UsAgainstAlzheimer's

Alzheimer's Talks
with Dr. Robert Rissman
July 8, 2016

Note: This transcript has been edited for content and clarity.

Welcome to Alzheimer's Talks, a monthly teleconference series presented by UsAgainstAlzheimer's where we connect you with leaders who are working to stop Alzheimer's.

My name is George Vradenburg. I'm Chairman and Co-Founder of UsAgainstAlzheimer's, a venture philanthropy organization working with industry, with patients, with researchers, and with government to transform the fight against Alzheimer's. Our goal: to find ways to stop this disease by 2020, although the national goal is somewhat more cautious, trying to find a means of prevention and treatment by 2025.

So, some good news out of Washington just in the last week or so. The House Appropriations Committee this week approved a $350 million increase year over year in NIH funding of Alzheimer's; it parallels a commitment made a few weeks ago by the Senate Appropriations Committee for a $400 million year over year increase in funding at NIH. Between those two, we hopefully will get a bill and a full budget passed by the end of the year in which one or the other—we hope the higher—number gets embedded in a budget for Fiscal Year 17, which technically starts on October 1 and runs through September 30 of 2017, although we have a national election coming up and our guess is that in fact Congress will not act on the FY17 budget until after the election.

The Senate draft bill also included language formerly called the Hope Act but now embedded in that draft bill which would increase Medicare benefit payments to doctors for a longer session with Medicare beneficiaries working through the health planning and evaluation processes that we know are attendant to the more complex disease which is Alzheimer's. So good news on that front.

We are so honored today that Dr. Robert Rissman is joining us to speak about his work.

Dr. Rissman is Associate Professor in the Department of Neurosciences at the University of California San Diego School of Medicine and he's the director of the Alzheimer's Disease Cooperative Study Laboratory at UCSD. He heads a research group studying how changes in stress signaling pathways confer increased vulnerability to neurodegeneration including Alzheimer's.

Since all of us are subject to a lot of stress during the course of our lives, this is going to be of interest to everybody on this call, and indeed everybody who's not on this call. He is going to talk with us today about his work related to chronic stress and the impact of stress circuitry on the risk for Alzheimer's. A really interesting topic, as I say, of relevance and importance to all of us, so Dr. Rissman, we thank you for joining us today.

Just a reminder to everyone, if you have a question during the call, please press *3 on your p hone. By pressing *3 you will be placed into the question queue. Please have your question r eady to share briefly with a member of our staff. If you are listening to us online you can type

your question in the box, and we will get it directly. We'll get to as many questions as possible after Dr. Rissman's opening presentation. Please note that Dr. Rissman—none of our speake rs, quite frankly—is not able to answer personal medical questions. And with that thank you for being here this afternoon and please, give us your opening thoughts, and then we'll get to questions.

Dr. Rissman: Thank you, George. Thank you everyone for having me on the line today. So, as you mentioned, George, I'm a professor of neurosciences at UCSD, and I think that we're going to be talking about the stress signaling work today but lucky for me I have several jobs here so one of them is running my basic sciences lab which is focusing on stress; as you mentioned I'm also the biomarker core director for the UCSD Alzheimer's Disease Cooperative Study. And that is a national clinical trials organization that's based at UCSD and we run disease-oriented trials in Alzheimer's disease. Many of them are early-stage, some of them are later stage trials. I am also the neuropathology core director for the Shiley-Marcos Alzheimer's Disease Research Center here at UCSD and that core is involved in banking tissue from Alzheimer's patients who are involved in our longitudinal cohort. So people come in, and they are able to be assessed and be followed over the course of memory impairment.

So with that said, I can get in a little bit to the work we're going to be talking about today related to stress signaling. I originally became interested in this field through looking at the idea that Alzheimer's disease is primarily a sporadic disease. It's the most common form of dementia in the elderly and being sporadic, it has no known cause. It's some combination, likely, of environmental and genetic factors. So what I really wanted to do here is find some way to mimic an environmental factor that could influence the development of the disease.

And part of the reason I wanted to do that is, as many of us know, there are no disease modifying treatments yet for Alzheimer's disease. That is, there's no treatment that can stop it or change the course of the disease at all. We do have a couple of symptomatic therapies, drugs that will make people feel better for a short period of time, but as we get later into the stages of the disease, those things become ineffective. The idea, the goal of my research and the goal of everyone's research is to find a cure for this disease and something that would permanently work.

