Alzheimer's Talks Edited Transcript
Concussions, Traumatic Brain Injuries, and the NFL
with Dr. Bruce L. Miller

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George Vradenburg: Welcome to Alzheimer's Talks. A monthly teleconference series presented by USAgainstAlzheimer's where we bring you leaders in the Alzheimer's field working to stop this darn disease and to inform the country about the status of novel individuals and efforts around the country. Thank you for joining us today to hear from Dr. Bruce Miller at the University of California in San Francisco, about whom a little more in just a minute.

My name is George Vradenburg and I'm the Chairman and Co-founder of USAgainstAlzheimer's. If you are joining us for the first time and not familiar with the organization, we are an entrepreneurial and disruptive organization believing strongly in the power of collaboration and working together to bring about change, acceleration in the path to a means of prevention and treatment. We are working with government, industry, the scientific community, and finance community in the quest to finance and discover a cure for Alzheimer's and to get a product into the marketplace and reimbursed by funders. We work through a variety of networks of affected individuals across the country: women, Latinos, African-Americans, researchers, clergy and caregivers and we are consistently and constantly looking for new networks of affected individuals. The faith community in particular has expressed strong interest in stepping up and uniting against this disease recently. We also work through coalitions. Leaders Engaged on Alzheimer's Disease (LEAD) is now a 71 organization coalition committed to advocacy and the Global CEO Initiative on Alzheimer's, which we convene, is now a global organization working with governments around the world including the G7 and the G20 the OECD and WHO on a global plan, including companies by the way from Takeda in Japan to Roche in Europe and companies all across the board.

I hope that you'll join us because we need everyone involved, hence the name of our organization USAgainstAlzheimer's, because it is only as a team sport, as a team effort, that we're going to be able to beat this disease. If you have not already joined us, please go to http://www.usagainstalzheimers.org and sign up. We need everyone pulling together to stop this disease.

We have several hundred people today registered for the call from 40 states and the District of Columbia as well as from a number of countries: Austria, Canada and India, others will dial in directly. There are over 500 people who have asked us for a transcript and highlights of today's

call because they can't make it because of scheduling reasons. We'll send information about how to get a transcript to everyone who is registered for the call today.

I'm so happy that Dr. Bruce Miller is joining us today. We are grateful to Janice Wade-Whitehead, the Executive Director of Alzheimer's Tennessee and Founding member of our WomenAgainstAlzheimer's network for introducing us and recommending Dr. Miller for an Alzheimer's Talks. I know that you are anxious to hear his remarks so I'll just give you a very abbreviated version of his lengthy and impressive bio.

Dr. Bruce Miller holds the A.W. and Mary Margaret Clausen Distinguished Professorship in Neurology at the University of California in San Francisco. One of the most preeminent Alzheimer's Disease Research Centers in the country. He's also the director of the UCSF Memory and Aging Center. Dr. Miller is a behavioral neurologist focused on dementia and has done extensive work in frontotemporal dementia. He oversees a healthy aging program, which includes intriguingly an artist in residence effort. In addition he leads two research consortia, the Tau Consortium and the Consortium for Frontotemporal Dementia Research. And he works with the National Football League to help with the education and assessment of players and their brain health. Dr. Miller has received numerous awards, authored over 500 publications and been featured in Fortune magazine, the New York Times, as well as on Charlie Rose, PBS NewsHour and other media programs. We're so fortunate to have him join us today.

As a reminder to everyone and for those who are new to the call, if you have a question during the call please press star 3 on your phone. By pressing star 3, you'll be placed into the question queue. Please have your question ready to share briefly with a member of our staff and then we'll try to get you on the air live with Dr. Miller as soon as possible when we open up for questions. If you are listening to us online, you can type your question in the box on your screen, we'll get to as many questions as possible after Dr. Miller's opening presentation.

Thank you again Dr. Miller for joining us today, we look forward to hearing your comments on your work.

Dr. Bruce Miller: Thank you. I'm very, very honored to be able to talk to this prestigious group today and also great thanks to Janice Whitehead who I worked with in Tennessee and had a chance to think about traumatic brain injury and its relationship to Alzheimer's disease and related disorders.

