Introduction

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There is still controversy in the literature whether a single episode of mild traumatic brain injury (MTBI) results in short-term functional and/or structural deficits as well as any induced long-term residual effects.

Zhang et al., 2010[1]

Salve, Elephant!

Zhang et al.[1], in the opening quotation, might be credited with the most politic of understatements. The controversy regarding the effects of concussive brain injury (CBI) is antique, intractable, and intemperate. Of course, controversy is common in medicine. Human biology is only slowly yielding to post-Enlightenment empiricism. As a result, some people perhaps know a bit more than others, but no one knows how things really work. Uncertainty combined with the emotional impact of human malady and professional competitiveness is bound to generate contention.

Yet the degree of agonism dividing the traumatic brain injury (TBI) community is extraordinary. New initiates to the study of CBI may encounter virtually opposite opinions, both pronounced with sober confidence by eminent authorities. Medical students raise eyebrows when instructors with diametrically opposing views take turns at the podium. Young neuropsychology interns learn to couch the impressions in their draft reports to suit the biases of each supervisor. Patients and families of victims are at a loss regarding whom to trust. Fair or not, young contributors quickly acquire labels, like team jerseys, identifying them as champions of one side or the other.

It is important, at the outset, to welcome the elephant in the room. Experts reading this chapter know exactly what the author means. Attend any TBI conference, especially one that focuses on concussion or so-called "mild traumatic brain injury" (mTBI). The tension is palpable. Eager young scholars juggling poster tubes and paper coffee cups display arousal and hope. Published authorities display tighter smiles. The hail fellow well met theater observed between scholarly opponents at most professional gatherings is, in this case, either overacted or eschewed. The players know each other. The hierarchy is rigid. The lines are drawn in blood.

In a nutshell, some published authorities assert the following as if they were facts:

1. the cerebral consequences of a CBI are reasonably well known, and
2. a single CBI infrequently causes persistent human distress due to brain change.

Other authorities – and the editors of this slender introductory text – disagree.

Figures 1 and 2 illustrate several facets of the burning and seemingly entwined issues that drive the contributors to this textbook: concussion and traumatic encephalopathy. Figure 1 is one of innumerable graphs depicting the change in the prevalence of post-concussive symptoms after a CBI [2]. Note that: (1) the highest level of subjective distress typically occurs just after the injury; (2) fewer victims report distress as times goes on; and yet (3) the curve does not reach zero. It appears asymptotic because about 25% of victims in this study reported persistent symptoms. Figure 2 is a fairly recent

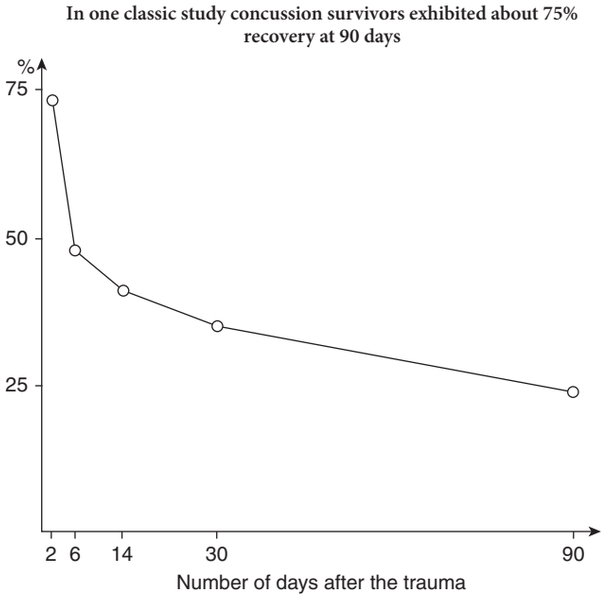

Fig. 1 Percentage of patients reporting one or more post-concussive symptoms on various occasions during the observation period.