When we think about Alzheimer's disease from a research perspective, we not only think about cognitive impairment in patients, but we look at things that we can mimic in mouse models and we have the technology now to be able to have animals models with cognitive impairment, animal models that develop the pathological hallmarks of Alzheimer's disease—for example, beta amyloid plaques, neurofibrillary tangles—we're able to have animals that even have some synaptic loss and even neuronal loss. So, I think those are very powerful tools for studying the disease.

When I first got into this, I wanted to avoid any manipulated mouse models; that is, we obtain these mouse models by inserting mutated human genes. So when I first started studying stress signaling, I just went and used regular, what we call, wild type mice, naive mice, ones that are not genetically modified in any way. And we used a brief stress paradigm in them to study how their brains changed during stress and how there could be changes in Alzheimer's related pathways in these mice after stress. When I began in this field, there was already a relatively lengthy literature looking at stress in animal models and it was largely based on a human cohort of data, the Religious Orders Study, that had followed actual human patients over time, and found that those who were more prone to experiencing stress or psychological distress, as they call it, they were more apt to have Alzheimer's disease later. So with the support from that epidemiologic data, the mouse literature showed that relatively strong stressors, physiological things that impact the animal's true wellbeing, were able to induce changes in a protein called tau in these mice. Tau is an important protein from the perspective

that it is the primary component of neurofibrillary tangles, pathology found in the Alzheimer's brain. Tau is a protein that supports the neuronal cytoskeleton; I see it almost as the spokes of a wheel, supporting the integrity of the wheel, in this case supporting the integrity of the neuronal shape. And it plays a role in also how growth factors and things like that can be transported inside a cell.

So being that tau plays a very important role in general, and is directly involved in Alzheimer's disease, many studies have looked at it and its relationship to stress. And indeed these studies were able to demonstrate a large increase in change in tau, a change called phosphorylation, which is thought to be an integral part of how neurons actually develop neurofibrillary tangles. So, with that data I then thought to ask the question as to whether or not stressors that are more relevant to our daily lives, what we call emotional stressors, could also cause change in tau phosphorylation, and how that might relate to other Alzheimer's disease endpoints.

I used a brief stress paradigm, what we call restraint; the animal is just briefly restrained in a tube and then we let them out, and I then looked at their profile of tau phosphorylation in their brains and we saw that there was quite a large increase. This increase was at very consistent sites in Alzheimer's disease brains. We then began to think about how this might be regulated, and one very important part of the stress axis is a peptide called corticotropin releasing factor [CRF], and this is a very, very small neuropeptide. It exists in your brain in two different ways; the first way is of course to activate your body's response to stress and cause the release of steroids into your blood, and then allow you to respond to a stressor. Another role that this peptide has is essentially as a neurotransmitter in your brain, a peptide that allows communication between cells; and it's located very heavily in a region of the brain that's involved in learning and memory and that area is called the hippocampus.

We found that, not only is there a great amount of CRF in the hippocampus but there's also a lot in the cerebral cortex, which is another area greatly affected by Alzheimer's disease. So we started to think, when we initially got into this, is how the CRF system was involved in Alzheimer's disease. And the literature had shown that there were changes in Alzheimer's brains in CRF, there was greatly reduced levels of the peptide, it was in these areas, like the hippocampus and the cortex that were very involved in AD pathology. People had also reported that there were relationships between corticotropin releasing factor and beta amyloid plaques in Alzheimer's disease.

We had a colony of mice that lack one or the other of the two CRF receptors. We started looking at how those receptors could regulate the tau phosphorylation response we saw early on. The essential result from that study is that we found that the type 1 CRF receptor was very important, that directly regulated a stress-induced tau phosphorylation response. Mice that did not have that receptor were not able to respond in the same way.