I think this is an incredibly under-looked and important area. I think for really many, many decades we have ignored the fact that head injury may not only have acute sequelae, problems associated immediately with the head trauma, but may actually be a risk factor for degenerative diseases. I think one of the things that has helped us to understand the head trauma as a risk factor has been studies of players in the National Football League and I think

they have certainly given me new insights into how head trauma might play a critical role in late life, with the degenerative conditions.

What I'd like to do today is just give a little bit of an overview around the whole idea of traumatic brain injury as a growing epidemic and talk a little bit about the frequency of this and some of the postulates about its relationship to degenerative disease of a brain. And then I'll say a word about some studies that have been done that show that this may well increase individual's susceptibility to a variety of different problems. After that I want to give a brief overview of dementia and emphasize really that there's not one single protein or one single clinical syndrome that accounts for most dementia, that really we see a diverse number of disorders as we age that are associated with cognitive impairment. And I think that's very important for understanding what happens to football players who have had traumatic brain injury. Then I'm going to talk about this very interesting new area, I credit the group at Boston University and Steve DeKosky, Bennet Omalu for really making us aware that people at a reasonably young age even can develop progressive cognitive and behavioral changes after head trauma and just talk about that whole new concept that we call Chronic Traumatic Encephalopathy. And then I want to describe for you some NFL players that we've seen and give you a sense of the diversity of problems that some of these wonderful people develop after they leave the limelight of sport. And then finally just a word or two which I think is hopeful around this philanthropy-based consortium that I'm a part of, focused around getting rid of this bad protein, misfolded tau, that is associated with degenerative disease following head trauma but also of course Alzheimer's disease.

So first, this whole idea of traumatic brain injury. I believe it's a growing epidemic. I think one of the reasons it's growing is because we're increasingly aware that following even mild head trauma, people can have profound symptoms, signs and disabilities that they may not get over in a few days. So we think that about 1.6 to 3.8 million individuals in our country develop sports-related concussions every year. I was recently talking with Wade Smith who has been interested in this in our local community and I think that we realized that football is one of the major culprits and I think there's a very high likelihood that a kid who plays football over four years in high school will develop at least one concussion. I think many of us have had a concussion, I have, experience initially headache, dizziness, nausea often for a few days, feel foggy and maybe a little bit confused, people have a lot of emotional changes and sometimes quite significant memory problems. For a mild concussion, luckily most people are better within two to 14 days. There's a lot of neuropsychological testing going on in the studying of concussion. We're really as a society starting to study this systematically. Most people's neuropsychological functions return to normal after five days and individuals never have problems again related to the concussive episode. I think that's the typical concussion. But there are individuals, and I think sports and the armed services are two examples of this, where

people may have chronic repetitive injury. We think that's particularly worrisome and a very strong risk factor for what has been called Chronic Traumatic Encephalopathy.

There's surprisingly little data about concussion and late life brain sequelae. There's some nice work done by Kevin Guskiewicz at the University of North Carolina, who began reporting around 2000 that there was a sense that concussive sport injuries may have cumulative effects, so after one no problems but after multiple events people begin to show more long standing problems. There have been some recent studies of the brains of predominantly football players but also hockey players and people who have had repetitive head trauma, a few veterans who've come back from Iraq and Afghanistan and were exposed to roadside bombs and in these individuals, and I'll say a little bit more about this, there are changes in the brain that suggest the concussion has had a permanent effect that is a progressive degenerative disease. And I think there are some new data that suggest that there is more permanent impairment after multiple concussions, the figure that I like to quote is around 17% of people who have multiple concussions complain of more long standing problems. And I think this whole area is making us rethink this concept of post-traumatic stress disorder. So we know a large number of people coming back from service, particularly those who have been in war-time settings live with profound problems readjusting to society. For the most part we think these are just physiological changes in the brain. The brain is functioning differently. But I think now in the last few years we start to wonder whether some of those individuals, particularly those who have severe problems, may actually have structural changes and begin to deposit bad proteins as an explanation for why they are not reintegrating back into society, totally different type of problem.

