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Good afternoon, Mr. Chairman, Ranking Member Collins, and distinguished Members of the Committee. It is a great honor to appear before you today for this hearing on "Brain Injuries and Diseases of Aging." My name is Dr. Robert Stern. I am a Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology at Boston University School of Medicine. I am also the Director of the Clinical Core of the Boston University (BU) Alzheimer's Disease Center, one of 29 Alzheimer's research centers funded by the National Institute on Aging. In 2008, I co-founded the BU Center for the Study of Traumatic Encephalopathy (now referred to as the BU CTE Center) with Dr. Ann McKee, Dr. Robert Cantu, and Mr. Christopher Nowinski who is also testifying before you today.

For the past 25 years I have been conducting clinical neuroscience research, primarily focused on the cognitive, mood, and behavioral changes of aging, in general, and in neurodegenerative diseases, in particular. I have been on the faculties of the University of North Carolina School of Medicine, Brown Medical School, and, for the past 10 years, Boston University School of Medicine. In my role in the BU Alzheimer's Disease Center, I oversee all clinical research pertaining to Alzheimer's disease (AD), including studies aimed at the diagnosis, genetics, prevention, and treatment of this devastating disease.

Chronic Traumatic Encephalopathy (CTE)

Since 2008, my research has focused on the long-term consequences of repetitive brain trauma in athletes. In particular, I have been studying the neurodegenerative disease, chronic traumatic encephalopathy or CTE. CTE is a progressive neurodegenerative disease that can lead to dramatic changes in mood, behavior, and cognition, eventually leading to dementia. It is similar to AD but is a unique disease, easily distinguished from AD and other diseases through post-mortem neuropathological examination. CTE has been found in individuals from ages 16-98, including youth, college, and professional contact sport athletes (including football, hockey, soccer, and rugby players), military service members exposed to blast trauma and other brain injuries, and others with a history of repetitive brain trauma, such as physically abused women, developmentally disabled head bangers, and seizure disorder patients. (See **Table 1.**)

Although CTE has been known to affect boxers since the 1920s (previously referred to as "punch drunk" or dementia pugilistica), it is only recently—since CTE was diagnosed in several deceased former professional NFL players—that this disease has received greater medical and media attention. However, the scientific knowledge of CTE is in its infancy. The little that is known is based primarily on post-mortem examinations of brain tissue and interviews from the family members of the deceased athletes. What these studies have shown

is that, in some individuals, early repetitive brain trauma triggers a cascade of events in the brain leading to progressive destruction of the brain tissue. The hallmark feature of CTE is the build-up of an abnormal protein called tau (See **Figure**; based on the work of Dr. McKee), one of the abnormal proteins also seen in AD (McKee et al., 2013). These changes in the brain can begin years, or even decades, after the last brain trauma or end of athletic involvement, and can lead to memory loss, poor judgment, impulse control problems, aggression, depression, suicidality, movement problems, and, eventually, progressive dementia (See **Table 2**).