So we started then thinking about how drugs that impact the CRF system could be used in Alzheimer's disease to perhaps prevent tau phosphorylation and then the development of neurofibrillary tangles. And we began testing a series of already-existing CRF receptor drugs; these drugs would block the ability of that receptor to signal when CRF binds to it. And we were able to find very similar data. We found that animals that received these drugs were not able to exhibit tau phosphorylation responses and they were essentially free of this increase. So, we started thinking about how this could be a potential therapy for Alzheimer's disease. In doing that, you also have to start thinking about other pathways that are involved in Alzheimer's disease as well, not just tau. As some of us know, beta amyloid plaques are thought to be formed very early in Alzheimer's disease. They don't directly correlate with cognitive loss in the disease and that's likely because they are occurring so early and they are causal in impeding the ability of cells to talk to one another and therefore cells begin to

get lost very early on. It's only later we start seeing these tau changes which then correlate directly with the disease severity.

So then we started thinking how we could incorporate this drug into an Alzheimer's model and we then turned to a transgenic model of the disease which has two human mutations. These mutations, of course, are very rare in humans as all of the genetic mutations are, but that's nevertheless what we had available to us. So what we did is, we treated animals, these Alzheimer's disease mice, with a CRF receptor 1 drug and we treated them for quite a long period of time, for five months. And we looked at whether or not these animals would develop not only changes in tau but also changes in beta amyloid and how it would affect their synaptic loss and also the cognitive impairment that is seen in these mouse models.

And we saw really interesting results. They weren't exactly what we were expecting, but that's kind of the way science is. We saw really large changes in plaques, in amyloid plaque accumulation, and we saw a very big change also in cognitive impairment in these mice. By giving this drug, for five months, before they really developed full blown pathology we were able to prevent the cognitive decline and greatly reduce the levels of beta amyloid plaque that are forming in these animals.

We then also looked at how synaptic changes are affected by not only the disease but the drug itself as well. So, synapses are ways that cells communicate with each other and we know that these things are lost very early in the progression of Alzheimer's disease, possibly before you see any change in cognition at all. And using this drug, we were able to prevent the loss of synapses in the mouse model that we typically see. Animals that received the drug had levels equivalent to just normal mice. Animals that did not receive the drug had greatly reduced levels of synapses in their hippocampus. So I think that was a very interesting step.

The odd thing was that we didn't end up seeing any changes in tau. And I think a lot of that might be due to this model, not being a tau model per se, the way these animals display changes in tau is actually quite subtle. So our current work is looking to see whether or not we can impact tau pathology in a tau model as well.

Another thing we're looking at is: at what stage would we have to treat with a CRF receptor drug in order for it to be effective, and how long would we have to treat for? So I think what we've done here so far is essentially what one would call a prevention paradigm. We've shown that we can prevent or delay onset of the disease but the question still remains whether or not that can be continued and whether or not it could reverse the disease. For example, if we take an animal who already has been developing the signs of Alzheimer's, has plaques, has cognitive impairment, could we reverse that phenotype? I think this treatment holds a lot of promise so far; there's more work that needs to be done but I think we're in pretty good shape so far for this being a potentially useful treatment.

I think the biggest problem with all this data is that the drugs I have been using have been tested before and there were some either hints of toxicity when they were treated in people, or the drugs were not effective for the period of time and things that they were tried for. So that said, they were never tested in an elderly population; it was never tested for dementia or any type of cognitive impairment, so what we really need to do at this point is develop new drugs that would be good for the disease that are safe for long-term use in humans, and can be effective in treating the disease. Although that sounds kind of simple it actually takes a significant amount of time to get everything ready and launched and do the screenings, to develop these new drugs. So we're in the process of doing that now.

That's the basic summary of the work that we've done recently on stress signaling and Alzheimer's disease and I'd be happy to take any questions.

George Vradenburg: I'm just going to ask a few clarifying questions because you're talking about a, should we call it, a CRF receptor peptide. Is that what we're talking about?

Dr. Rissman: CRF itself is a peptide, it's a small protein neurotransmitter, but then we have CRF receptors. These are the things that CRF actually binds to, on your cells and then induces an effect in those cells. The drug here would block the receptor.

George Vradenburg: So, this does not sound like stress in the sense of an external, acute psychological event . . .

Dr. Rissman: Right.

George Vradenburg: . . . which is the normal terminology for what we consider to be stress, so is the presence or absence of this receptor the consequence of some external stressor, some external psychological event, a trauma-related incident or a chronic condition that people might be finding themselves in, financial or emotional, or is this just a biological condition?