Source: Lidvall et al., 1974 [2] Fig. V.1

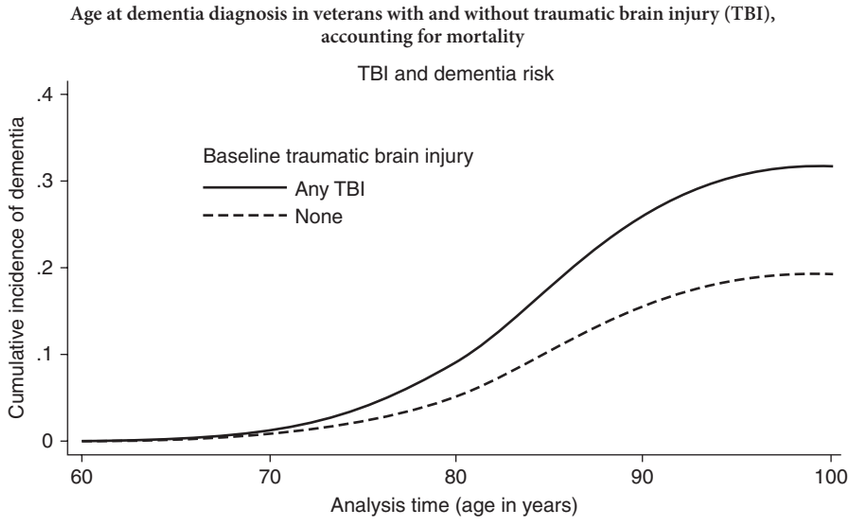

Fig. 2

The cumulative incidence of dementia is shown for veterans with TBI at baseline (solid line) and without TBI at baseline (dashed line), accounting for the competing risk of mortality. Age is used as the time scale to indicate age at dementia diagnosis.

Source: Barnes et al., 2014 [3] http://n.neurology.org/content/83/4/312.short

depiction of the association between prior TBI (mostly concussion) and dementia[3]. Note that: (1) in late middle age, veterans with a history of any TBI begin to deviate in regard to the incidence of dementia from those without a history of TBI; and (2) again, cumulative incidence increases over time.

Students of CBI must account for the findings reported in Figures 1 and 2. Of course, one explanation might be faulty research. Perhaps these findings and all of the similar peer-reviewed findings cannot be reproduced and should be roughly dismissed as statistical flukes or methodological errors. However, for the sake of argument, what if these observations are true? What process might explain both curves?

Assuming for the moment that Figure 1 displays authentically observed data, and that the study is representative, it implies that persistent post-concussive symptoms are common. It does not explain why. In the forthcoming chapters, the reader will have the opportunity to consider many theoretical explanations that have been advanced to account for the commonplace report of persistent post-concussive symptoms – from permanent organic brain injury to self-conscious malingering. Science has yet to prove the cause of persistent post-concussive symptoms – or, more accurately, to measure the relative contribution of multiple potential causes in any individual case. For the time being, however, we will hopefully all accept one compelling conclusion from Figure 1: people's responses to a CBI vary.

Now assume for the moment that Figure 2 also displays observed and representative data. If so, it appears that people who have suffered a TBI (in most cases; a CBI, in most cases, many years prior to the study) have an increased risk of developing dementia at an early-than-usual age. That is, despite the somewhat reassuring downslope of the curve in Figure 1, suggesting that most victims do not complain for very long periods of time, one is confronted with the worrisome upslope of the curve in Figure 2, suggesting that at least some, if not *all*, victims remain at risk of neurological disorder even if decades have passed since their CBI. (This raises the question of whether anybody ever recovers from a concussion – a question to which we will return.)

What process accounts for both curves? The correct answer is "nobody knows." This is perhaps a slightly atypical admission in the introduction to a medical textbook – to acknowledge our collective and embarrassing ignorance. Yet the only intellectually honest position in CBI studies is to note the giant gaps in empirical investigation that currently divide us from better understanding. In a nutshell, virtually no research has answered the question, "How can we characterize the spectrum of long-term – perhaps lifelong – neurobiological consequences expected after a human concussion?" The word *spectrum* is key. There is no single and identical effect from any two concussions. Resistance to that fact is one of the barriers to knowledge we must overcome.