David Perry from our group, and we're about to report this data, did what we call a meta-analysis. He looked at all of the big studies that have been done on concussion and looked at the risk factor for different diseases following the concussion. And I will just comment that there are not many good studies, most of the studies are small, there's a problem with definition of the head trauma and longitudinal evaluation, so we need much more data in this. But I think David's data points out that if you've had a traumatic brain injury it increases your risk for Alzheimer's disease by about 1.5 times a person who has not had this, the same with Parkinson's disease. It increases the likelihood that someone will have an ongoing depression two-fold, it increases the likelihood that someone will have a diagnosis of bipolar illness by one-and-a-half-fold. This is clearly a risk factor for multiple different clinical syndromes and I'm going to argue that probably multiple different neuropathologies, so not everyone gets the same thing following the traumatic brain injury. But clearly, this is a risk factor for dementia. There's also, I think, increasingly strong data that suggests traumatic brain injury, particularly repetitive, traumatic brain injury, may be a risk factor for Lou Gehrig's disease, or ALS.

Following traumatic brain injury certain brain areas are most vulnerable. It tends to be the brain areas that sit against bone, that's the anterior temporal lobe, an area that's involved with memory and behavior, the frontal lobes which I think we all know are involved with drive, inhibition of bad behaviors, involved with the regulation of mood. So I think it's no surprise that when someone has a serious traumatic brain injury that memory and behavior are very, very prominent symptoms. This is the part of the brain that is injured. It's also known that other parts of the brain are injured as well, so we have seen shearing of the white matter, the part of the brain underneath the cortex and it's also associated with cognitive, emotional and motor deficits. So I think most often following a traumatic brain injury we see a mixture of these types of symptoms, the symptoms are static, they often don't deteriorate and we see a slow healing process. But there are individuals where after a period of stabilization, there is a renewed deterioration. And that's I think what interests our Alzheimer's community in particular.

We know like head injury, dementia is an incredibly important problem. Mr. Vradenburg has emphasized the importance in our society and he's advocating at the level of Congress to help us deal with this. 5 Million people in the United States suffer from dementia, it's the sixth leading cause of death, one in three seniors die with dementia. We have about half a million people in the U.S. dying with dementia every year and someone develops dementia every 68 seconds. I think it's important for understanding what happens to these football players and other people who have suffered traumatic brain injury is just emphasize that there's not one pathology associated with dementia so the most common cause of dementia is Alzheimer's disease but certainly not the only cause of dementia. Alzheimer's is associated with the aggregation of two bad proteins, amyloid beta 42 and tau - that's the plaque amyloid beta 42 and the tangle tau. Parkinson's disease and dementia with Lewy bodies are associated with the aggregation of a protein called alpha-synuclein that makes up the Lewy body. Frontotemporal dementia, which I study, is associated with the aggregation of different proteins. Some individuals aggregate tau, other individuals aggregate a protein called TDP-43 and a third group of people aggregate a protein called FUS.

Here at UCSF, we have followed the thinking of Stanley Prusiner, which is that one of these proteins in the brain misfolds, in the case of Alzheimer's disease it's A beta 42. It begins to aggregate within an individual neuron, eventually that neuron dies and it spreads the amyloid beta 42 to the neurons adjacent to it. And so we have this spreading of these bad proteins across the brain, across different circuits in the brain, and it is this anatomy that allows clinicians like myself to make a diagnosis during life of Alzheimer's disease, Parkinson's, dementia or frontotemporal dementia. I think one of the principles that we're learning from National Alzheimer's Centers, and UCSF is one of these such centers, is that the older we get, the more likely we are to have multiple bad proteins in the brain. So I think after the age of 80, pure Alzhiemer's disease is less common than Alzheimer's disease associated with Parkinson's

proteins and frontotemporal dementia proteins, TDP-43 in particular. So it seems that the misfolding of one bad protein may trigger the misfolding of others. So we have a very complex understanding of how these diseases progress overtime. Stan Prusiner got the Nobel Prize in 1997 for showing that one misfolded protein in a rare disease called Creutzfeldt-Jakob Disease could spread from one cell to the next and lead to neurodegeneration. I think recently we've learned that the tau protein and the amyloid beta protein also spread across the brain in a very similar fashion. So we can imagine a single insult like a vascular insult to the brain or a traumatic insult that suddenly releases proteins that shouldn't be released, they misfold in this new environment and that is the first step in a progressive degenerative condition.