Dr. Rissman: I think it can be both. I think that you could have chronic stress that can induce changes in your brain that would allow you to be susceptible to Alzheimer's disease later, but I see Alzheimer's disease as a stressful condition for your brain. You have these pathologies that are developing, there are changes in cells, you don't have signaling between your cells in a normal way, so although we can rely upon external stressors as we did in our early studies, some of those may not be needed, being that Alzheimer's disease is such a stressful condition. I mentioned early on epidemiologic changes in people, those people who are more prone to experience stress, are much more prone to have the disease itself. So I think that underscores the relationship between an external stress and Alzheimer's disease. But we've also found that things ongoing in your brain internally that are stressful can also be involved.

George Vradenburg: So, we're talking about two potential causes of this, the operation of the CRF receptor, either external or internal, and the external is chronic stress or acute stress? I mean, not all stress is created equal, right, so how do we distinguish between external stress, which is harmful in this particular context, and not?

Dr. Rissman: A really great question, and that's very difficult to discern. I see an acute stress, which is a single episode, to be something that our bodies would respond normally to; it's something we need to be able to respond to in order to be able to survive. That could be something, for example, like a brief scare, or like you mentioned, financial hardship initially but so long as that would go away, you wouldn't have this overtaxing of the stress circuit in your brain, and things would be able to return to normal. What I see as the problem is exposure to long-term stress, and its effect on the signaling pathways in your brain, that not only initiate stress, but like we talked about, those CRF pathways that are involved in neurotransmission in your actual cortex and hippocampus.

George Vradenburg: Just a reminder to everyone, if you've got questions, press *3; we've got some questions coming in, but just a reminder, press *3 on your phone to be put into a phone queue and we'll get to you in a second. I'm just asking some clarifying questions here.

Dr. Rissman, do we have an easy way to diagnose the presence or absence of a CRF receptor problem or absence of problem?

Dr. Rissman: No, unfortunately not. These things can be looked at postmortem, once we have a person's brain, or whether we're looking at an animal's brain, we can tell, but not in real time, at the moment.

George Vradenburg: It doesn't show up in your blood, in some form or fashion, or imaging device of some form or fashion?

Dr. Rissman: No, it doesn't. It's not something that's very easy to detect at this point. Remember that CRF is something that can exist also in your periphery, right outside your brain. So it's very difficult to discriminate what's going on in your brain from what's going on outside.

George Vradenburg: Do we have a sense, do you have a sense, of the prevalence of CRF receptor impairment in the population? Is there any way to tell? Is there a surrogate for this, like, what percentage of the population has chronic stress versus normal?

Dr. Rissman: I think there have been some interesting epidemiological studies that have looked into that, but again, they are looking at stress related symptoms. It's hard to really say there are changes in the stress axis, the CRF axis, so the answer is, not really. There really have not been studies to directly address that.

George Vradenburg: Question here from Laura online: Have you seen differences in APOE-4 carriers, in their response to stress?

Dr. Rissman: That's a great, great question and for those who don't know, Apolipoprotein E is a very important genetic risk factor for Alzheimer's disease. It confers increased risk but is certainly not a lock for developing the disease, even if you have both alleles of E-4, as we call it.

We have not started looking yet, in Apolipoprotein E mice, and we have not yet done a thorough analysis of banked human tissue to see whether or not those particular cases have more stress in their history. But it's a fantastic question that I think should be looked into.

George Vradenburg: So the natural question arises, and Jane Stelboum has just asked it. If in fact chronic stress is a potential risk factor for Alzheimer's, shouldn't we talk more about the management and reduction of chronic stress in our lives, things like yoga and meditation and those kinds of behavioral changes?

Dr. Rissman: I think that would be very important. It's just not known at this point as to whether any of those things will have an effect. So in science we test things in a trial format, with certain numbers of people, and people being followed over time, so without having those data available, it's really hard to say. I would, though, say that it's probably not going to be that possible to reduce stress in our lives completely, particularly chronic stress. It seems to be part of our makeup as humans to become stressed and to respond to situations with stress. What I would think would be the better thing, is if we could develop a drug that could impact the CRF system and not close it down, but to dampen it down so that we don't have such a large response in our brains and in our bodies every time we are exposed to a stressor.

George Vradenburg: Do you have an opinion yet as to whether there might be a means of recovery from damage once the chronic stress is reduced? Or is it persistent, once the chronic stress has been experienced?