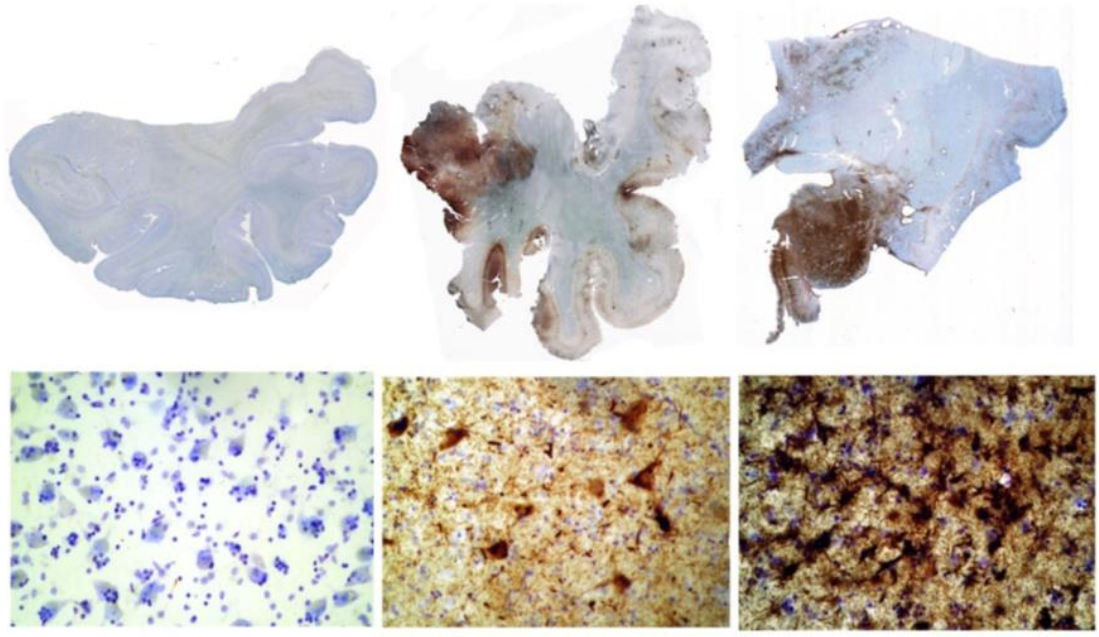

Figure of CTE Neuropathology. Left Top: Section of brain of 65 year old healthy man demonstrating no evidence of abnormal tau depositions. Left Bottom: Microscopic enhancement of same brain sample demonstrating no evidence of tau neurofibrillary tangles that would have shown up as brown from immunostain. Middle Top: Section of brain from 45 year old John Grimsley, a former NFL football player who had a five year decline in functioning (e.g., poor memory, short fuse) prior to his death from an accidental gunshot wound; brown areas are abnormal tau deposits. Middle Bottom: Microscopic enhancement of Grimsley's brain demonstrating neurofibrillary tangles. Right Top: Section of brain of 73 year old former professional boxer who died in a nursing home with clinical diagnosis of dementia pugilistica after several year decline in functioning; brown areas demonstrate widespread tau deposition. Right Bottom: microscopic enhancement of boxer's brain demonstrating widespread tau deposits

The Symptoms of CTE

Although the cognitive changes in CTE are very similar to those in AD, many individuals with CTE develop the significant changes in mood and behavior relatively early in life (Stern, et al., 2013) that can lead to significant distress for the individual with CTE as well as their family, friends, and other loved ones. These mood and behavioral impairments caused by CTE are typically misdiagnosed and attributed to routine psychiatric disorders, stress, substance abuse, or pre-existing personality traits. However, it is completely expected that the areas of the brain

damaged in CTE would lead to these problems, including depression, impulsivity, emotional lability, irritability, and behavioral dyscontrol. It is noteworthy that the much heralded "NFL Settlement" (currently in limbo while the judge examines several issues) began as a class action to address the issue of CTE in former NFL players and to provide the players and their families with appropriate compensation for the losses and distress experienced due to CTE. However, the "settlement," as it is currently written, does not provide any compensation for individuals with the mood and/or behavioral impairments so common in CTE. For example, the families of well-known former players who died of suicide and were found to have CTE post-mortem, such as Junior Seau and Dave Duerson, would not receive any benefits under the currently written settlement if they died after the acceptance of the settlement. Rather, only individuals with the memory, cognitive, and functional independence difficulties associated with Alzheimer's disease dementia would meet criteria for compensation.

Table 1. All cases of neuropathologically confirmed cases of CTE have had a history of repetitive brain trauma. CTE has been diagnosed in the following individuals:
Professional football players
College football players
High school football and other contact sport athletes
Professional soccer players
Semiprofessional soccer player
Professional rugby players
Boxers
Mixed martial art athlete
Combat military service members
Others, including a domestically abused woman, seizure disorder patients, developmentally disabled headbanger

Like other neurodegenerative diseases, CTE can only be diagnosed through post-mortem neuropathological examination of brain tissue. Dr. Ann McKee from our BU center has examined the brains of more athletes and others with repetitive brain trauma than any other neuropathologist. As part of the investigation of these post-mortem cases, I have had the great privilege and honor to interview the family members of approximately 100 deceased former athletes who were diagnosed with CTE after death by Dr. McKee and her team. From these interviews I have begun to learn about the clinical course and presentation of this disease. But, more importantly, I have learned about the tremendous pain and suffering the family members experienced while their loved one's life was destroyed by the progressive destruction of the brain. I have spoken with spouses of former professional football players who slowly lost their ability learn new information, communicate with others, dress, feed, and toilet themselves. I have interviewed

the adult children of former professional and college football and rugby players whose fathers had dramatic changes in personality, the development of aggressive and out-of-control behavior, and suicidal thoughts. And, I have spoken with the parents of young athletes in their 20's or 30's who impulsively took their own lives.