So what about Chronic Traumatic Encephalopathy? What do we know about this condition? And actually we've known about it for almost a hundred years but I think we've only begun to think about it in relationship to Alzheimer's disease and frontotemporal dementia in the last five to ten years. It was first described by a gentleman named Martland, and he used the phrase 'punch-drunk' symptom complex and he pointed out that this could happen in boxers from repeated blows to the head. And he suggested that repeated traumatic brain injury could actually lead to this punch-drunk, we would call this a dementia state. 1937, Millspaugh coined the term 'dementia pugilistica'. He said there are number of boxers who get repeated head trauma and these individuals develop a progressive dementia, he called it dementia pugilistica. By the time I trained in the 1970s we were well aware that boxers, but I think most of the awareness was around boxers, could develop a progressive dementia after they left the ring. Corsellis described what he called psychopathic deterioration, so really a behavioral change, deterioration in boxers. And so as an individual who studies frontotemporal dementia, I began to realize that what Corsellis called psychopathic really was the behavioral change that I saw in association with frontotemporal dementia. This was really the last major study until around 2000. Corsellis, described dementia pugilistica in three stages. The first stage people had changes in mood, some individuals developed psychosis, false beliefs, it was associated with profound social instability and erratic behavior. So who were those patients going to see in the first stages? Clearly psychiatrists, marriage counselors, sometimes the legal system. So this is in the initial stage, predominantly behavior and mood. Second stage, we started to see features that remind us of Alzheimer's disease: memory loss, and in some individuals mild parkinsonian symptoms. So when you think about it, in the first stage, we have clinical features of frontotemporal dementia and in the second stage we have features of Alzheimer's disease and Parkinson's. The third stage which is the dementia stage, we have Parkinson's shuffling gait, trouble with speech, eye movement changes, and eventually this leads to death and I think there are a number of reports in boxers over the past 25 years that described this progressive dementia pugilistica.

Ann McKee, Bennet Omalu, Steve DeKosky, Bob Stern around the same time began to focus on football players. Although this certainly applies to boxers, mixed martial arts individuals, some hockey players after their careers. Clinical symptoms began after a latency, sometimes only years but sometimes several decades. Initially, and this really mirrors what the previous authors described, they showed irritability, impulsivity, aggression, disinhibition, depression, memory loss and suicide. And sadly, it was the suicide of football players that allowed these pathologic investigators to realize that even though in some of these individuals we saw mostly psychiatric symptoms, the cause for the psychiatric symptoms was actually a degenerative disease process. These patients, those who did not commit suicide, moved on later to slowing of cognitive deficits, dementia, sometimes Parkinsonian symptoms, sometimes Alzheimer's symptoms, sometimes ALS. And what they described was predominantly a unique pathology. I think this is the pathology that we call Chronic Traumatic Encephalopathy. So just to back up a minute, I think when you hear that someone has symptoms of three diseases, Parkinson's, frontotemporal dementia, Alzheimer's disease and maybe even ALS, you have to wonder is it possible that they have all four of those pathologies in the brain and I think in some instances actually they do. We're just beginning to grapple with how head injury could trigger these diseases but there's a lot of very interesting work that suggests that following an acute traumatic brain injury, particularly severe ones, we don't have much data on mild traumatic brain injuries there's actually a release of the bad Alzheimer's protein, A beta 42. So there's some amyloid imaging studies that have been done in Cambridge by the neurosurgery group, by Hong, which suggest that at least in some individuals when you study them after a traumatic brain injury, their brain looks like they have Alzheimer's disease. It is loaded with the A beta 42. Now we think most people over time clear that bad protein, but perhaps some people who are at risk for Alzheimer's disease for other reasons, the clearance may not be so easy and that may be the first stage in the development of an Alzheimer type process. The feature that is unique to the Chronic Traumatic Encephalopathy, of these football players predominantly, is bad folding of tau. And this tau isn't like Alzheimer's disease exactly, it's where the tau is fairly focal and localized. In the players you see this tau spreading across the whole cortical surface. There is the most severe and dense deposition of tau that I have ever seen in the human brain. So in these individuals it looks like a traumatic brain injury, for some reason, triggers the release of tau and then it spreads across the brain. It begins, usually, in the frontal and temporal lobe so we often see frontotemporal dementia type symptoms. We've been looking at the National Football League players and one of the remarkable new developments in Alzheimer's disease and frontotemporal dementia imaging has been the ability to image amyloid with different compounds and also to image tau. And so we are just beginning to study the clinical symptoms in these NFL players but with this we have this powerful ability while these individuals are living to see whether the Alzheimer protein amyloid or the tau protein, which can be associated with Alzheimer's or other degenerative diseases, is present in these football players.