Dr. Rissman: That's a difficult question to answer. So some of our initial studies have shown that we are not significantly able to reduce changes in cognitive impairment, and in pathology in mice, when we give the drug, once they've developed those symptoms, but it's very possible, with further study and more careful analysis that maybe there will be something. But in general, I think, and this is not just my opinion, but it could be the opinion of many, Alzheimer's disease is something that takes many decades to develop and once there are changes in your brain, that are related to your cells, like loss of synapses and development of pathology, it seems to me like those things are very, very hard to reverse. Your brain is developed in a very complex way so then attempting to regenerate, let's say, areas that have been damaged, it's just not something that we know, that's straightforward to consider. So this, like anything else, is likely best fit for a prevention.

George Vradenburg: So that last question was, just to give credit where credit is due, from Jerry Jones from Howard, Ohio.

Another question, from Marvin Berman, from Plymouth Meeting, Pennsylvania: What do you think of the possibility of using brain wave biofeedback and this is a sophisticated question, near infrared phototherapy as treatments for stress disorders?

Dr. Rissman: You know, I haven't done any of that type of work, so I really can't speak with certainty about it. I think anything, at this point, that would affect the way the brain signals may be helpful for Alzheimer's disease. And you know, that doesn't preclude this infrared hypothesis either; I've heard that one before and there's a couple of companies, I think, that were pursuing that at one point. It's an interesting concept but we just don't know.

George Vradenburg: We've a question here from Revell Goodwin from Centreville, Maryland, asking you to describe what you think chronic stress is. What constitutes chronic stress?

Dr. Rissman: Chronic stress is a stimulus that would impact an individual continuously for a long period of time. In rodents, we see chronic stress as a period continuously over two weeks. In humans, it could possibly be something over many many months or even over many years.

George Vradenburg: Question here from Jen Romnes: Could stress cause an even earlier onset of Alzheimer's? Specifically, Jen's mom had the APP gene, died at age 55, and her grandmother and great-grandfather passed away with Alzheimer's disease in their seventies; is there a possibility that chronic stress can cause earlier onset as well as an increased risk?

Dr. Rissman: Yes, there is. There is some data, some published data, that show that animals who are exposed to stress develop the disease earlier than those who don't. Though I think that's mostly restricted to the pre-clinical literature, the animal literature, I think it's quite relevant to people. And I think that the epidemiological data on humans also shows the same thing. We talked a little earlier about the Religious Order Study that found that people who experienced stress developed the disease, not only at a greater rate than people who did not, but also they found that it was slightly earlier as well.

George Vradenburg: You mentioned, in your comments, that the drugs relating to this CRF receptor have been previously tested and have not been effective, at least for the time of administration. But you also mentioned they hadn't been administered for Alzheimer's. I'm curious as to what other therapeutic areas these CRF receptor drugs might have been used for?

Dr. Rissman: Sure. They were used for generalized anxiety disorder. They were tried for irritable bowel syndrome. They have been tried even more recently for alcoholism. But all of these cases were in people who were relatively young. It's never really been in someone who is over the age of 50 or 55. And of course, the Alzheimer's population is typically quite a bit older than that.

George Vradenburg: You mentioned that the administration in your particular study was with mice over a five month period, which you characterized as lengthy. What is five months as a percentage of a mouse's life?

Dr. Rissman: Your average mouse would live approximately two years, so it's not half of their lives but it's over a very very critical time period of their lives. So to me, that's a very great percentage considering how short they live. One other thing to consider is actually when we did it, so it's five months started at a very early time, and going through the time when they would have initially developed the pathology. So, it's important to do it for a long time, but also to do it for a long time at the right time.

George Vradenburg: Do you think maybe administering a little later in the mouse's life, in sort of midlife as opposed to early life, would be more effective over a shorter period?

Dr. Rissman: I'm not sure. I think if we gave it, when the animal already had full-blown disease, I don't know what we would see. From our preliminary results, there may not be any change so I think getting in early is the key here and giving sustained treatment is the key.

George Vradenburg: Jackie Mark asks the question: If it's to be used for prevention, what is your judgment about the age at which people might use this drug, were a drug to come on the market?

Dr. Rissman: That's a great question. I think Alzheimer's disease begins, and many people think this, begins ten to twenty years before we actually see anything. So we may have to start focusing on people in their early fifties or even in their forties with this drug if we want to really be effective in preventing it.