Table 1 Barriers to knowledge about concussive brain injury

I. Insufficient empirical investigation
II. Lack of a meaningful outcome measure
III. Misplaced faith in a dated conceptual trichotomy
IV. Misplaced faith in flawed modes of inquiry
A. Misplaced faith in authority
B. Misplaced faith in consensus
C. Misplaced faith in cognitive testing
V. Bias, temperament, and conflicts of interest

That having been said, the insight of science is gradually detecting some light at the end of our tunnels. Over about the last decade or so, new empirical findings have discredited the old "we know what happens in concussion and there is little to worry about" mantra. This textbook will show that science supports three dramatically different conclusions:

1. The pathophysiology of concussion is highly variable and poorly understood.
2. The long-term consequences of concussion are highly variable and largely unknown.
3. There are lots of reasons to worry.

Knowledge Versus Opinion

At the risk of getting sucked into the muskeg of epistemology, multiple factors block the route to knowledge. (Table 1 offers

a partial list.) A brief examination of these factors may be enlightening, although, admittedly, some factors are better supported by verifiable evidence than others, and some might provoke disciplinary defensiveness.

I. Insufficient Empirical Investigation

An interesting meeting was held in Bethesda, Maryland in July of 2013. The meeting, hosted in part by the National Institute of Neurological Disorders and Stroke, was titled, Brain Trauma-Related Neurodegeneration workshop [4]. The purported goal was to survey "experts" regarding the best research approach to determine whether and in what way concussions may increase the risk of later neurodegeneration. At the opening of that meeting the present author delivered a brief address titled The Hans-Lukas Teuber Memorial Research Presentation. The thrust of those remarks was simple: the National Institutes had been down this road almost 50 years before. They had convened a remarkably similar meeting in year 1968. The title of that one: *Late Effects of Head Injury* [5]. One of their own, a nominal neuropsychologist but actual polymath named Hans-Lukas Teuber, said,

> It is my firm belief, after struggling with these problems for a good many years, that these difficulties can be overcome if we take the following steps: First, we should abandon the distinctions between broader and narrower definitions of the posttraumatic syndrome … Second, I propose we suspend our belief in the separateness of neurological and behavioral signs and symptoms … Finally … If one wants to advance the understanding of head injuries and their consequences, one had better study reasonably large groups of cases for which the initial trauma is fairly well demonstrated and constitutes the *sole* criterion for inclusion … Over the long run, clinicopathological correlations will make sense.
>
> Teuber, 1969 [6], pp. 13–14

In other words, Teuber exhorted his peers,

> Stop fooling around with short-term, small-scale studies that never consider the ultimate impact of TBI on the patient. Abandon the pretense that some symptoms are *neurological* and some are *psychological*. It's high time to perform large-scale, prospective, long-term studies of TBI, considering cognitive, non-cognitive, and somatic changes [6].

Sounds reasonable.

The Institutes declined to follow Dr. Teuber's advice. If they had done so, we would now have almost 50 years of data tracking the effect of concussion on the human brain. TBI does not seem to have been a priority. One reason may have been the misunderstanding, prevalent in the 20th century, that CBIs were benign. Whatever the cause, investigators of CBI are perhaps 50 years behind investigators of vascular disease, infectious disease, and cancer.

In fairness, consider the education of the participants at that long-ago meeting: Most had been taught that concussions are trivial. Despite Koch and Filehne's 1874 report about the impact of repetitive concussions [7], despite the eye-opening data published by Michael Osnato and Vincent Gilberti in 1927 demonstrating that even mild TBIs may cause a lasting "traumatic encephalitis" [8], and Martland's paper [9] of the next year (1928) about the chronic encephalopathy of boxers titled "Punch drunk," despite Courville's passionate, scholarly, and courageous book *Commotio Cerebri* [10], published in 1953, explaining why minor head injuries can have a major life impact, the typical medical student from the 1960s and 1970s graduated with the belief that concussions generate temporary and innocuous effects.