What have we seen so far? Well we've seen about 30 retired professional American football players. We've seen five just in the last few months so I think we're seeing more and more. The vast majority of these players have come to us because they're symptomatic so they are really bothered by the symptoms that they're having, a few of them are not, and we've begun to get amyloid PET and also tau PET on some of these players. So what are we seeing? We're not seeing one thing, that's for sure. I think that these individuals show very, very different syndromes. In one, we see the concussion syndrome that doesn't go away. These players tended to be younger, they are just getting out the league, they have a chronic post-concussive syndrome, sleep disturbance, bad headache, foggy feeling and just don't feel like themselves. I think the NFL has started to monitor this much more closely and I think more and more individuals like this are kept out of playing because we realized that going back onto the field with these symptoms could be extremely dangerous. The second, and this is the syndrome that I'm very worried represents Chronic Traumatic Encephalopathy, is a delayed onset so again, sometimes years, sometimes decades, of a behavioral disorder. And then the third syndrome we tend to see is delayed onset cognitive and motor syndrome often and I think this is the degenerative disease. The question is what degenerative disease? Is it pure Chronic Traumatic Encephalopathy? Pure tau? Or is it Alzheimer's disease or is it Parkinson's disease? And honestly I think we see, and we're getting some pathology now, all three of these different findings.

So I'll just give you a story or two and then I'll tell you the results on a couple of these players and then I'm going to end by talking about our focus on treatment of tau. So here's a 33-year-old player, lovely gentlemen and extremely bright, who played in the League for about 8 years but about 6 years into his career he started to be forgetful, severe migraine headaches, irritability, depression, insomnia, variable attention, having trouble with his memory, on testing he did reasonably well but we saw a little bit of trouble with his ability to recall. Brain MRI was normal, he was given very aggressive treatment of the headaches and the migraines and got much better. Two years or so after his migraines were controlled, he developed a new onset of cognitive symptoms and brief confusion episodes in the morning when he would awake. We're worried, we're starting to do more investigations and I think one of the concerns is that this may be progressing into a degenerative disorder. Here's another player who had the delayed onset behavioral syndrome. 65 years of age, 8 years of rage attacks usually triggered by alcohol. This happened 27 years after he retired from football. Depression, insomnia, Parkinsonian features, modest cognitive deficits, we diagnosed him with mild dementia. We think it's a mixed dementia with frontotemporal, possibly CTE features, and probably Parkinson's disease as well. Third player delayed onset cognitive syndrome, 73, memory loss, word-finding trouble, can't navigate, pretty classic Alzheimer's syndrome, impaired memory on our testing, over two years he progressed to dementia and this gentlemen shows no amyloid in the brain. We're very worried that this turns out to be a Chronic Traumatic Encephalopathy. And then finally, a 51-

year-old man with special and calculation troubles 25 years after retirement, he improved with the treatment of possible Alzheimer's disease. He has been stable for one year and in this gentleman we see classic Alzheimer's changes with amyloid imaging. So this is not one entity, there are a variety of syndromes but I think molecular imaging is going to help us to define what disease or diseases these individuals suffer from.