George Vradenburg: You mentioned earlier that in previous tests in other contexts, this drug had shown certain toxicity. So if we administer this drug to people who are otherwise asymptomatic, and going to do it over a long period of time, you really want to make sure it's safe. Do you have a judgment here over whether the toxicity shown in other contexts might be a problem with a drug applied in the Alzheimer's context?

Dr. Rissman: Well, I think the more recently developed drugs like the one we used in our study, they don't really have much of a toxic profile. They were mostly ineffective in meeting their primary endpoints in those trials. But that said, if you're going to go into an elderly population and administer a drug for a long period of time, you need something very clean. This is a vulnerable population that may or may not have altered responses to drugs in general. So I think it just underscores our need to develop new drugs that target this system. My personal opinion is that the ones we have probably would be fine. The toxicity was relatively minor, isolated in certain cases and there's the whole political backing in science related to this that we don't need to go into, but these drugs are likely quite well suited for treatment but they may never go back into people because of the complicated history that they've had.

George Vradenburg: Question here from Laura, let's see if I can interpret it correctly. What are your thoughts about the research that is finding that anti-anxiety insomnia medication may increase Alzheimer's disease risk? How does that work into your research?

Dr. Rissman: I think that those findings are quite complicated to interpret. It seems sort of strange to me that increasing stress would reduce your risk simply because of things that stress does to your brain, as we've found. I guess I don't really have a firm answer to that, but I would again just caution interpretation of things that are read out there. These are more observation than heavily tested studies.

George Vradenburg: I know that you recently released some findings from a study that you did on potential signals that you're discovering, about predicting who may have MCI [mild cognitive impairment] that might convert to Alzheimer's. Could you just briefly describe that study and that research?

Dr. Rissman: Sure. So this is somewhat unrelated to the stress signaling work that we've been talking about so far. In another part of my lab, we search for novel biomarkers of Alzheimer's disease and in this particular case, we use banked blood samples from patients who participated in one of our clinical trials several years ago; these patients all had mild cognitive impairment. We were able to isolate very small, what we call microvesicles. These little microvesicles are substances that are released from your cells. They can be used to transport things between cells but they are also used to get rid of proteins from your cells and excrete them out into your blood and then, very likely, through your urine. So we were able to find, when we harvested these microvesicles, from MCI patients, that those that were derived from neuronal cells, from the neurons in your brain, they had very high levels of several proteins involved in Alzheimer's disease, one of them being tau. And we found that changes in the levels of those proteins in these microvesicles, which incidentally we call exosomes, so in neuronally derived exosomes, could actually predict what patients would transition from mild cognitive impairment to Alzheimer's disease. And we found a couple other markers were also quite related to that transition and that other one is beta amyloid as well. So it just sort of underscores our ability to possibly develop a blood based biomarker for Alzheimer's disease which would be very advantageous being that our current methods involve lumbar puncture and cerebrospinal fluid analysis, and also neuroimaging, which is fantastic but a bit costly.

George Vradenburg: Well, and of course the ability to distinguish those who have MCI and are on a path to Alzheimer's from those who have MCI and are not on a path to Alzheimer's is useful both in terms of trials, of anti-Alzheimer's drugs, but also eventually in determining which populations ought to get an anti-Alzheimer's drug as opposed to those who should not.

Dr. Rissman: Right, and I think you're raising a very important point here. We use Alzheimer's disease as a very general term. But I think we're learning, slowly but surely, that that population is quite heterogeneous, meaning that there are some people in an Alzheimer's population who don't actually have Alzheimer's disease; they have some other form of dementia or they have some other disease just in general. So I think this idea of precision medicine, of identifying patients more carefully, is going to be key going forward.

George Vradenburg: I agree. So, we have a question here on the phone from Michael Ellenbogen. Michael, would you like to ask your question?

Caller: Sure. There are different kinds of stress, good stress and bad stress. I am wondering if you know if the good stress can also contribute to the problem. The reason I ask that is, I had a very high level stressing job; I did not consider it that way, most people would. I'm just wondering if that kind of stress also leads to the kind of problem that you're referring to?

Dr. Rissman: A great question that I don't have an answer to. It's still very early in understanding how different stressors control signaling in our brains. Thus far we really only understand between emotional stressors and physiological stressors and how those

pathways are. But whether or not someone is actually perceiving stress or not, I don't know how that would impact those pathways at all. I mean, it's an excellent question, it's just not one that I have a solid answer to.

