



Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) Webinar Series

January 14, 2016 1-2:30 p.m. (ET)

Do Head Injuries Cause Chronic Traumatic Encephalopathy?

Operator: Welcome and thank you for standing by. At this time, all participants are in a listen only mode until the question and answer session of the call. To ask a question during that time, please press start then one. Today's conference is being recorded. Any objections, you may disconnect at this time. Now I'd like to turn over the meeting to Kathy Helmick, you may begin.

Kathy Helmick: Thank you. Good day and thank you for joining us for the DCOE Traumatic Brain Injury January webinar, entitled, "Do Head Injuries Cause Chronic Traumatic Encephalopathy?" My name is Kathy Helmick, and I'm the Deputy Director for the Defense and Veterans Brain Injury Center. I will be your moderator for today's webinar. Before we begin, let's review some webinar details. If you experience technical difficulties, please visit DCOE.mil/webinars to access troubleshooting tips. Please feel free to identify yourself to other attendees via the chat box, but refrain from marketing your organization or product. Today's presentation, references and resources are available for download from the files pod and will be archived in the online education section of the [DVBIC 00:01:18] website.

All who wish to obtain continuing education credits, or certificate of attendance, and who meet eligibility requirements must complete an online CE evaluation. After the webinar, please visit DCOE.CDS.PESGCE.com to complete the online CE evaluation and download and print your CE certificate or certificate of attendance. The evaluation will be open through January 28, 2016.

Throughout the webinar, you are welcome to submit technical or content related questions via the Q&A pods located on the screen. All questions will be anonymous, please do not submit technical or content related questions via the chat pod. I will now move on to today's webinar, "Do Head Injuries Cause Chronic Traumatic Encephalopathy?"

Contact sports have long been suspected of causing prolonged or permanent neurological injury in some athletes. The 2005 findings of unusual brain pathology in a retired NFL football player magnified concern for this association. The brain pathology involved accumulation of the protein tau in masses called tangles or threads. Today, more than 150 cases of CTE have been confirmed by

autopsies, with the vast majority being athletes in contact sports. Records show these individuals suffering a range of cognitive, emotional, behavioral, and motor symptoms. In some cases, co-occurring neurological conditions were present that also could account for some observed symptoms.

The distribution of accumulated tau masses, the criterion for diagnosis, in the clinical presentation of CTE remain controversial among researchers. At this time, there is no consensus regarding the clinical presentation of CTE that could enable diagnosis in living persons. There is no fluids nor neuroimaging biomarker validated for diagnosis, although some imaging approaches show promise in their ability to differentiate different neurological conditions and normal aging. The literature on CTE is also limited by the strong influence of a few individual researchers whose studies may be influenced by selection biases.

This webinar will address the current neuropathological diagnostic criterion for CTE and highlight recent findings that support or refute the Association of CTE with multiple concussions. At the conclusion of this webinar, participants will be able to describe the brain pathology observed in CTE, recognize the cognitive, behavioral, and neurological signs attributed to CTE, understand limitations of the current literature on CTE, articulate what is known and not known regarding the association of multiple concussions in CTE, discuss the potential risks of contact sports such as football and later development of CTE.

One final programming important note. Due to the point/counterpoint format of this presentation, the presenters are taking drastically opposing stances an attempt to give each position its fullest representation. Therefore, it would be an appropriate to attribute any quotes or beliefs to the presenters based on what is said in this webinar. Anyone on this webinar that is seeking official quotes or statements from DVBIC, or from Dr. Bunner or Dr. Marion should contact the DVBIC public affairs office at info@DVBIC.org. Thank you for that, that's very important.

Now we'll move to introductions with our two speakers. Dr. [Anne] Bunner is a program analyst in the research division of the Defense and Veterans Brain Injury Center. She previously served as an associate director for clinical research at the Physicians Committee for Responsible Medicine. She has authored numerous publications in several laboratory and clinical research areas, and she received her PhD in biology from the Scripps Research Institute. Welcome, Dr. Bunner.

Next, Dr. [Donald] Marion is the senior clinical consultant in the Clinical Affairs Division of DVBIC. He was an academic neurosurgeon who was focused on the clinical pathophysiology and treatment of traumatic brain injury for more than 25 years. He's previously served as the professor and chair of the Department of Neurosurgery at the Boston University School of Medicine, a professor and vice chair of the Department of Neurosurgery at the University of Pittsburgh School of Medicine, and was the director of the Brain Trauma Research Center at the

University of Pittsburgh. He received his M.D. from the University of California. Welcome Dr. Marion.

Now I will handed over to Dr. Bunner, to start the webinar.

Dr. Bunner:

Thank you, Miss Helmick. First of all, I have to say that the views expressed here are my own and do not represent those of the Department of Defense, I do not intend to discuss any off label or investigative products or devices, and I have no [relevant 00:06:48] financial relationships to disclose.

I'd like to get a feel for audience, in terms of current knowledge of chronic traumatic encephalopathy. There will be a polling question popping up on your screen. It would be great if you could select the statement that best reflects your current understanding of CTE. I'll give a few seconds for the answers to come in. Thank you for your participation. Okay, thank you so much. We have a good number of responses here. It looks like most people have some understanding of CTE, and I hope that we can help you understand more today.

Dr. Marion and I will be doing a count/counterpoint, as Miss Helmick mentioned. I plan to convince you that repeated head injuries are the primary causative agent in the development of CTE. In the second half of the presentation, Dr. Marion will attempt to convince you that I'm wrong.

A little bit more detail about what we'll be discussing. I will be presenting some background information on CTE, a little bit of history, information about symptoms and pathology. I will discuss how CTE as distinct from Alzheimer's disease in normal aging, and I will acknowledge the limitations in the current literature on CTE. I will also offer counterpoints to arguments that you'll be hearing later from Dr. Marion.

Dr. Marion will be arguing that there is insufficient evidence to establish causation between sports concussion and CTE. He will get to have the last word. He will start off by attempting to discredit several CTE researchers, and then he will offer a series of red herrings, including a discussion of the benefits of benefits of team sports. Dr. Marion will also describe, using small words that my tiny lady brain can understand, the difference between a cross-sectional and a longitudinal study.

I'd like to start off with a quote. Dr. Marion will be offering some choice quotes later in the presentation. This is from a two time undefeated world champion welterweight boxer, Terry Marsh. "I don't need the British Medical Association to tell me getting hit on the head can't do me any good." I wanted to present this because it very concisely demonstrates that the position that Dr. Marion will argue, that TBI does not lead to serious neurological [inaudible 00:09:15] is absurd on its face. It just defies common sense to argue that repeated concussion is not associated with chronic neurological impairment. Terry Marsh,

his career ended early, when he was diagnosed with epilepsy, which we all know can be a complication of TBI.

What is chronic traumatic encephalopathy? It is a progressive neurodegenerative disease associated with repeated head trauma. It has only been observed in the context of repeated head trauma, predominantly among those who play contact sports. This includes boxers, football players, and hockey players. CTE is diagnosed by postmortem examination of brain tissue. There's currently no way to diagnose CTE in living persons.