Ongoing questions: what is the relationship of trauma to Alzheimer's, frontotemporal dementia, Parkinson's, and Lou Gehrig's disease? Can we prevent this by changing rules in traumatic sports? What are other factors - genetics, obesity, steroid use, drugs, alcohol, chronic pain medications? And then finally, can we develop anti-tau therapies? So we have started something called the Tau Consortium. It brings the world's best basic scientists and clinical scientists together to find tau drugs with a sense of urgency, Stan Prusiner here at UCSF is looking for tau lowering drugs, Ana Maria Cuervo in New York is looking for drugs that will help the cell to get rid of bad proteins, this is called autophagy. I think the effort is extremely exciting. We are ready in this stage, where we're giving antibodies to individuals who have too much tau in the brain with the hope that this will improve symptoms and stabilize the disease. So this is our major effort related to this. Last comments, 2015 we have already major inroads into therapy, tau antibodies for patients with tauopathies and Alzheimer's disease. We have autophagy drugs that are moving close to the clinic that will help us clear tau from the brain. We have wonderful longitudinal studies, looking at biomarkers to help decrease the number of people that we would need in a clinical trial, and I think the ability to image tau and amyloid in the brain is going to transform our understanding of these diseases and hopefully lead to powerful therapy.

So thank you very much and again, I'm honored to speak today.

George Vradenburg: Well thank you very much Dr. Miller. Your research is intriguing and clearly you are at almost the beginning of what sounds like a very complex and long adventure and for those of us who are struck with the sense of urgency about this, I'm confident that we would like to develop a little more resource for you so that you could pursue multiple avenues of inquiry in parallel.

This is for the callers, just a reminder that if in fact you have a question for Dr. Miller, we would love to have you strike star 3 on your phone, get into a question queue and we'll get a question to Dr. Miller right away.

I have one upfront and then we have some questions that are coming in. You've talked about boxers and football players but I'd be curious as to what the multiple sources of either traumatic or mild traumatic brain injury might be. I'm thinking here car accidents, bike accidents, motorcycle accidents, other kinds of activities of daily living that might indeed cause

some sort of trauma. Do you have a sense of what the sourcing of the various kinds of trauma in our society might be similar to what you're seeing in boxing or football or perhaps different but nevertheless the source of risk-producing trauma.

Dr. Bruce Miller: Right. A great question and I think there are two different types of traumatic brain injury. One is I think exemplified by football where you get multiple mild to sometimes moderate traumatic brain injury, shaking of the brain, concussion, and I think the repetition of it looks like it may be a very significant risk factor. So perhaps one concussion is a lot different than 30 or 40. Same may be true with the roadside bombs. There may be just huge, huge shaking of the brain. An individual may not even lose consciousness but I think we're starting to realize or at least believe that that may be a unique category of traumatic brain injury. But then the other thing that I think this has made us realize is that any traumatic brain injury in theory is bad, particularly in certain individuals. And I think for most of us, a mild traumatic brain injury, a concussion, has no real sequelae. We recover, brain clears any bad proteins if they were released and there is no effect on our life and we live to a hundred. Other people that's very different and I think we all carry different genetics and different brains. I think trying to understand who is at most severe risk with traumatic brain injuries is something that our group and many others is going to work on. But I would say in general, I would take that all the away across from heading in soccer to mild concussion after a fall, we should do everything we can to eliminate anything that might shake up the brain and perhaps in a susceptible individual release bad proteins.

George Vradenburg: We have a question that came in online from Cornelius Diamond who asked the general question about plasma-based biomarkers in Alzheimer's disease but it raises the question of whether there's a potential blood marker to distinguish the kinds of pathologies that you've described after a traumatic brain injury or the prospect of progression or lack of progression in any of these pathologies?

Dr. Bruce Miller: Yeah, it's a great question. I think there's a lot of exciting work in this area. Henrik Zetterberg and Niklas Mattsson from Sweden have shown pretty definitely that if you have a very significant head trauma, perhaps associated with coma, that you release a lot of tau into the spinal fluid and into the blood and they can actually measure this and show that it stays around for a long period of time and then slowly diminishes. I think the data on amyloid is a little less clear. And I think we're beginning to wonder whether this may be helpful in determining relative risk of somebody after a traumatic brain injury. How much tau there is in the blood or spinal fluid, the same with the amyloid imaging, but I think despite major efforts across the world, I don't think we have a blood test yet that is sensitive or specific enough to guide us. I think we're all hopeful that that may change but I think there's still a reasonable level of uncertainty around blood levels that makes it hard to be too sure what that means.

