DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

State of Play: Brain Injuries and Diseases of Aging

Testimony before the

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Special Committee on Aging

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Mr. Chairman and Members of the Committee:

I am pleased to testify at today's hearing on brain injury and diseases of aging. I will present my perspective as a neurologist, scientist, and Deputy Director of the National Institute of Neurological Disorders and Stroke (NINDS) on what we know, where there is uncertainty, and how the NIH is working with other agencies, the private sector, the scientific community, and patients to address the gaps in our knowledge.

Traumatic Brain Injury (TBI)

I begin with a reminder that TBI is remarkably common, especially among the elderly. The U.S. Centers for Disease Control and Prevention (CDC) estimates that every year at least 2.5 million people in the United States suffer TBIs and more than 50,000 die[1]. As the CDC notes, this estimate does not include very large numbers of people who experience mild TBI but do not seek emergency care. Adults aged 65 years and older have the highest rates among all age groups of TBI-related hospitalization and death. Older people also recover more slowly and die more often from these injuries than do younger people. The most common cause of TBI in this age group is falling. This month, NIH and the Patient Centered Outcomes Research Institute (PCORI) announced a five year $30 million national study that will test a uniquely patient-centered approach to reducing rates of fall-related injuries among non-institutionalized older adults. The National Institute on Aging (NIA), which leads this study for the NIH, also supports research on age differences in TBI, as well as research on dementia.

[1] http://www.cdc.gov/traumaticbraininjury/get_the_facts.html

Although I will focus today on consequences of TBI that may not become apparent for decades after trauma, bear in mind that TBI can immediately affect many aspects of brain function. Problems with attention, memory, and thinking, especially "executive function," are common and persistent after moderate and severe TBI, as are social and emotional problems. Most people with mild TBI appear to recover completely, but perhaps ten percent report lingering problems months after injury, classified as the *post-concussive syndrome.* Why some people have persistent problems is an important, but poorly understood, public health issue. This May, at the White House "Healthy Kids and Safe Sports Concussion Summit," the National Collegiate Athletic Association (NCAA) and the Department of Defense (DOD) announced that they will jointly initiate the largest study to date of concussion and head impact exposure in sports to better understand the features that predict long term problems.

CHRONIC TRAUMATIC ENCEPHALOPATHY

Simply put, there is compelling evidence that repeated blows to the head can lead to a specific form of dementia. This phenomenon was recognized in boxers as early as the 1920's and was thus labeled *dementia pugilistica.* Now called *chronic traumatic encephalopathy,* or *CTE,* this disorder has been identified in the autopsied brains of athletes from other sports, including football, hockey, and soccer, and in brains from a few military veterans who were exposed to blast injury as well as other forms of TBI[2]. In addition to other signs of degeneration, including loss of brain cells in advanced disease, the brains of deceased people with CTE exhibit characteristic abnormal clusters of a protein called *tau* inside neurons. Tau aggregates are also one of the two key

[2] Brain 136:43-64 2013

findings in the brains of people with Alzheimer's disease, along with deposition of a protein called *amyloid* outside the cells. Multiple studies have demonstrated that tau is altered and amyloid precursor protein is increased after head injury in animals, and a recent human study using amyloid-PET (positron emission tomography) scans demonstrated transient increases in amyloid in the brain after moderate to severe head injury[3]. Amyloid-PET scans use small tracer doses of radioactive markers tailored to bind to amyloid to create an image of amyloid deposition in brain. Tau-PET scans, now in late stage development, will provide the ability to scan for tau deposits as well. The anticipated introduction of Tau-PET scanning could revolutionize the study of CTE by providing the ability to diagnose the condition during life. Abnormal tau deposition inside brain cells is the pathological signature of CTE and Alzheimer's and is also implicated in other forms of neurodegeneration, including frontotemporal dementia (FTD) in which mutations in the tau gene cause neurodegeneration. Surprisingly, recent evidence suggests that tau and other abnormally aggregating proteins can spread from cell to cell in the brain, which may represent a key insight leading to new strategies to treat Alzheimer's, CTE, Parkinson's, and other neurodegenerative diseases. Because CTE may be the purest form of an acquired neurodegeneration, studying CTE may provide clues on cell to cell tau propagation for other neurodegenerative disorders.