Table 2. Clinical Features of Chronic Traumatic Encephalopathy

Behavioral Features	Mood Features	Cognitive Features	Motor Features
Explosivity	Depression	Memory impairment	Ataxia
Loss of control	Hopelessness	Executive dysfunction	Dysarthria
Short fuse	Suicidality	Lack of insight	Parkinsonism
Aggression and rage	Anxiety	Perseveration	Gait Disturbance
Impulsivity	Irritability	Impaired attention	Tremor
Physical/verbal	Labile emotions	and concentration	Masked facies
violence	Apathy	Language difficulties	Rigidity
Paranoid delusions	Loss of interest	Dementia	Muscle weakness

Diagnosing CTE During Life

I also have been privileged to meet over 70 former NFL players who have come to Boston to participate in my NIH-funded research study entitled, *Diagnosing and Evaluating Traumatic Encephalopathy with Clinical Tests*, or DETECT. I hear their histories, I speak with their family members, and I listen to their fears that they have CTE or that their fellow former football players have or will get CTE. They have all witnessed firsthand the tragic downward spiral of CTE that sadly seems to have become an expected consequence of playing the game they loved. The goal of the DETECT study (which was the first grant ever funded by NIH to study CTE) is to develop objective biological tests, or biomarkers, in order to detect and diagnose CTE during life. The study involves the examination of a total of 100 former professional football players (selected based on positions played and existing clinical symptoms) and 50 same-age non-contact sport elite athletes. All research participants undergo extensive brain scans, lumbar punctures (to measure proteins in cerebrospinal fluid), electrophysiological studies, blood tests (e.g., for genetic studies and novel potential biomarkers), and in-depth neurological, neuropsychological, and psychiatric evaluations. In addition, I have recently received Department of Defense funding (with my colleague, Dr. Martha Shenton of the Brigham and Women's Hospital) and a separate grant from Avid Radiopharmaceuticals (part of Ely Lily) to examine an exciting new Positron Emission Tomography (PET) ligand (developed and owned by Avid) that is specifically designed to attach to the abnormal forms of tau protein found in CTE. Preliminary results of the DETECT study are very promising. However, it is just the first step. Future research is needed, including

longitudinal designs with much larger samples and the inclusion of newer techniques and technologies, as well as post-mortem validation of the findings during life.

To me, the ability to diagnose CTE during life is the next critical step in the study of CTE. It will lead to the ability to answer important questions about this disease, such as: How common is CTE? What are the risk factors for CTE? Can it be prevented? How can we treat it? In other words, at this point, we actually know very little about this disease (See **Table 3**). One thing we do know about CTE is that every case of post-mortem diagnosed CTE has had one thing in common: a history of repetitive brain trauma. This means that the repetitive brain trauma is a necessary factor in developing this disease. However, it is not a sufficient factor. That is, not everyone who hits their head repeatedly will develop this progressive brain disease. There are additional, as yet unknown, variables that lead to CTE, such as genetic susceptibility or specific aspects of the exposure to the brain trauma. Some have argued that brain trauma cannot possibly cause CTE, using the argument that there are many older former football players and other athletes with dramatic brain trauma history who are completely healthy. This irrational argument is analogous to those made years ago that cigarette smoking does not cause lung cancer because there are many people who smoked for decades who never develop lung cancer. An important next step in CTE research is to examine the specific additional risk factors, including genetics and exposure variables.