That belief is mistaken. Both animal and human research strongly confirm the many historic warnings: some victims of concussion suffer lasting harm (see Chapter 2). We are gradually coming to appreciate that, as a result, concussion creates an immense burden on human well-being and social function. TBI is mostly concussion. TBI is the most important cause of disability for people under age 45 [11] Moreover, unlike illnesses that are becoming less common due to therapeutic advances, TBI is a growing epidemic:

> According to WHO [World Health Organization], because incidence is increasing swiftly in low-income and middle-income countries (mostly owing to road traffic accidents), TBI is predicted to become the third leading cause of global mortality and disability by 2020. Furthermore, evidence suggests that TBI is a risk factor for dementia, substance abuse, and other psychiatric disorders. However, few improvements in clinical outcomes for patients with TBI have been achieved over the past two decades, and no effective therapy for TBI has been approved by any regulatory agency [12].

Two thousand years of study. No effective therapy. Despite the magnitude and severity of the problem, despite the pitiful progress in finding solutions, the effort to understand concussion has been inadequately researched.

It is important to make a distinction: one question is whether the most promising research has been performed. A different question is whether TBI research is underfunded. That is, perhaps research funding has been more than adequate but the selection of projects has been unwise. That difficult issue will be addressed periodically throughout this volume; but again, there are two possibilities. One: some of the choice of projects has been unavoidably limited due to the lack of technological capabilities. For instance, at one point in history, structural magnetic resonance imaging (MRI) with a few pulse sequences was the state of the art. Scholars using structural MRI cannot be criticized for failing to detect subtle or long-term brain changes that are apparent with more advanced methods. Similarly, normal rodent brains fail to exhibit a progressive deposition of several aging-related and apparently toxic proteins associated with neurodegeneration. Until transgenic animals could be developed, even a high-quality long-term prospective study of the impact of concussion on rats could not have revealed, for example, increased tau.

However, some of the disappointing choice in research projects is due to a blinders-on mentality, insensitive to the early evidence that concussion can produce long-term changes in brain and behavior. Discounting that evidence (and judging

it a waste of money to keep following the patient), many clinical investigators abandon their prospective longitudinal studies at three months.

The second problem, related to the suboptimal choice of research projects, has been the inadequacy of research funding. Every disease has its advocates. Many advocates bemoan what they perceive as inadequate funding. This sometimes bears the taint of special pleading. The question is: does objective evidence exist of disproportionately low funding for TBI research?

> So here we have a disease that results in 80,000 new disabilities annually and the spending on research is a drop in the bucket.
>
> Geoffrey T. Manley, 2011 [13]

> If you think research is expensive, try disease.
>
> Mary Lasker, 1901–1994 [14]

There are many ways to measure research funding for a disease, e.g.:

- total funding for the disease
- funding per patient based on population prevalence
- funding per patient based on annual incidence
- funding relative to the impact of the disease on function
- funding relative to the impact of the disease on economics
- cost of research per life-year gained
- cost of research per quality-adjusted life-year gained.

Some data are available regarding TBI research funding. The best way to summarize the story: things have been dark for a long time, but there are glimmers of light at the end of the tunnel.

Confining our attention to the United States, a review of the most recent "Estimates of Funding for Various Research, Condition, and Disease Categories" [15] reveals that total actual spending on behalf of TBI in 2016 was $105 million. Estimated (enacted) spending for 2018 is $84 million. The respective 2016/2018 figures for HIV/AIDs research: $3.0 billion and $2.47 billion; for diabetes: $1.1 billion and $951 million. Thus, in 2016, compared with TBI, the National Institutes of Health (NIH) invested about ten times as much in diabetes research and 29 times as much in HIV/AIDs research.

In terms of research investment per affected patient, this calculation depends on whether one looks at disease prevalence (total population affected) or incidence (annual rate of new cases). Figure 3 compares the incidence of TBI in the United States with several other conditions. It is self-evident that TBI occurs with much higher frequency than other disorders that receive a good deal of media attention.