A little bit of history. CTE was first described as punch drunk syndrome by Harrison Martland in 1928, its symptoms including gait problems, cognitive decline, tremors, and others. In the context of the concussion movie, and Dr. Bennet Omalu being in the news, I wanted to be clear that the phrase chronic traumatic encephalopathy was coined by Macdonald Critchley it first appeared in the literature in 1949. It was observed as early as 1967 that the brain of a boxer had neural fibrils and quote, senile plaque, which is one way of describing the particular neuropathology of CTE. Bennet Omalu, in 2005, reported the first case of CTE in a former NFL football player, and he is credited with bringing awareness to the risks associated with that sport. At this point, we have at least 153 autopsy confirmed cases, according to a 2015 systematic review.

Our knowledge of the clinical signs and symptoms of confirmed CTE is limited to retrospective reports of deceased persons, such as interviews with family members and reviews of medical records. CTE is believed to be associated with a variety of behavior, cognitive and motor function symptoms. These include mood swings, disinhibition, irritability, violent outbursts, impulsiveness, confusional episodes, problems with attention and concentration, memory impairment, language impairment, visual facial difficulties, tremor, [sound 00:11:28] problems, gait problems, and Parkinsonism, to name a few. These symptoms are mostly non-specific and could be due to other diseases and conditions. In fact, they often are. In one case series, 25 of 68 CTE cases were also diagnosed with motor neuron disease, Alzheimer's disease, Louis body disease, or frontotemporal lobar degeneration.

That said, just in the last three years, three different groups have proposed research or clinical diagnostic criteria for probably CTE. All three criteria require a history of brain trauma, symptoms consistent with those reported in the literature that cannot be attributed to an alternative diagnosis, and all three identify behavioral and cognitive disturbance as important for a diagnosis of probable CTE. The three groups differ on the importance of motor dysfunction for diagnosing probable CTE. None of the criteria rely on neuroimaging findings or other biomarkers.

Changes in brain anatomy that are gross in scale. That is, visible to the naked eye, often occur in the brains of CTE victims. For example, the septum pellucidum is a thin double membrane in the center of the brain. Normally, the two parts of the membrane are joined and divide the lateral ventricles as shown

in the image on the top. With cavum septum pellucidum, which literally means the cave of the septum, the two parts of the membrane and may be torn as shown in the image on the bottom. It's also common to see reduced brain wake, enlarged ventricles, and thinning of the corpus callosum in CTE. Though these gross pathological changes may not be present, there's a moment in "Concussion" movie, when Will Smith, playing Dr. Bennet Omalu, says that the brain of former NFL player and CTE victim, Mike Webster is quote/unquote perfectly normal to the naked eye. That was true in that case, but it's not true in every case.

On a smaller scale, CTE is associated with accumulation of tau protein in two forms in the brain, neurofibrillary tangles, or NFTs, which are dense aggregates of toxic protein, often globular or diamond shaped, and neuritic threads, or NTs, which are elongated threads of protein aggregates, and look like little bits of string on photomicrograph. NFTs and NTs occur in the cerebral cortex, but there's inconsistent data regarding specific locations. I'll talk more about that in a moment. I should also mention that beta amyloid plaques, which are often associated with Alzheimer's disease, occur in about half the CTE cases.

I'm on slide 23 now. I mentioned that there is inconsistent data regarding the specific location of NFTs and NTs. There are mainly two researchers, Dr. Ann McKee and Dr. Bennet Omalu, who have different findings on this question. Researcher Ann McKee finds tangles and threads at the depth of the cortical sulci. Sulci are the valleys in the folds of the brain tissue. In the image, you can see the folds of the brain tissue, and the brown staining indicates accumulation of [tau 00:14:39].

Moving on to slide 24. That is in the perivascular space. In this image, the blood vessels are the [oval 00:14:59] shaped white and blue structures, and the tau aggregates are red. You can see how the tau aggregates are more dense near the blood vessels. In contrast, researcher Bennet Omalu finds tangles and threads distributed throughout the cerebral cortex, and sometimes in the brain stem. There is special concentration of NFTs and NTs around the sulci or blood vessels in his findings. These images show NFTs and NTs not clustered around blood vessels. Here you can see how the NFTs can be rounded, as in the image on the left, or pointed, as in the image on the right, and how the NTs are thin and long. At this point, I am not able to reconcile these disparate findings regarding NFT and NT locations, but I'm confident that future studies will shed light on the apparent conflict.

Let me back up a little bit, because I seem to be saying that the central pathology in CTE is these NFTs and NTs, but I haven't explained how or why they lead to cognitive, behavioral, and motor symptoms. Unfortunately, that's not really know, but in defense of CTE researchers, I will say that it's not known in Alzheimer's disease either. We do know that tau protein is present in normal, healthy brain tissue, but ideally, proteins are like toothbrushes, they are manufactured, they serve a function, they wear out, they are recycled. When proteins accumulate, as in NFTs and NTs, it's like a garbage worker strike. It's

hard to move around and do business when there's [inaudible 00:16:34] everywhere. To make things worse, NFTs and NTs are resistant to the brain's trash truck cells, which are called autophages.

As long as we're talking about metaphors, I'll take this opportunity to bring up the "Concussion" movie again. In the movie, one actor compares the formation of neuritic threads to pouring wet cement down kitchen pipes. The trouble with that analogy is that cement in any form does not normally occur in kitchen pipes, whereas tau does normally occur in healthy brain tissue, just not so much of it.

The other thing I'd like to point out is that the signs and symptoms of CTE suggest that there is brain dysfunction, not loss of function. Cognitive dysfunction, motor dysfunction. It's not like with some stroke patients where you see that they lose certain functionality, like the ability to taste bitter flavors, or the ability to process information on the left side of their field of vision. If we were to pour wet cement down my kitchen drain, that would be a loss of functionality, the function of drainage, which for me is kind of central.

I previously mentioned that not all CTE cases are alike. Dr. McKee has proposed four stages of CTE pathology that are thought to occur in a progressive fashion. These stages are based on a series of postmortem examinations, so we can't know how the disease might have progressed if these people had lived longer, or what their brains might have looked like if they had died a few years earlier. However, Dr. McKee would argue that clinical data suggests the disease is progressive and therefore we can assume that the mildest pathology occurs first, and the more severe pathology occurs last. Of course, when the mildest pathology is accompanied with the mildest symptoms, that supports the whole theory.

In these drawings, the red represents accumulated tau, and I will talk about this in more detail in a moment. First, I want to clarify that both CTE and Alzheimer's disease are diseases of tau accumulation, or tauopathies, but tau deposits are found in different patterns in the two diseases. Here, we're going to compare the accumulation in CTE on the left and Alzheimer's disease on the right. With CTE, the tau accumulation starts mainly in the frontal cortex, whereas in Alzheimer's disease, it starts in the locus coeruleus. As CTE progresses, the diencephalon becomes affected, whereas in Alzheimer's the accumulation moves to the [trans entorhinal 00:19:07] cortex and the [entorhinal 00:19:10] cortex.

By stage III CTE, tau accumulation is widespread in [inaudible 00:19:17] cortex. At a similar point in the progression of Alzheimer's disease, tau accumulation remains concentrated in regions including the basotemporal cortex. At stage IV CTE, the medulla, cerebellum and cervical spinal cord show tau accumulation. In Alzheimer's disease there is typical no tau accumulation in the cerebellum.