George Vradenburg: We have some general questions here that I have online, that I'm going to put forward. They don't relate precisely to your research but they raise interesting questions.

Jeffree Itrich asks: Doesn't everyone have levels of beta amyloid in the brain, and why do plaques—toxic plaques—develop in one person and not another? And she also asks: Does tau factor into whether someone's amyloid actually develops into a toxic form?

Dr. Rissman: Great. So, beta amyloid is a protein that is being made in all of our brains, right now. It's a natural product of the cutting of a larger protein. We don't know exactly what it does but we do know that it's produced and excreted from the brain. In Alzheimer's disease, for reasons that we don't thoroughly understand, that protein, a beta, accumulates as plaques. So why one person would have accumulation of amyloid in their brain and why another wouldn't, is not something that we understand now. We know that these patients, these very rare conditions where they have a genetic change, we know that it's likely due to an overproduction of beta amyloid that leads to the accumulation in the brain. So, we really don't know. It's very unusual that someone would have a large number of plaques in their brain and yet not have cognitive impairment. But I think that that ties in to the second part of Jeffree's question, which is the role of tau in beta amyloid. So, in Alzheimer's patients, the amyloid that you'll see in their brain has also tau inclusions surrounding those plaques. And a patient who might have beta amyloid accumulated in their brain and has no cognitive change, they would not have those tau accumulations surrounding the plaque.

George Vradenburg: Suggesting that there's some role of tau in the toxic qualities of beta amyloid?

Dr. Rissman: Correct. I think this is, the story of these pathologies in Alzheimer's disease have had sort of a little bit of a sordid past. It's coming to light now that because beta amyloid accumulates so early before you see any symptoms, it's potentially causal in creating everything downstream. But there's also the hypothesis that beta amyloid doesn't do a whole lot and it's changes in tau that actually impact the function of your cells that can then lead to disregulation of beta amyloid and accumulation so, the field is a little divided on this still.

George Vradenburg: A general question from Larry Bangerter who asks—he's been diagnosed with dementia recently—Is there a way to test to find out which form of dementia he actually has?

Dr. Rissman: I think going to one of our nation's Alzheimer's Disease Research Centers may help with this. They sometimes have the ability to use their cognitive testing, and other testing, to determine whether or not a memory impairment can be more localized to one area of the brain.

George Vradenburg: Tina asks about her grandmother who had Alzheimer's although it was called hardening of the arteries back then. Is it hereditary?

Dr. Rissman: Tough question to answer. You know, we do see some relationship in families but largely it's what we call sporadic, of unknown cause. So it's not directly linked. Just because you've had a relative who had it, it doesn't mean that you're also very likely to get it.

George Vradenburg: So, I think we're coming to the end of our question period. Dr. Rissman, thank you so very much for describing two quite different aspects of your discovery work and from all of us who have experienced this disease in our families, thank you for your pursuit of this course in your profession and your devotion to this cause, and of course we really applaud your work and cheer you on, and hope that you become a Nobel Prize winner and cure this disease. So thank you for being with us, and thank you for describing your work.

Dr. Rissman: Thank you for having me on.

George Vradenburg: Our next call is set for August 16 at 4 p.m. Eastern with Dr. Jeffrey Iliff from Oregon Health and Science University. He's going to be discussing his research on sleep and Alzheimer's disease. If you're interested in being registered for this call, click here.

If you haven't already joined UsAgainstAlzheimer's, please do so by going to www.UsAgainstAlzheimers.org and sign up. We'll send you a recap of this call, invitations to future calls, and important updates and simple ways that you can get involved. Most recently our digital army, so to speak, of well over 200,000, has been very, very active with Congress in urging them to increase the rates of investment in Alzheimer's disease at NIH. I hope that you'll join us and help by joining that digital army. It's taking all of us, hence the name of our organization. US AgainstAlzheimer's, in order to make a difference; no one person's going to solve this disease. Thank you to everyone on the phone or online for participating in this Alzheimer's Talks.

In a couple of weeks, we'll have a copy of the recording and a transcript on our website for you to share with your friends. Thank you all for joining us today. Thank you Dr. Rissman and to all of you, good afternoon and have a great weekend.