George Vradenburg: We have a question here from Laura. Laura, would you like to ask your question of Dr. Miller?

Question: Sure. Hi. Thank you Dr. Miller. We very much appreciate your excellent research. One general question is what would you recommend for somebody who just incurred a concussion or a head injury to do to try and avoid any long-term effects if possible?

Dr. Bruce Miller: Yeah. I think the one of the good things about the NFL is I think they're really pioneering better ways of approaching a concussion. I think bed rest, not having any sort of stress in the first week following a concussion, no work, I think what we believe in the long run is that this sort of approach is going to help people. Is the data really, really strong? Not clear but I think we believe it makes sense that if you have a head trauma and you go out and continue working hard and live through horrible headaches and keep pushing, this is probably not good for the brain. I think it's really a warning. It's time to rest. It's time to take some time away from sports, from exercise, from working hard and as the symptoms improve, I think that's when you can begin to move back into your ordinary day-to-day life.

George Vradenburg: We have a question that came in before the call from Barbara Auten of Baton Rouge, Louisiana that asks about childhood concussions, which raised the issue of whether or not the age at which you get a concussion may be a risk factor or not a risk factor for some more sustained progressive condition?

Dr. Bruce Miller: Also a great question. I think we've learned that the general consensus is that the young brain is more malleable and does better with a significant injury than an older brain. But that I think doesn't really answer Barbara's question and talking with a lot of the football players, a lot of them feel that maybe some of their disease process started in pee wee football and it's possible that the young brain may also be very susceptible to these sorts of concussions. I think it really emphasizes that we have to be very, very cautious with our children and grandchildren to make sure that they are not put in an environment where they are going to suffer from these concussions but I think we're worried. Again, I don't want to overemphasize the risk, the risk of one-point-five-fold is not huge, it's like the risk, probably a little bit less, in being diabetic or having high blood pressure, but head trauma is definitely a risk for Alzheimer's disease and related conditions.

George Vradenburg: You mentioned the distinction between having one concussion versus multiple concussions. Is there any research or do you have a belief about the relative risk of one versus multiple on the one hand versus the other factors that might be present in the person that might be greater distinguishing or differentiating characteristics in terms of risk of permanent injury?

Dr. Bruce Miller: I think, as you're getting a sense, the really hard research in this area is just not there yet but I think the fact that a higher percentage of football players than any other sport other than boxing seem to develop these degenerative diseases, makes us believe that it's not just the severity but the frequency. Boxing is a good example of individuals getting repeated hits to the head and some of them concussive, some of them sub-concussive, no real symptoms. Nice study again with Zetterberg out of Sweden that looked at amateur boxers after four rounds. They wear really big gloves and they're almost never knocked-out, but they found that there was elevation of tau in the spinal fluid in nearly all of these amateur boxers and here what we see is repetitive trauma again and again and again, even though it's quite mild. So I think the growing consensus is that repetitive is much, much worse than a single event. Probably even more so if they come one on top of another. I think the brain has good mechanisms for clearing the bad tau and the amyloid, if you give it some time. But if you don't give it any time and you continually stress the brain, we're really worried that this is going to lead to bad outcomes.

George Vradenburg: Let me ask, this is a question actually from Virginia Zerpa. Any information about the effects of viral meningitis on the brain and it's potential as a risk factor for the development of dementia?

Dr. Bruce Miller: Yeah. A great question and I am pretty sure there's never been a study on this. Again I think any sort of insult to the brain whether it's diabetes or high cholesterol, we think these are all risks. Whether some sort of inflammatory injury to the brain associated with viral meningitis might be a risk in later life, don't think it's been studied, it should be though.

George Vradenburg: Carole Roberts Wilson, you have a question of Dr. Miller. Could you ask your question please?

