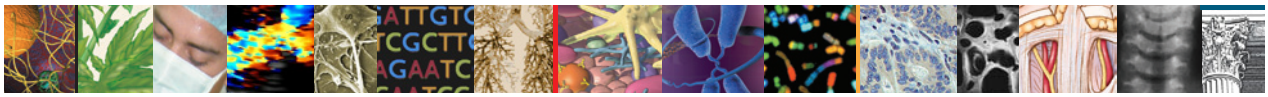

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Perspective

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Traumatic Brain Injury — Football, Warfare, and Long-Term Effects

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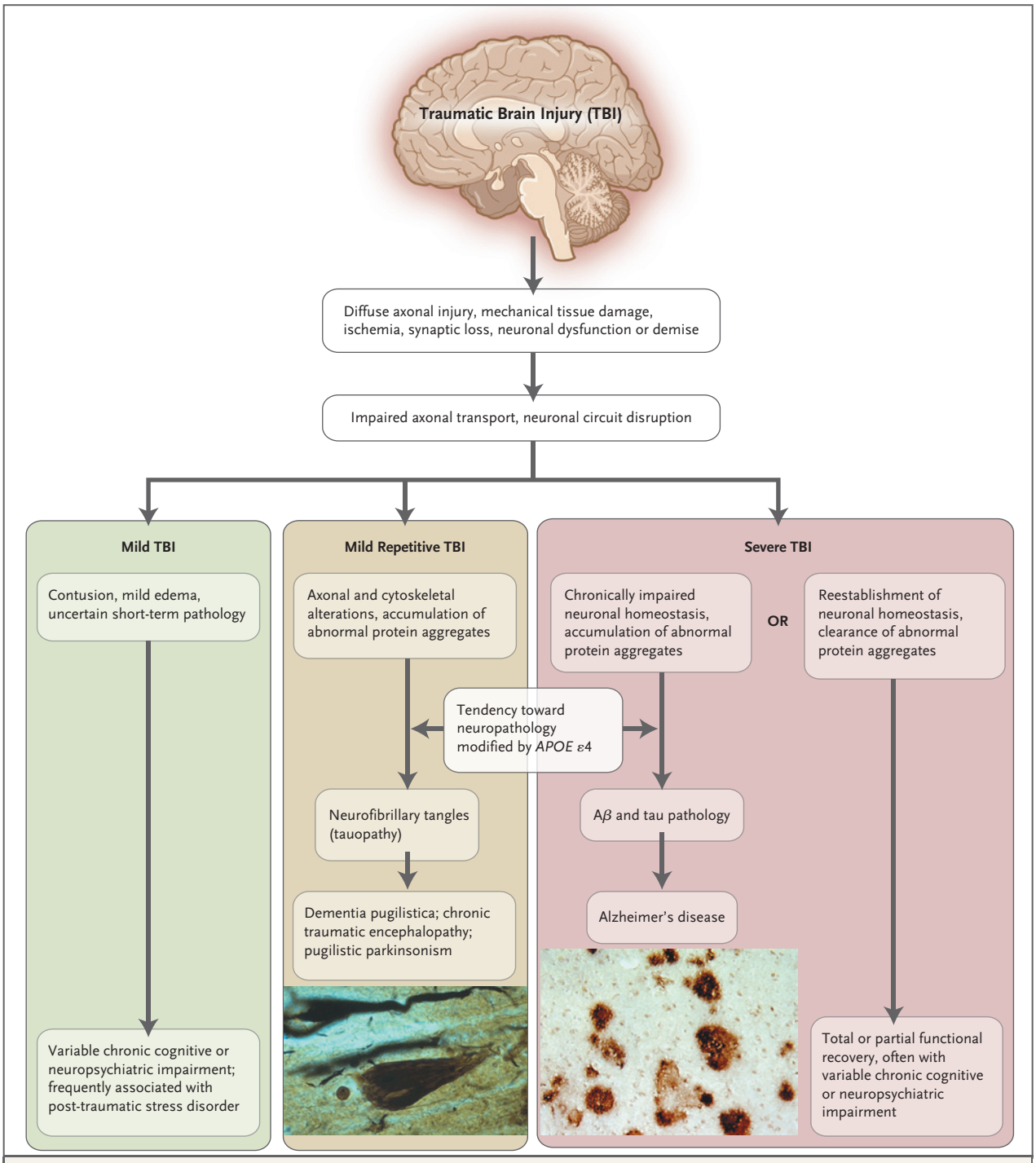
In late July, the National Football League introduced a new poster to be hung in league locker rooms, warning players of possible long-term health effects of concussions. Public awareness of the pathological consequences of traumatic brain injury has been elevated not only by the recognition of the potential clinical significance of repetitive head injuries in such high-contact sports as American football and boxing, but also by the prevalence of vehicular crashes and efforts to improve passenger safety features, and by modern warfare, especially blast injuries. Each year, more than 1.5 million Americans sustain mild traumatic brain injuries with no loss of consciousness and no need for hospitalization; an equal number sustain injuries sufficient to impair consciousness but insufficiently severe to necessitate long-term institutionalization.

