a message with a question or comment. Thank you. Goodbye and have a great weekend.

Goldstein: Thank you very much.

Note: The transcript has been edited for clarity, there is a full recording at:
http://www.usagainstalzheimersnetwork.org/alzheimers-talks