There are also differences in the distribution of tau accumulation in terms of how deep it is found in a cortex. In this image, the triangles represent accumulations of tau. The top of the image represents the surface of the cortex, closest to the skull, and the bottom represents the bottom of the gray matter. In Alzheimer's disease, tau accumulates at a deeper level than in CTE.

So far, I've been showing you images or drawings of brains from deceased persons, but there are efforts to develop imaging approaches that enable diagnosis of CTE in living persons. Positron emission tomography, or PET, detects radioactive tracers, AKA radio ligands. CTE researchers have used radio ligands that bind tau to visualize tau aggregation in living persons. In this image, the warmer colors represent more tau, and you can see how the brain on the right, from a former NFL player, has much more tau than the control brain on the left.

One recent study compared former NFL players who had mood and cognitive symptoms with healthy controls and Alzheimer's disease patients. The tau distribution was distinct in the three groups, and the neuropathology in the former NFL players was consistent with pathology seen in confirmed CTE cases. In the image, which is colored as previously, with more tau being warmer colors, the brain in the center is from a former NFL player. You can see the distribution and concentration of red and yellow colors are different from those of the Alzheimer's brain on the right, and the control brain on the left.

I'd like to see if you've been paying attention. There should be another polling question popping up on your screen. Signs of CTE do not include endocrine dysfunction, behavioral and emotional symptoms, cognitive impairment, or motor function problems. Okay, well, this is a slam dunk. So far, the vast majority of you are correctly identifying endocrine dysfunction as something that is not attributed to CTE. Good job.

I have one more polling question for you. The neuropathology of CTE is distinct from Alzheimer's disease because- if you could please read the statements and select the one which is most true. Great job, everyone, the majority of you, 86%, are correctly identifying that tau deposition occurs in distinct patterns in the two conditions. Thank you so much.

At this point, I'd like to acknowledge that there are some limitations in the CTE literature we have now. There have been no longitudinal or epidemiological studies that could distinguish CTE from other neurological conditions. What I mean by that is that the diagnostic methods required to distinguish CTE from other neurological conditions are not typically done when determining cause of death, so we don't have longitudinal information that correlates CTE brain pathology to environmental or clinical variables. The pathological mechanism of CTE is unclear, as is true of several other neurological conditions.

Dr. Marion will be pleased to hear me admit that a causative link between TBI and CTE has not been unequivocally established. The CTE literature also suffers

from selection bias, and Dr. Marion will explain that more. It's also been noted that there's rampant duplication of cases in the literature, as many as 43% of cases are actually duplicates.

Moving on to slide 37, I'm going to respond preemptively to two of the more substantive arguments that the good Dr. Marion will present to you today. Dr. Marion will argue that the presents of NFTs in cognitively normal deceased elderly persons, for example, in the Honolulu Asian Aging Study, is evidence that NFTs are not caused by TBI and that CTE is not a distinctive disease. Let's think about the logic here. Does neuropathology in the non-demented alter the logic. I'm saying that repeated TBI leads to clinical signs of CTE, and NFTs and NTs.

We don't know how, but most researchers think it's the NFTs and NTs that are causing the clinical signs and symptoms. We also know that aging, or drugs, or genetics, or metals can cause neuropathology that does not lead to CTE like signs and symptoms. My question would be, where and how are many of these NFTs and NTs are present in these non demented deceased persons. In 2013, at an NINDS workshop on CTE pathology, Dr. Dennis Dixon of Mayo Clinic noted that none of the individual pathologic features, such as tau pathology, are unique to CTE, but what confers uniqueness is the peculiar distribution within the brain.

Moving on to slide 38, the model I would propose, based on data from the Honolulu Asian Aging Study, is that things like drugs or aging, et cetera, can cause NFTs and NTs in different forms and/or different places than in CTE, and those individuals do not experience clinical levels of symptoms. Dr. Marion will make a great deal of hay about one small, longitudinal study that showed high school football does not increase long term risk of neurological diseases, but high school football is not on trial here. There is abundant evidence that TBI does increase the risk of subsequent diagnosis of both neurological and psychological diseases.

A recent meta analysis looked at the risk of diagnosis of Alzheimer's disease or other disease at at least one year after TBI. A total of 57 articles were included in the meta analysis, and anywhere between two and 19 studies were examined for each outcome considered. The studies focused mostly on mild TBI, and severe TBI was excluded. The authors found that the risks were increased after mild TBI for Alzheimer's, Parkinson's, amyotrophic lateral sclerosis or ALS, and mild cognitive impairment. Overall, risk for any neurological diagnosis after TBI was elevated by 55%. There are other limitations in the particular study that Dr. Marion will present. We have no information about how these former high school football players, whether they had TBI before, during or after high school, or whether they had college football careers. I'll you decide how relevant that study is.

At the beginning of the presentation, I told you that I would convince you that repeated head injuries are the primary causative agent in the development of CTE. I do want to be clear that there is insufficient evidence to definitively

conclude that repeated TBI causes CTE in the same way that there was insufficient evidence to definitively conclude that OJ killed Nicole, but the evidence we have available was enough for Federal Judge [immutability 00:27:13] to hold the NFL financially liable for neurological conditions suffered by former players. Genetics, chemicals, aging, comorbidities, et cetera, cannot explain the totality of CTE cases. Regardless of the inconsistencies and limitations in the current literature, there is no plausible alternative explanation for the fact that every single CTE case has occurred in persons with history of repeated TBI and/or a long career in contact sports. My question to you is, what level of evidence is required for us to take measures to protect these athletes that we claim to greatly admire and value.

[inaudible 00:27:54] I'd like to prepare you for Dr. Marion's presentation by noting the strategies by science denialists. There was a time that some people insisted that CTE was not a distinct neuropathology, similar to how people have argued that other scientific realities do not exist. Then, with more evidence, the goal post gets moved, and now the argument is that TBI does not cause CTE. There are a few other characteristics you will notice in Dr. Marion's presentation, and I encourage you to apply this sort of critical thinking when you hear people talk about the dangers of vaccinating children against measles, for example.

You will hear Dr. Marion cherry pick favorable evidence to support his position. He will rely on weak evidence and testimonials like those quotes I mentioned. He will present lots of irrelevant evidence. He will present a logic that violates well-supported hypothesis in Alzheimer's disease research, and he may lob a rather comical personal attack in my direction. As Neil DeGrasse Tyson has said, the good thing about science is that it's true, whether you believe it or not. Thank you so much for your attention.

I will now turn the presentation over to Dr. Marion. There will be time for questions at the end.

Dr. Marion:

All right. Thank you Dr. Bunner. As Dr. Bunner said before, I will attempt to present to you that there's insufficient evidence to establish causation between sports concussion and chronic traumatic encephalopathy. First, I do want to disclose that these are my views being expressed, not official views of the Department of Defense or [inaudible 00:30:02], and I will not be discussing off label use of products or devices, [and 00:30:10] I have no financial disclosures.