Subconcussive Trauma

It is important to note that CTE is not a disease restricted to former *professional* athletes. It has been found in individuals who only played their sport up through the *college* level and even just through *high school*. It has been found in warfighters who were exposed to blast trauma and other injuries. Another important issue to note is that post-mortem confirmed CTE has been found in individuals who have had no history of known or reported symptomatic concussions, but, nonetheless, were exposed to a tremendous amount of repetitive hits to the head that did not result in the symptoms of concussion. These "subconcussive" blows are quite common. It is estimated that the typical lineman in football experiences between 1000-1500 hits per season (i.e., at every snap of the ball at every play of every game and every practice), each at 20-30*g*. These hits are not just experienced by professional players. For example, a study by Broglio and colleagues (2011) found that high school football players received, on average, 652 hits to the head in excess of 15*g* of force in a single season. One player received 2,235 hits! To put this in perspective, a car going 35 mph into a brick wall experiences approximately 20*g* of force. There is now growing research evidence that even after one season, repetitive

subconcussive trauma can lead to cognitive, physiological, and structural changes to the brain. And, it appears that this exposure to repetitive subconcussive blows is associated with the development of CTE. This, perhaps, is one of the most frightening aspects of CTE. Over the past few years, there has been a tremendous increase in public awareness of *concussions* and the need to prevent and manage them. The "concussion crisis" in sports is a hot topic in the media, on playing fields, and in doctor's offices. However, when it comes to the long-term consequences of sports-related brain trauma, concussions are likely the tip of the iceberg. That is, subconcussive trauma appears to be as important or more important in the development of CTE.

Table 3. CTE Research is in its Infancy: What are the Important Questions to Address?
How common is CTE?
Is it a critical public health issue?
Above and beyond having a history of repetitive brain trauma, what are the risk factors for CTE?
Do genetics play a role in determining who gets CTE?
What types of brain trauma exposure increase risk?
Is there a certain age in childhood or adolescence when the brain is more vulnerable to brain trauma, increasing CTE risk?
How can we diagnose CTE during life?
Are there specific biomarkers that can accurately detect the abnormal tau deposition in the brain during life?
Can we distinguish between Alzheimer's disease and CTE by clinical examination?
How can we treat the symptoms of CTE effectively?
Can we modify the disease course if we intervene early?
Can CTE be prevented?
What is the biological mechanism for the development of CTE?
How does the abnormal tau move from one part of the brain to another?

Increased Funding for CTE Research

In order to tackle the complex issue of CTE, we must expand upon current approaches to conducting research in neurodegenerative disease. We must break down the traditional silos of individual research labs, research institutions, and disciplines, and begin to conduct multidisciplinary, collaborative research across research centers, bringing together the very best scientists, novel methodologies, and state-of-the-art technology. Most importantly, we must not forget that our research must focus on reducing individual human suffering and improving public health. Alas, this requires tremendous financial support. And, as you all know, current NIH funding is tragically low. The budget cuts to NIH in recent years have resulted in a tragic slowdown in the momentum of scientific discovery, and have led many scientists -- both young

investigators and older senior researchers – to leave their careers in the biomedical sciences. A recent survey by the *Chronicles of Higher Education* (Baskin & Vossen, 2014) of 11,000 senior researchers found that almost half of the respondents already abandoned an area of scientific investigation they considered key to their lab's mission. And more than three-quarters had reduced or eliminated their recruitment of graduate students and post-doctoral fellows because of reduced funding.

I want to express my deepest gratitude toward this Committee and its members for leading the recent effort to increase NIH funding of Alzheimer's disease research. However, **we must have additional funding to support research focusing on CTE and the long-term consequences of repetitive brain trauma in athletes, military service members, and other members of society**. In addition to direct federal funding, this effort will require public-private collaborative funding, such as that which supported the revolutionary Alzheimer's Disease Neuroimaging Initiative or ADNI. What might come as a surprise is that in 2012, the National Football League (NFL) donated $30 million to the Foundation for NIH to support peer-reviewed research studies on injuries affecting athletes, with brain trauma being the primary area of focus. However, that is just the beginning. We need much, much more.

In summary, many of our most cherished games in our country, such as football, hockey, and soccer, often involve repetitive blows to the head, potentially leading to a progressive brain disease with later life behavior, mood, and cognitive changes, as well as the development of dementia. We must learn as much as possible, as quickly as possible, in order to determine who may be at increased risk for CTE and other long-term consequences of the repetitive head impacts experienced by athletes at all ages, and to develop methods of preventing and treating the symptoms of CTE. I want to close by thanking the Committee for your interest in addressing this important issue and for your commitment toward improving the health and well-being of older Americans.

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