Question: Well you know, I'm a speech pathologist. I work with a lot of people with Alzheimer's, dementia, Parkinson's and other things, but everyone has a caregiver and the problem we have when we're working with them, with caregiver groups, is that they don't see themselves as caregivers. They never use the word caregiver, so how do you get to that point where they recognize that situation?

Dr. Bruce Miller: Yeah. I agree this is a problem and we know from caregiver studies that they may be an at-risk population, suffering the continuous stress of a hopeless situation certainly increases depression, 10% of caregivers talk about a serious health problem that develops in this setting. A lot of times things that they ordinarily do to protect the brain like exercising, keeping their blood pressure under control, get thrown away in the course of looking after a loved one. We look eye to eye with every caregiver that we see in our clinic and talk about their

health. I think it's a warning to them that this is time to protect yourself because if you don't, you will get sick and you won't be a caregiver, you're going to be a patient.

George Vradenburg: I was sitting with a very close friend who, for 20 years has been a caregiver of her husband with dementia, and I was sitting with her at a conference in which we saw the troops coming back talking about PTSD, the hypervigilance, the sense of always being on alert in the sense of not being able to calm down, not being able to avoid the stress associated with always being hypervigilant about a new noise or a new movement or something like that. And my friend, the caregiver, said that's exactly the way I feel because I have to worry 24/7, 7 days a week, 30 days a month, about different behaviors or different mood changes or even sometimes physical reactions on the part of my care recipient and I feel exactly as that soldier described about the hypervigilance that occurs on a caregiver's part and a troop's part. It was really kind of an interesting observation.

Now I don't know whether that causes a greater risk or a risk factor for dementia or for other kinds of progressive neurodegenerative diseases but certainly some of the symptomatic or the subjective feeling of a caregiver was, at least in this instance, reflected the same as what a returning wounded warrior was expressing.

Dr. Bruce Miller: It's fascinating, yeah.

George Vradenburg: Well, I thank you very much, well let me ask this is the question from Erin. Maybe it's not quick, but we do have a few minutes left. I'm curious about the link with sleep disturbances, sleep apnea is more common among football players than the general populations and is known to contribute to or accelerate the cognitive decline. Does treating sleep disturbance in your NFL patients mitigate or help their condition?

Dr. Bruce Miller: Yeah, it's a very important area and Kristine Yaffe here at UCSF has done a lot of work with sleep that in general suggests (her work is mostly in women) that bad sleep patterns are a risk factor for later cognitive deterioration and it's pretty clear that if you aggressively treat individuals with sleep apnea that in many instances their cognitive complaints diminish or disappear altogether, some they don't, and I think there's a feeling that perhaps long standing sleep apnea untreated may actually be a risk factor for degenerative diseases.

George Vradenburg: Well I'll tell you, this discussion today simply leads me to the impression that we are just beginning and maybe even pre-beginning to understand the variety of pathologies, whether the language we use to describe these differential pathologies is accurate or not, and the risk factors and risk predictors for faster or slower progression or any progression, we've just began to tap this field. So thank you for doing what you do Dr. Miller, it is extraordinarily important work, highly valued by the field, obviously there was interest in

your talk today and the level of questioning, the intelligence of the questioning reflects the fact that your work is important to so many people.

Dr. Bruce Miller: Well, thank you.

George Vradenburg: Sorry we didn't get to everybody's question but I do want to thank everyone that's on the phone and online for participating on this Alzheimer's Talk. 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.

Our next call will be Thursday, February 12th at 4 PM Eastern. We'll send out an invitation and a reminder to everyone. This call will be part of our ongoing collaboration with the Alzheimer's Drug Discovery Foundation and we'll feature a researcher that has been the object of some grants from the fund, Dr. Roberto Brinton from the University of Southern California. We'll send you info about the call, including how to sign up, in the next couple of weeks. As always please stay on the line if you'd like to leave us a message with a question or comment, we're particularly interested in what you would like to discuss on future calls.

Thank you again Dr. Miller for spending some time with us and for your work, as I've said, and thank you all on the call for joining us today and have a good afternoon and a great weekend. Bye-Bye.

Dr. Bruce Miller: Thank you very much. Goodbye.