Again, will start with a polling question. The clinical signs of CTE are which of the following? I'll give you a few seconds. Great, again you know, obviously are very attuned to this topic, and about 80% of you chose the correct response, which was that the clinical signs of CTE are actually quite nonspecific, and can be caused by numerous medical and psychiatric conditions, which is sort of a great segue into my talk. Unfortunately, something that my opponent doesn't buy into.

She mentioned Neil Degrasse Tyson, and I want to say that he's a, I'm a big fan of his as well, and one of his quotes I'd like to point out is that one of the biggest problems with the world today is that we have large groups of people who will accept whatever they hear on the grapevine, just because it suits their worldview, not because it's actually true or because they have evidence to support it. The really striking thing is that it would not take much effort to establish validity in most of these cases. Some people, and I'm not pointing any fingers, would prefer [reassurance 00:31:58] for research.

I would also point that a close friend of mine, Senator Nikki Haley recently pointed out that during anxious times it can be tempting to follow the siren call of [inaudible 00:32:13] voices [inaudible 00:32:14] how to, some people think you have to be the loudest [in order to 00:32:19] win to make the difference. This is just not true. Often the best thing we can do is turn down the volume, and when the sound is quieter, you can actually here was someone is saying. Despite the movie "Concussion" and all the hype about CTE as a result, I would ask that for a few minutes at least, you turn down the volume and listen to a few of the facts. I appreciate that someone who did their doctoral training in La Jolla, and was sitting on the beach all the time speaks more about cementing kitchen pipes than those of us who aren't in California who are thinking more about science, with Nobel Laureate professors, but will do what we can here.

The first thing I want to point out is that everything that Dr. Bunner has talked to you about is based on 153 cases. 153. Were I trained, that was a pretty small number for trying to establish scientific importance. This morning I did a quick clinicaltrials.gov search, and looked up what typically you find in their minimal number of patients, or the patients they think they need to enroll. For medications, for example, for congestive heart failure, rivaroxaban, Jansen Pharmaceuticals thought they needed 5,000 subjects. For lifestyle modification and the influence of coronary artery disease, University of Texas thought they needed 1,300 patients. Even for just, you know, looking at the Association of one thing versus another, as we are, serum glucose levels versus coronary artery disease, still they thought they needed 230 patients, so considerably more than this paltry 153 cases that Dr. Bunner thinks can establish the importance of CTE.

In my discussion, going to cover four things, four points. The first is, how strong is the association between the histology, the tau and the amyloid blockers. I'm going to talk to you about what really is the evidence that boxing and football cause CTE. Then three, what do the longitudinal studies show, and I'm sorry that Dr. Bunner doesn't [think 00:35:00] those are important, but I. Then, finally, are there important benefits to team sport. Again, apparently she doesn't, but let's proceed.

Just a quick question, something that I actually didn't appreciate, which do you think is more at risk, being a cheerleader or boxer? It turns out being a cheerleader will and you in the emergency department more often than boxing will. Dr. Bunner alluded to the NIH consensus conference in Boston in March of this year, well last year, actually now. It was the first consensus conference to

evaluate the neuropathologic criteria of diagnosing CTE. It was hosted by Ann McKee.

Kind of the problem with that conference, though, was not only was it hosted by an McKee, it was attended primarily by Ann McKee's minions, people at either worked with her or were on grants with her, with very few exceptions, actually. The attendees that were there did not include some of the most prominent people in science today that have written and talked about CTE, including Dr. John [inaudible 00:36:18], Harvey Levin, Bennett Omalu himself, as far as "Concussion", and Joseph Maroon, who also was in that movie. David Brody, Grant Iverson, Paul McCrory, and [inaudible 00:36:32]. It was a very select group. I'm not too surprised then, that the result of that meeting was pretty much what Dr. McKee had written about in numerous articles that she had published in the past, which incidentally, were repeating those same cases that Dr. Bunner talked about and 43% or so cases that were repeatedly reported in the literature.

The histopathology, from the consensus conference at least, it is, as Dr. Brennan pointed out, the location of the tau accumulation that is presumably pathognomonic for CTE. Again, an important point here is that it's an autopsy diagnosis, so you really can't make this diagnosis premortem. The big problem here is this 153 select cases, and so, if I were to call up Dr. Ann McKee right now, and say, Dr. McKee, I've got this person who had kind of funny neurologic signs and symptoms, and then died suddenly, so I wonder if I could send you this person's brain. Dr. McKee's first, next question to me would be "What sport did that person play in?" If said, well, "you know, that wasn't really somebody who is playing in sports", she'd say "yeah, I'm really not interested". This this kind of getting the bias that Dr. Bunner had talked about before, the selection bias that Dr. McKee is looking at cases that are quite select. Cases that she has decided she wants to look at in trying to make her case that there's an association between sports related head injuries and chronic traumatic encephalopathy.

If you look at large studies of normal aging, however, you're going to find that deposition of amyloid and tau, including hyperphosphorylated tau, is pretty common. In this particular study, 44.2% of all brains had this, without any clear association with specific neurologic signs or symptoms. If you kind of just go through, at this isn't even really cherry picking, as Dr. Bunner talks about, but just randomly going through the [pub med 00:39:18] and find the studies all over the place. A number of studies show there's really no clear cut correlation between tau depositions or amyloid deposits and neurologic problems. That's not only true for chronic traumatic encephalopathy, or that edge TV call CTE, but also for Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and any other number of neurodegenerative diseases you can imagine.

What I thought was even more interesting, that my colleague really [inaudible 00:40:03] told me about was this Edinburgh study of individuals who chronic opiate abusers, who also had hyperphosphorylated tau and [local 00:40:19]

brain lesions, including Dr. Bunner, including in the sulci of several of those brain. By the way, opioid abuse and tau deposition patterns in opioid abuse or not a part of those random samples of [slices of brain 00:40:37] that Ann McKee had her select neuropathologists look at back in, I believe it was March of 2015 in Boston. It's incorrect to say that you only see the pattern of tau deposition in CTE that she talked about. You may also see that with chronic opioid abuse.

[inaudible 00:41:09] the role of CTE is controversial in tau deposition, [inaudible 00:41:15] amyloid. It's interesting to note that in earlier publications of Ann McKee and her colleagues, they were quite clear in citing that amyloid plaques not normally associated with CTE, but have since kind of change their tune, and Bennet Omalu was pretty much always associated with amyloid plaque, with CTE, as well. Here's that in from the Honolulu Asian aging study that Dr. Bunner referred to earlier on, but it's a very well done study with a very large number of subjects. More than 153, I'd point it. That doesn't show us a clear correlation between clinical signs and symptoms prior to death and the location of the density of amyloid and tau deposition.

More studies, and I won't bore you with this, because it just kind of goes on and on, and as I said, you can find them all over the place. Their problems, then, in answer to this first issue, there are problems with the association between the tau and amyloid deposition in the clinical disease. What about this evidence, say boxing are multiple head injuries cause CTE? It seems to me from very early on there have been concerns about plaque and its potential to cause significant head injuries. The more I looked into boxing, the more I ... especially talk to my director, who's an alum of West Point, the more I change my thinking about boxing. Certainly, early on, C. Everett Coop, who was very outspoken on a number of issues, thought boxing should be eliminated from the Olympics. The American Medical Association thought boxing was horrible. I certainly had colleagues, in my current [roles 00:43:30] that if said the same. Let's step back, let's let the noise come down, and let's think about this a little.