The skull provides the brain with a protective thick, bony encasement, yet its irregular interior presents opportunities for damage to the fragile tissues it has evolved to protect. Direct mechanical trauma injures cortical tissue; traumatic hematomas damage subcortical structures and precipitate vasospasm and ischemia; and sudden movement of the skull on its vertebral axis produces rotational, acceleration, or deceleration injury, damaging the long axons interconnecting brain regions. Research regarding traumatic brain injury has long been challenged by the range of these lesions and clinical manifestations, several of which are frequently present concurrently.

Many complications of traumatic brain injury are evident immediately or soon after injury. Acute post-traumatic sensory, motor, and neurocognitive syndromes are presumed to occur as a result of contusions and axonal disruption. Seemingly mild closed-head injuries (i.e., those without skull fracture) may lead to diverse and sometimes disabling symptoms, such as chronic headaches, dizziness and vertigo, difficulty concentrating, word-finding problems, depression, irritability, and impulsiveness. The duration of such symptoms varies but can be months. Post-traumatic stress disorder frequently accompanies traumatic brain injury, though the relationship is poorly understood.

Causal relationships between traumatic brain injury and delayed sequelae have been less studied because of the variable latency period before overt neurologic dysfunction. Severe single-incident injuries, with or without skull fracture, may lead to permanent brain damage, with incomplete recovery and residual sensory, motor, and cognitive deficits. If consciousness is lost for more than 30 minutes, the



Spectrum of Pathologic Features and Outcomes of Traumatic Brain Injury (TBI).

In the left inset, Bielschowsky silver stain shows intraneuronal and extracellular neurofibrillary tangles in temporal cortex from a retired boxer with dementia pugilistica.[1] The right inset shows diffuse Aβ plaque deposits in temporal cortex from a subject who sustained severe TBI.[2]

risk of Alzheimer's disease is increased, even if there is substantial recovery from the initial trauma.

Our incomplete understanding of the pathogenesis of traumatic brain injury doesn't permit the construction of a rigorous temporal sequence of events. The most frequently proposed cellular mechanism is diffuse axonal injury (see figure), which is associated

with alterations in many physiological processes. Altered proteostasis is among the most obvious, because proteopathy is often evident at the histopathological level. Here, the pathways of idiopathic and post-traumatic neurodegeneration apparently overlap, since identical protein aggregates accumulate in both conditions. As early as 2 hours after severe brain injury, increased levels of soluble amyloid-β (Aβ) peptide and deposition of amyloid plaques are evident in the brains of 30% of survivors, regardless of their age.[2] Acute, single-incident traumatic brain injury is also found in the history of 20 to 30% of patients with Alzheimer's disease or parkinsonism but in only 8 to 10% of control subjects. Presumably, as-yet-undetermined genetic, environmental, and physical factors distinguish people who are destined to have delayed post-traumatic parkinsonism from those destined to have a delayed dementia identical to Alzheimer's disease.

Neurocognitive effects of repetitive mild head injury were initially recognized in boxers, with a syndrome that was distinct from the clinical and pathological sequelae of single-incident severe traumatic brain injury. The clinical syndrome of dementia pugilistica (punch-drunk syndrome) is associated with prominent tauopathy, with typical neurofibrillary tangles and neuropil threads, distributed in patches throughout the neocortex. In contrast to the diffuse Aβ amyloidosis that occurs after single-incident traumatic brain injury and in the absence of neurofibrillary tangles, the brain that is affected by dementia pugilistica shows no Aβ deposition; although tauopathy is prominent, the mesiotemporal region, where such tangles first appear in Alzheimer's disease, is typically spared. The traumatic tearing of neuronal connections (axonal shearing) disconnects or impairs cortical circuitry, thalamic circuitry, or both, contributing to cognitive impairment and dementia. Studies in the 1980s showed that among retired boxers, the numbers of rounds boxed, not win–loss records, were the best predictors of cognitive impairment. However, among boxers who had been knocked out approximately the same number of times, those who carried the *APOE ε4* allele were more likely to develop dementia pugilistica than those who did not.[1] Parkinsonism can also be associated with dementia pugilistica, in which case the term pugilistic parkinsonism is often used. A preponderance of neurofibrillary tangles and the absence of Lewy bodies distinguish pugilistic parkinsonism from idiopathic Parkinson's disease; nigral neurons are lost in both conditions.