Although we know that repeated TBI can cause CTE, there is much we do not know about this disease. Perhaps the most critical roadblock is the lack of diagnostics that can definitively identify CTE in living people. Consequently, CTE can only be confirmed or refuted upon examination of the brain at autopsy. Without such a

[3] JAMA Neurology 71:23-31. 2014

diagnostic, we cannot estimate how frequently CTE occurs or how the number, timing between concussions, severity, and direction of blows to the head affect the likelihood of CTE. We do not know how age, gender, lifestyle, genetics, or other individual differences affect susceptibility. We do not have a good understanding of the clinical features that are specific for CTE, especially in the early stages. The latter is especially concerning given that varying degrees of tau pathology have

sidelines to detect concussions or help determine in the days following when an athlete is ready to return to play.

TBI and DEMENTIA

In addition to CTE from frequent brain trauma, there are compelling reasons to investigate whether multiple TBIs, or even a single TBI, increase the likelihood that a person will develop Alzheimer's disease or other types of dementia. TBI, especially moderate and severe, can certainly cause immediate, long lasting cognitive problems. This may affect persons' "cognitive reserve" and would diminish their ability to compensate for brain changes due to aging or neurodegeneration, increasing the likelihood that functional problems become apparent. In addition, the underlying mechanisms of damage to the brain from TBI and from neurodegenerative disorders are closely intertwined. Chronic inflammation, as well as tau and amyloid changes, are associated with both conditions, raising the concern that changes due to TBI might accelerate age-related neurodegeneration such as Alzheimer's disease. Some large epidemiological studies have found an association between later dementia and a prior history of TBI, especially moderate and severe TBI. This includes, for example, a prospective study of World War II veterans and a recent very large nationwide population study in Taiwan[5]. However, other large epidemiological studies have not found an association, especially for mild TBI[6]. It is also unclear whether the TBI associated dementias that are detected in these studies arise from Alzheimer's disease, CTE, or other types of dementia.

[5] Neurology 55:1158-66 2000; PLOS ONE 8:e62422

[6] Neurology 53:1959-62 1999; J Neurology Neurosurgical Psychiatry 84:177-82 2013; reviews in J. Alzheimer's Disease & Parkinsonism 4:137 2014 & Lancet Neurology 11:1103-12 2012

Research is continuing to address these questions. In addition to the studies already described on long term consequences of TBI, an NIH supported study is following a cohort of former NFL football players to determine, among other questions, whether genes affect susceptibility to later problems. The DOD is funding a parallel study to the

the NAPA Council has incorporated those recommendations into the National Alzheimer's Plan.

DEVELOPING TBI INTERVENTIONS

NIH supports research to develop interventions that prevent immediate and delayed problems from TBI, from laboratory studies in animals through large, multi-site clinical trials. NIH research has contributed to better critical care that has dramatically improved survival from severe TBI. NINDS and partners in Europe and Canada recently launched the International TBI Research Initiative. This prospective, observational study of 3,000 adults and children with TBI in the United States, coordinated with large studies by the European Union and the Canadian Institute of Health Research, will inform TBI classification and identify those therapies associated with the best outcome. NIH laid the foundation for meaningful comparison across these and other future studies by working with the research community and other federal agencies through the NINDS Common Data Elements program to harmonize the data that are collected and the way data are categorized. The DOD and NIH-led Federal Interagency TBI Informatics System (FITBIR) provides a database for sharing information from these and other TBI studies among qualified investigators.

BASIC RESEARCH

Progress in basic neuroscience has yielded advances in understanding the biology of the brain in health and disease, and an impressive array of tools to study the brain that will dri, and othe2(he)4(br)3(a)4drihehe

functional architecture in more than 1000 people, that is, a map of how different brain areas are connected and work together in the living brain. Pathologic studies demonstrate that damage, called "shear injury," in the brain's connections or "white matter" is common in moderate and severe TBI. Shear injury, which may occur diffusely throughout the brain, is relatively invisible with conventional imaging techniques. The Connectome will greatly enhance the ability to recognize and quantify the disruption in communication pathways between brain regions, and why some people's brains compensate better than others. Complementing this project at a more fine grained level of analysis, the President's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is developing tools with the spatial and temporal resolution to yield a dynamic, real time picture of how circuits formed by millions of interconnected nerve cells and synapses work. The BRAIN Initiative may ultimately yield insights about how TBI, Alzheimer's, and other disorders affect the functioning of important brain circuits and how the brain attempts to recover or compensate for these changes.

This January an NINDS intramural research team showed the power of applying emerging methods from basic neuroscience to TBI[7]. These researchers developed a novel mouse model of mild TBI and used advanced microscopy and cell labeling techniques to watch in real time in living animals how particular types of cells responded to mild TBI from the start. The investigators saw the swarming of immune cells and leakage of dye out of blood vessels on the surface of the brain during the initial inflammatory response and the recruitment of brain supporting cells that

[7] Nature 505:223-228 2014

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