What is boxing? Boxing is actually the practice and employment of the art of self-defense. It's an art form. It's a unique form of physical self-expression. [involves 00:43:45] dynamics, mechanics and nuances. The beauty of the skill it takes to perform masterfully under extreme competitive conditions, unless you test your limits, you'll really never know your capabilities. The National Safety Council actually looked at 37 different sports, and it placed boxing 26 among sports that require treatment in hospital emergency departments. In fact, the most dangerous sports were bicycle riding, basketball, and football. Cheerleading [inaudible 00:44:20] and [fishing 00:44:20] actually have more injuries than boxing. Now granted, boxing is more dangerous than billiards.

Does boxing affect long-term cognitive functional behavior? Well, I can tell you that when I looked, early on in my training, one of the real superstars of neurosurgery was a fellow named [Thoralf Sundt 00:44:44] who was the chair of surgery at [the Mayo Clinic 00:44:48] in Rochester, Minnesota, and he's widely believed to be one of the top or three neurosurgeons in the world, pioneering

cerebrovascular procedures, he personally did the burr hole on Ronald Reagan, when Ronald Reagan fell off the horse and had a subdural hematoma. Died of bone marrow cancer at age 62. The current Secretary of Veterans Affairs is a former West Point alum, and seems to be doing quite well in that position. Our current director Colonel Sidney Hinds, is a West Point alum, all of these individuals boxed as part of their curriculum, and especially there at West Point.

What about football? Well, in the early days, there were concerns. Chicago Tribune reported in 1904 that there were 18 football deaths and 159 serious injuries, mostly among prep school players. Mind you that Dr. Bunner thought that prep school or high school shouldn't count. That seems to count in those days, at least. The annual Harvard-Yale football series was canceled for two years because of violence [in football playing 00:46:04], but the Intercollegiate Athletic Association was formed based especially on Teddy Roosevelt's concerns, and his [inaudible 00:46:14], now known as the NCAA. I think those rules and regulations that they implemented [inaudible 00:46:21]. Teddy went on to say that in life as in the football game, the principle to follow is hit the lines hard, don't foul, don't shirk, but hit the line hard. [inaudible 00:46:32] sympathy for the person that's [battered about 00:46:40] a good deal, [football is not 00:46:41] fatal.

I wanted to just talk to you a little bit about numbers, because [inaudible 00:46:49] i hate to keep harking back to this 153, but I will, 153. If you look at any given year, there's over a million high school football players in this country. There are 70,000 college football players, and over a thousand [or 00:47:11] 1,700 [professional football players 00:47:13]. I would ask, and that's [I think 00:47:18] in a year. I would ask Dr. Bunner, where are all these cases of CTE, given the tremendous number of people who would seem to be at risk?

What's more, now you can go a step further, and you connection look at the number of injuries to the head by using helmet sensors, which the group that, again, [that you're testing 00:47:50] have done, and I'm running a little bit short of time, so I'll kind of quickly go, but it's pretty easy to look at these slides, and you can see that people who play football are hit in the head multiple times, 11 hits per game, and here is a seven and eight year old, and nine to 12 year olds or high school players, there's an estimated 240 hits per player per year. In NCAA football, 4.8 to 7.5 hits per game, and these are hits that like, [inaudible 00:48:27] or at a threshold that a lot of people think is, well, you're getting at about the 50th percentile for causing a clinical concussion. There's no question that high school players, college players, and even Peewee football players are getting hit in the head, but for some reason, Dr. Bunner, they're not getting CTE. I don't understand it.

How can we really answer this question? What kind of a study is this that we need? Is a good enough to just have [inaudible 00:49:05] theories, or these anecdotal reports that Ann McKee writes about and that Dr. Bunner likes to talk a lot about, or is there a better study that we can use? I would say maybe there is. Maybe there is something called the longitudinal [cohort 00:49:23] study,

where you could go to a town, say like, Rochester, Minnesota, where [inaudible 00:49:29] for decades has been collecting all of the medical records and all the medical histories of all the residence of Olmsted County in southern Minnesota, and so has a superb database for looking at [inaudible 00:49:45] medical care. Such a study was in fact done.

There were, in 1946 through 1956, there were just two high schools in Rochester, Minnesota. The one my nephews went to, which was Lourdes High School, and Rochester Public High School. They could go to the yearbook for these high schools, they could find male students who played football, and another cohort of male students who were in the band, [inaudible 00:50:14] player or whatever, and they followed these folks out through 2010, and published about the incidence of neurodegenerative disease in this group. In fact, they found that among those individuals, there were, let's see, there were 438 football players, compared with 140 non-football players, and to cut to the chase, there was really no difference between Parkinson's disease, Alzheimer's disease, ALS, or any other neurodegenerative disease, between the two groups. These multiple concussions that we saw in the Virginia Tech [inaudible 00:51:02] that these high school players likely had at least as many or more of, because they didn't have these next gen Riddell Helmets that the players have now. Still, they didn't have a higher incidence of CTE.

The first issue that I wanted to talk about is, or actually the [inaudible 00:51:29] is the importance of team-based sports. Traditionally, you talk much about, when you were talking about CTE, you kind of get locked into this, oh my God, you know, this person is going to be demented at age 14 if it's a football. What about educating them to be a team member, and to be able to function better in society and better in social gatherings and social groups, or in the workplace. There was a meta-analysis done from 1993 to 2012, which totaled 3,658 publications. This meta-analysis showed that club based or team-based sports are associated with well-being and reduced the stress and [inaudible 00:52:22], improved self-esteem, improved social interaction, and fewer depressive symptoms.

In another study, 50,000 or so ninth-grade public school students did an anonymous voluntary statewide survey. Students involved in sports, alone or in combination with other activities, showed significantly higher odds than the other [students 00:52:47] not involved in group sports, for exercise, [inaudible 00:52:50], healthy self-image, with significantly lower odds for an emotional distress or suicidal behavior, family substance abuse, and physical and sexual abuse victimization.

What about the coaches' perspective? Participants who were considered the [inaudible 00:53:08] coaches [inaudible 00:53:10] survey, and these coaches ranked the variables of having fun, learning life skills, being part of a team, and developing confidence, and excitement associated with team sports. Finally, what about the parents' perspective of [inaudible 00:53:25] children who played sports. Even from the parent's perspective of 4000 or so parents surveyed, that

they found children who participated in both team and individual sports, or team sports alone had greater health-related quality of life. I would point out that the benefits of sports participation or stronger for girls. Perhaps Dr. Bunner is not in favor of Title 9.

What can we conclude in addition to that? We can conclude that data reporting is inconclusive [inaudible 00:54:12] studies, that in a recent comprehensive review of CTE reports, 43% of cases were re-reported. There's a significant likelihood of selection or ascertainment bias. The premortem symptoms are often derived from interviews with family members, it's not objective and it subject to recall bias. The Boston University case series of CTE [subjects 00:54:37] overall and 27% of the CTE subjects showed [gratuitous 00:54:41] neuritic and vascular amyloid, so the distinction between Alzheimer's disease is a little bit arbitrary.