Examination of the brains of several professional football players and wrestlers has revealed the pathological underpinnings for the cognitive and neuropsychiatric decline seen in these men in later life. Although cognitive decline in longtime professional football players has been noted for years, the first autopsy report from such a player appeared in the literature only recently.[3] The pathological findings in this and subsequent cases were identical to those of dementia pugilistica. In all cases, cognitive decline began years after retirement from the game. The term chronic traumatic encephalopathy was introduced as a clinicopathological construct for the neurodegeneration associated with football and wrestling, to distinguish the sequelae of these sports from the late effects of boxing. Whereas in dementia pugilistica the numbers of rounds boxed or knockouts can be roughly correlated with neuropathology, football players' concussion histories have been poorly maintained, and no dose–response relationship for traumatic brain injury has been established in football or wrestling. One contributing factor is that in football and wrestling cultures, injuries tend to be downplayed in order to keep players in the game, whereas in boxing, knockouts are recorded as part of scoring.

Traumatic brain injury leads to the accumulation of several neurodegeneration-related proteins, including synuclein, ubiquitin, progranulin, TAR DNA-binding protein 43, amyloid precursor protein, and its metabolite, Aβ. New research will target the roles that these abnormal protein structures play in determining the severity of injury and the ultimate outcome. Aβ-lowering medications, which are under study for Alzheimer's disease, improve outcomes after traumatic brain injury in rodent models,[4,5] suggesting a pathway toward potential therapeutic interventions. In future studies, the presence and fate of amyloid pathology in severe traumatic brain injury can be monitored in vivo with amyloid-binding ligands (as seen on positron-emission tomography) and by quantifying levels of Aβ, tau, and phospho-tau in cerebrospinal fluid. Ligands for visualizing other pathological proteins during life are also in development.

One goal of research on traumatic brain injury and chronic traumatic encephalopathy is to understand why acute traumatic brain injury involves Aβ accumulation, yet the neuropathology of chronic traumatic encephalopathy is tauopathy, largely in the ab-

sence of obvious amyloid plaques. Laboratory modeling of traumatic brain injury should facilitate the elucidation of the underlying cellular and molecular changes. Better modeling is required, since the configurations of the brain, skull, and spine in species that are used to study traumatic brain injury in the laboratory (rodents and swine) are imperfect models for human disease. Nevertheless, genetically modified rodent models hold promise for delineating pathogenesis in post-traumatic neurodegeneration, as they have done in idiopathic diseases.

Data from helmet concussion monitors that are used on soldiers and football players can aid in predicting the character and location of lesions from an impact of a given force at given coordinates while improving the accuracy of diaries of people at risk for traumatic brain injury. Accurate diaries, in turn, should help in determining more accurately the number and severity of head injuries, allowing estimation of athletes' cumulative risk. Individual differences in trauma tolerance and genetic influences must also be elucidated. These data can inform prospective studies of the cognitive, neuropsychiatric, and motor performance of soldiers, athletes, and other exposed populations, as well as informing the design of behavioral and pharmacologic interventions for prophylaxis or therapy. A challenge will be translating our improved understanding of the pathogenesis of traumatic brain injury into rational, evidence-based changes in public and sports policy that will minimize exposure to such injuries and their chronic neurodegenerative sequelae.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Promoting Prevention through the Affordable Care Act

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Too many people in our country are not reaching their full potential for health because of preventable conditions. Moreover, Americans receive only about half of the preventive services that are recommended[1] — a finding that highlights the national need for improved health promotion. The 2010 Affordable Care Act[2] responds to this need with a vibrant emphasis on disease prevention. Many of the 10 major titles in the law, especially Title IV, Prevention of Chronic Diseases and Improving Public Health, advance a prevention theme through a wide array of new initiatives and funding. As a result, we believe that the Act will reinvigorate public health on behalf of individuals, worksites, communities, and the nation at large (see table) — and will usher in a revitalized era for prevention at every level of society.

First, the Act provides individuals with improved access to clinical preventive services. A major strategy is to remove cost as a barrier to these services, potentially opening new avenues toward health. For example, new private health plans and insurance policies (for plans or policy years beginning on or after September 23, 2010) are required to cover a range of recommended preventive services with no cost sharing by the beneficiary. These services include those rated as "A" (strongly recommended) or "B" (recommended) by the U.S. Preventive Services Task Force (USPSTF), vaccinations recommended by the Advisory Committee on Immunization Practices (ACIP), and preventive care and screening included both in existing health guidelines for children and adolescents and in future guidelines to be developed for women through the U.S. Health Resources and Services Administration (HRSA). Examples of covered services include screening for breast cancer, cer-