The fourth [inaudible 00:54:54] concussion in sports, which is a very robust and very, I think, important work group composed of leaders in sports concussion medicine in this country, agreed that chronic traumatic encephalopathy represents a distinct tauopathy with an unknown incidence in athletic populations. Cause-and-effect relationships have not yet been demonstrated between CTE and concussions or exposure to contact sports, and at present, the interpretation of causation in modeling CTE case study should be to proceed cautiously. In essence, they're saying parents should take a deep breath before suggesting that therefore their sons or daughters shouldn't play contact sports.

Finally, I'd summarize and say that while many of these athletes have a history of exposure to head impact, [inaudible 00:55:52] contact sports, there's insufficient evidence to establish causation between sports concussion and CTE. It's likely that many of the cases with neuropathologic [findings 00:56:03] represent the normal aging process, the effects of opiate abuse, varying [inaudible 00:56:09] generations. Whether particular genetic causes [inaudible 00:56:15] for the risk of [inaudible 00:56:18] is also yet to be determined.

[I'll conclude with 00:56:23] [a polling 00:56:23], selection, selection bias a bias in scientific investigation, [inaudible 00:56:32]. Okay, so about 60% of you chose the right answer, which is it's [caused 00:57:00] by sample, it is not representative of the population as a whole. Again, I'll look at Ann McKee's cohort, which is by far the largest out there right now, and she's very selective on the patients and the cases that she's going to do, or that she's going to do an autopsy of. [She also is 00:57:21] very selective on the cases that she publishes about. That's a selection bias.

All right. I guess that's it. Thank you for listening today, I much appreciate it, and I guess we have time for questions?

Kathy Helmick:

Thank you Dr. Bunner and Dr. Marion for your presentation. If you have any questions for our presenters, we already have gotten quite a few, please submit them now in the Q&A pod located on the screen. Now, I'm going to give you a

little background on a product, brief highlight, we want to highlight a study manual in today's webinar. The Defense and Veterans Brain Injury Center has a research network of 12 military treatment facilities, and the Department of Veteran Affairs Medical Centers across the country. DVBIC's research portfolio includes approximately 60 studies across the entire spectrum of TBI research priorities, from prevention to diagnosis, treatment, and ultimately, return to family, community and work, or continued duty.

One key study of those 60 studies is called the SCORE study, which stands for the Study of Cognitive Rehabilitation Effectiveness for mild traumatic brain injury. The National Defense Authorization Act for fiscal year 2010 test the Department of Defense with conducting a clinical trial to assess the efficacy of cog rehab in service members and veterans who sustained traumatic brain injury while in support of OAF and OEF and experienced persistent cognitive symptoms. This is intended to inform TriCare regarding coverage for cognitive rehabilitation and mild TBI.

[inaudible 00:59:06] investigators at Brook Army Medical Center, partnered with researchers at the San Antonio Medical Center, and the Department of Veterans Affairs to execute this RCP, which studies for types of cog rehab intervention. Psychoeducation. Number two, self-directed computerized cognitive rehabilitation. Number three, therapist directed manualized cognitive rehabilitation. Lastly, integrated interdisciplinary cog rehab, including cognitive behavioral psychotherapy. Outcome measures included cognitive functioning, post-concussive symptoms, cognitive complaints, cognitive fatigue, quality of life, health care use, and work status. Results showed significant benefit of the therapist directed and integrated treatment compared to the psychoeducational current standard of care.

DVBIC will publish the results of the SCORE trial study later this year. The SCORE study manual is a detailed, seven chapter description of the interventions and design of the SCORE trial, designed to enable replication or extension by other researchers. This SCORE manual can be downloaded at the DVBIC website, at dvbic.dcoe.mil/research/study-manuals. If you go to the website, you will find that there.

This is an interesting point/counterpoint webinar that we had today. We have about 25 minutes or so, 26 minutes, to be answering some questions that we have gotten from the field. Hopefully folks have submitted their questions, and I have five that I've picked to start us off, and let me [take 01:00:55] the question from the field, and then we can go into the answers. The first question reference slide 33, if there's a way we can pull it up, or if our presenters, namely Dr. Bunner, if you could go to slide 33. The title of slide 33 is PET shows CTE like pathology in former NFL players, and there's a column of controls, mild TBI, and Alzheimer's disease. The question from the field is, "In the scans that were displayed a few slides ago, what was the age match between the three examples of healthy control, NFL, and AD?" Dr. Bunner, do we have that information?

Dr. Bunner: I'm not sure. I have some notes. The control group had an age range of 30-84 years. The Alzheimer's disease group had an age range of 51-87 years, and I'm sorry, I don't have that information. I could get it to, say, the specific person who asked the question, though, if I have a chance to look in more detail at [Bario et al 01:02:05].

Kathy Helmick: I believe the origination for this question, although it's not written here, is when we compare different age groups, with healthy and Alzheimer's disease, as we would expect Alzheimer's disease to be an older population, how would you answer the question about making the case that these are findings when the age distribution could show otherwise from just natural aging? Do you have any comments on that? Either one of you?

Dr. Marion: Yeah, I think that's an important point. With amyloid in particular, the association amyloid [deposition 01:02:44] in the clinical [features 01:02:45] is really muddled, and most studies are, just show that, there's a wonderful aging study in California, at a retirement community, that has been going on for probably 60 or 70 years. They've just shown, even as you getting to your 80s and 90s, that there is really no good [inaudible 01:03:07] between amyloid deposition in the patient, or the degree of amyloid deposition in clinical dementia. That's what I would say about that. I think-

Dr. Bunner: But this is about tau.

Dr. Marion: I think, well, neurofibrillary tangle is similar. They haven't shown any association with that, either. The strongest evidence, I think, frankly, that we have is the possibility that it is the location of the tau that you point out, and that-

Dr. Bunner: Distinctive pattern.

Dr. Marion: Distinctive, but certainly not tau itself, certainly not [inaudible 01:03:41] tau, and the only thing I hesitate on is the stereoisomer, if it's a [inaudible 01:03:51] tau, what's the story there?

Dr. Bunner: I'd also like to point out that PET is not a high resolution technique, and it doesn't really, it tells us about the regions of the brain where the tau is accumulating, but it can't tell us about the depth of which levels of the cortex, and a can't tell us if it's at the bottom of the sulci.

Dr. Marion: Right. [Very good 01:04:15]. Yeah.

Kathy Helmick: Okay. Question number two. For either of you. "Has there been any findings of tau proteins in soldiers with a history of multiple blast exposures?"

Dr. Bunner: To my knowledge, there has been five cases of military veterans who were confirmed to have CTE. That's not counting NFL players who are also veterans. Most of those had blast exposure, but there was also evidence that some of

those five people had exposure to contact sports, or may have had other sources of TBI exposure. We don't really know, we can't really say very much about the relationship between CTE and blasts, but I'm going to ask if Dr. Marion has anything to add.

Dr. Marion: It sounds like you're suggestion that what we need is a longitudinal study.

Dr. Bunner: Maybe, but I'm not sure what that is.

Dr. Marion: No, I think, she points out some very good things, which is we don't really have anybody that just had blast exposure. You don't, [inaudible 01:05:23] to go into the military typically played football in their own high school. Maybe played football in college. Are greater risk takers almost by definition. It's hard, I think, to, and I don't think we have nearly enough evidence to point towards blasts as being a sole cause of anything.

Kathy Helmick: Since we are on the subject of blasts, in November 2015, we had the State of Science Blast Conference, sponsored by the DOD blast program office. When will the final report be posted on those proceedings so that if folks had further questions about the epidemiology of blast related, and correlations to CTE, when we know about that?

Dr. Marion: I'm on the [signing 01:06:11] committee for that, and I can tell you it's going to be mid next month.

Kathy Helmick: Mid-February.

Dr. Marion: Yeah.

Kathy Helmick: Okay, so for those that are listening that are interested in the epidemiology of blast related correlations to CTE, it was a three day conference in November, those proceedings summary reports will be out mid-February. Let me ask another question. "what does the literature show for individuals that are [concussed 01:06:36] that allows sufficient time to heal, in terms of the development of CTE?"

Dr. Bunner: Oh, I don't think we can really say much about ... because there's so little data, we can't predict, this person has had X number of concussions in X number of years, and therefore, their risk is, you know, so many times more elevated than it would have been if they hadn't had those injuries. We just really don't know. I think that the question does get at an important element of how concussion can have more serious consequences if they occur, if multiple concussions occur in a concentrated period. Whereas, if there is time to recover, that's better for everybody. Do you have anything to add?

Dr. Marion: No, I think you're spot on. The truth is, we don't know. We don't have the [good studies 01:07:31] to talk about how much time you need to recover, but you're

right, we do know that multiple concussions that occur, especially before you've recovered from the first, are bad, and your outcome is going to be worse.

Kathy Helmick: I think the originator of this question is really looking towards the role of healing, and complete healing, prior to that next concussion, and whether or not the lack of sufficient healing can contribute to the lack of proteins being eliminated, bad proteins being eliminated.

Dr. Marion: You know, it's a tough question because the closer you look, the more interesting things you find. For example, if you look with diffusion tensor imaging, an MRI, you'll find a significant proportion of people have had a concussion, or several concussions, who become asymptomatic clinically, but six months or a year later they still have abnormalities on DTI or diffusion tensor imaging, and macro imaging. [Most human beings 01:08:43] that we see all those [inaudible 01:08:46] abnormalities that you see in DTI, but you know.

Kathy Helmick: Next question. "Is there literature describing any association between traumatic brain injury from other contact sports, such as soccer, in CTE?" We talked a lot about boxing in football, but are there other context sports that are percolating to the top in terms of being corollaries to the development of CTE?

Dr. Bunner: There's been a lot of work on soccer. Heading. There's a researcher named Dawn Comstock, who has access to a huge database of high school sports injuries, and has published in epidemiological data about that. I believe the take-home message from one of her last studies on soccer heading was that it's actually contact between players that's more likely to cause injury than contact with the ball. I'm not sure if that really directly answers the question, though. The question was, could you repeat it? Oh, was it just about whether or not people are looking into-

Kathy Helmick: Other sports.

Dr. Bunner: Other-

Kathy Helmick: A lot of the press, a lot of the literature has been about boxing and football. Are there other context sports that have percolated to the top that should be looked at as well?

Dr. Bunner: Well, there was an epidemiological study last year which showed that women's lacrosse was one of the top sports for concussions. I don't remember which team that came out of. Then, the same researcher, Dawn Comstock, also published an epidemiological study, I think maybe just in December, about how cheerleading was one of the top sports for concussions. I guess if we're not talking about football, hockey, and boxing, then we should be talking about women's lacrosse, soccer, and cheerleading.

Dr. Marion: Yeah, in soccer is the highest risk sport for concussion in women. I second your judgment of Dawn Comstock, she is phenomenal. She used to work for the CDC, and now she works [inaudible 01:11:05].

Dr. Bunner: Carlyle.

Dr. Marion: Yeah. She has this database, and increasingly is enrolling high schools from around the country, who then send her all their injury data. Her publications are amazing, and she's really got a nice [inaudible 01:11:24] of head injuries of high school sports of all types.

Kathy Helmick: Do we know the base rate of CTE symptoms and NARA pathological markers in populations other than contact sports or repeated MTBIs from other sources?

Dr. Marion: Well, first of all, no one agrees on a clinical syndrome that is pathognomonic or that represents CTE. There is no clinical syndrome, [inaudible 01:11:59] syndrome, that defines chronic traumatic encephalopathy, so the answer is no, we don't, because you don't have a clinical, a [inaudible 01:12:10] clinical corollary.

Dr. Bunner: Well, I would comment that there are three main categories of the symptoms, and they're all going to have different base rates. For the behavioral and emotional symptoms, moods swings, irritability, et cetera, those are going to be pretty high and they're going to be especially high in populations that have psychological comorbidities. Some of the cognitive symptoms are going to be highest in people who have the cognitive impairment or maybe something else that, like a medication that affects their cognition, for example. The motor function symptoms are going to have the lowest base rate, because those are only really going to be observed in people who have some kind of condition, generally.

Dr. Marion: But you would agree, Anne, that you can have pathognomonic features of, let's say pathognomonic features of CTE at autopsy and not have any of those clinical [problems 01:13:10].

Dr. Bunner: I'm not sure that are cases, though, that would fall into that category. Where the pathologist would look at the slide from the brain and say, "This person has CTE" and then you were to talk to the family members and say, "Oh, no, their mood was always steady, there was never any confusional episodes or any funny motor symptoms". I don't think we have any cases like that. I mean, I could look, but-

Dr. Marion: I would have to look, too, but I believe Ann McKee, in her 2014 paper, where she summarized, you know, she wrote that big [JAMA 01:13:54] paper, I think, where she talked about clinical symptomatology, about the hundred and whatever cases she had at the time, there were cases in there, as I recall, that were asymptomatic.

Dr. Bunner: That may be true.

Dr. Marion: Yeah.

Kathy Helmick: Okay, a few more questions. "For either presenter, have genetic or lifestyle factors that are highly correlated with risk for developing CTE among contact sport athletes and/or service members with multiple TBIs been identified?" Genetic or lifestyle factors.

Dr. Bunner: Lifestyle factors. Well, having TBI is a lifestyle factor. I think. Let's see. The gene that's been associated with Alzheimer's, APOE, apolipoprotein of the epsilon 4 allele, that's associated with, well, it's associated with a few different things, including Alzheimer's disease, but also things like being prone to gambling addiction or things like that. There seems to be ... well ... there seems to maybe be some association between worse outcomes after TBI and the groups that have epsilon 4 allele. As far as CTE goes, there's been so few cases that we really have no information about any correlates between genetics and risk there.

Dr. Marion: [inaudible 01:15:24] for the epsilon 4 allele.

Dr. Bunner: No, I think it was presence of the epsilon 4 allele that this looked at in a few different studies, but I can't remember exactly which outcome was, but it was just generally poor outcomes with the epsilon 4 allele. Any other comments about the lifestyle question?

Dr. Marion: Yeah.

Dr. Bunner: I mean, I think if you take risks, you're going to get hit in the head.

Kathy Helmick: Given the widespread use of opioid painkillers in the NFL population, including an abuse rate over four times the general population, how do we rule that out as a cause tau protein accumulation?

Dr. Marion: That's a good point. I don't think you can. I don't think you can. The group Edinburgh's quite convinced that they have cases where there is no evidence of TBI, particularly evidence of opiates abuse where they see this tau accumulation.

Dr. Bunner: That's a great question, and I actually didn't know that about NFL players.

Kathy Helmick: Thank you for asking that question out there. "What do the speakers think of the worry and perhaps iatrogenesis with the worry about getting CTE later in life, even with one concussion, that exists in our mainstream population?"

Dr. Marion: I don't think there's any evidence of that, or for that. That's kind of almost like in the question of, well, we think about letting our sons or daughters play contact sports, you know, I don't think that the hundred and 52 patients from Boston

make me any less inclined today than I was yesterday of having my children or grandchildren benefit from contact sports, team sports.

Dr. Bunner: There's pretty significant evidence that fear seems to be associated with poorer outcomes. It's what they call diagnosis threat. If you give someone a cognitive test maybe a year after they've had a concussion, they'll do better on the test if you don't remind them that they had a concussion a year ago. I think it's better for everyone if we don't catastrophize whatever health conditions we may have.

Kathy Helmick: Fair enough. "A question about severe TBI. Most of our discussion this afternoon have been on mild TBI and concussions, but what does the literature say about developing CTE and severe traumatic brain injury, and how is it that decades of research on severe TBI have never raised this issue of CTE previously?"

Dr. Marion: I don't think it's been looked at. I don't think it's been looked for in severe TBI. You know, in the real world, when you're practicing in an environment where, for example, if you're a neurosurgeon in your taking care of these people every day, especially people a severe head injury, a lot of those people die in the hospital, or some of them end up in [homes 01:18:51] or chronic care facilities and then die of infectious causes later on. Typically an autopsy will not be done, or if it is done, they do sort of a cursory look at things, and it'll be clear that a lot of damage, but they probably won't spend a lot of time doing special screens that we have to do for tau. You don't get tau in a typical [ATU 01:19:19] staining.

I don't think we know that, Kathy, I think it's not been looked at. I don't know if I've told you about these cases that Steve [Jakosky 01:19:36] and I looked at in the past, that you know, when we [inaudible 01:19:42] therapy had a lot of younger people who I operated on very early on, and they had large amounts of amyloids in the temporal that I might remove, but a week or so later, if I had to re-operate, remove more temporal tissue, you could see that that amyloid within the [inaudible 01:20:01], as you described, Dr. Bunner, as these garbage trucks are cleaning up the amyloid that was left around. We know that amyloid occurs acutely after a severe traumatic brain injury. One of the questions is, what happens to it? Because if it accumulates, it does kind of gum up the wiring and [inaudible 01:20:28] in the brain.

Kathy Helmick: We have six minutes left, I want to ask you both a question, and then I'll give you both an opportunity to give two key messages to our audiences that you want them to have from today. The question first is, if you had a 10-year-old son who is very interested in playing contact football, would you, with your knowledge base of the literature on CTE, which you move forward with having your 10-year-old son engage in active contact football as a sport? Will start with Dr. Marion.

Dr. Marion: Yes, I would. With a couple of caveats. I'd like to know who the trainer is, I'd like to know that the Peewee or the group that he's playing with was abiding by state regulations for concussion management if it occurs, that he's not going to

go back into play right after a concussion, and that there are going to be trainers on the sideline that know what they're doing, and know how to deal with it or management.

Kathy Helmick: Okay, thank you. Dr. Bunner.

Dr. Bunner: I think you over estimate my ability to actually make decisions about any child I may have. I don't think I would have very much say in the matter. Oh, but you want to ... I mean, if I did, I don't know. I mean-

Kathy Helmick: It's more of a translations of knowledge, when you're basing [crosstalk 01:21:50] so don't picture the brown haired 10-year-old, just go with your gut. If somebody's consulting you, and asking-

Dr. Bunner: It seems to me that there are just way lower risk recreational activities that-

Kathy Helmick: Do something-

Dr. Bunner: -still offer the benefits of team sports that Dr. Marion shared with us.

Kathy Helmick: It sounds like Dr. Marion's a yes, and you're a, with trepidation. Okay. Let's finalize this portion with allowing you each to give two key messages that you'd like to give the 400 or so folks that we have in the phone. Dr. Bunner first.

Dr. Bunner: Well, I suppose my key message would be actually to quote from Terry Marsh, "I don't need the British Medical Association to tell me getting hit on the head can't do me any good." That's point number one. Point number two is to use critical thinking skills whenever anyone in the media or anyone behind a WebCam is giving you information about science.

Kathy Helmick: Excellent. Dr. Marion.

Dr. Marion: My main point, I think, is that, I think that the jury is still very much out about cause and effect for chronic traumatic encephalopathy. I am very concerned about making all kinds of assumptions as we have based on a relatively small [number 01:23:24] of cases that were not randomly selected and in no way represent [all of our 01:23:32], the people in this country, including those who do not have head injuries and those who have not died at a younger age. I'm worried about the clinical science are the clinical correlations, that they're not founded on good science, [inaudible 01:23:50] good science. Secondly, I do, I think there are benefits to team sports. Including football or basketball or baseball or soccer or any of those sports, that lifelong lessons learned, that helps people mature, and help them enjoy their lives more.

Kathy Helmick: Thank you Dr. Bunner and thank you Dr. Marion. Extremely helpful, and I hope that folks on the phone have enjoyed this. I do want to mention to resources at your disposal for further information about chronic traumatic encephalopathy.

If you go to the DVBIC website, dvbic.dcoe.mil, you can find a paper, a very academic and scientific type information paper on chronic traumatic encephalopathy, it was updated in January, so this month, with the latest scientific information and all citations.

Secondly, DVBIC has CTE talking points, if you need some bread-and-butter easy talking points to relate to many general audiences. Please feel free to reach out, it's info@dvbic.org, and we'd be happy to send you those DOD approved CTE talking points.

After the webinar, please visit dcoe.cds.pesgce.com to complete online CE evaluation and download or print your CE certificate or certificate of attendance. The online CE evaluation will be open through Thursday, 28 January. To help us improve future webinars, we encourage you to complete the feedback tool that will open in a separate browser on your computer. To access the presentation and resource list for this webinar, you may download them from the files pod on the screen or at the DVBIC website, dvbic.dcoe.mil/online-education. An audio recording and edited transcript of the closed captioning will be posted that link in approximately one week.

The chat function will remain open for an additional 10 minutes after conclusion of the webinar, to permit attendees to continue to network with one another. The next DCOE psychological health webinar topic, entitled "Scientific Reviews of Recent Studies on the Treatment of Post Traumatic Stress Disorder" is scheduled for 28 January, from 1300 to 1430 Eastern time. The next DCOE TBI webinar is entitled "Concussion in Winter Sports" and it's scheduled for 11 February at the same time, 1300 to 1430.

We thank you very much for attending, and your time and your interest in this particular topic area, and we hope everybody has a great and safe day. Out here.

Operator:

Thank you for your participation in today's conference, please disconnect at this time.