However, *incidence* data do not offer a good perspective on the proportion of affected people in the United States. Research investment relative to *prevalence* is theoretically a superior measure, although then we are stuck with attempting to estimate prevalence. Unfortunately, the TBI prevalence figures offered by the Centers for Disease Control and Prevention (CDC) fail to consider the less-than "disabling" effects of concussion – for instance, the many patients who return to work but work inefficiently with greater effort while experiencing irritability, headaches, and divorce – and fail to take into account the suspected contribution of concussion to later dementia. In other words, the CDC prevalence data only consider the small subset of patients regarded as "disabled" due to TBI. In 1999, the CDC's National Center for Injury Prevention and Control estimated that 5.3 million U.S. citizens (2%) were "living with disability as a result of a traumatic brain injury" [17]. A more recent estimate suggests the number is 3.17–3.32 million [18]. The validity of these numbers is highly dubious. As the CDC put it:

> These estimates likely underestimate the prevalence of TBI-related disability as they do not include persons with TBI who were treated and released from emergency departments or other health-care settings, those who

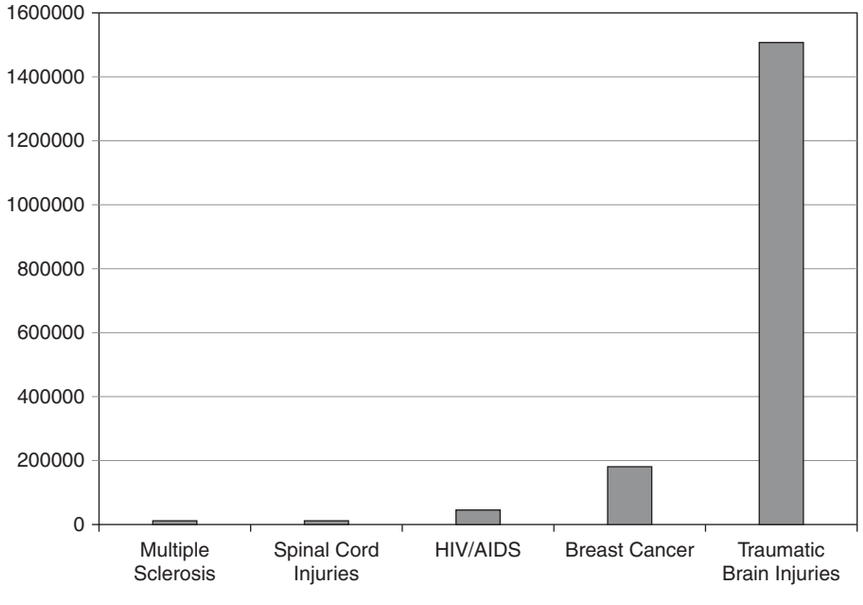

Fig. 3 Comparison of traumatic brain injury with other leading injuries or diseases in the United States. The cost of traumatic brain injury in the United States is estimated to be $48.3 billion annually. Hospitalization accounts for $31.7 billion and fatal brain injuries cost the United States $16.6 billion each year. Even with these staggering statistics, the United States spends less than $50 million annually on research into prevention and cure. Why?

Source: Zitnay, 2005 [16, p. 131]. Reprinted by permission from Springer

> were treated in a DoD [Department of Defense] or VA [Veterans Administration] facility, or who did not seek treatment [19].

That major caveat aside, using the 2008 prevalence estimate of 3.2 million, the annual research investment per TBI patient in 2013 was $27.50. The estimated U.S. prevalence of HIV/AIDs in 2009 was 1,148,200 [20]. Ideally, in order to compare with TBI, rather than the number of diagnosed patients, one would compare research investment per disabled patient (since only a subset of HIV-infected persons are disabled [21]). However, making the simplest calculation, $252 was spent per HIV/AIDs patient – almost ten times the level of investment made per patient with TBI.

The third approach is to consider the impact or disease burden per patient. Limited data are available employing this method. However, Gillum et al. [22] performed a novel analysis of NIH funding levels by disease burden. The authors did not specifically tease out "Injuries – TBI" from the broader CDC category, "Injuries." Nonetheless, as illustrated in Figure 4, it is again apparent that research investment is much higher than expected in HIV/AIDs (and, to a lesser degree, breast cancer and diabetes) and much lower than expected for injuries.

Finally, with regard to how research investments compare with the cost of a disease to society, a conclusion depends very much on the accuracy of the cost estimate. According to the CDC, "The estimated economic cost of TBI in 2010, including direct and indirect medical costs, is estimated to be approximately $76.5 billion" [23]. My guess about the credibility of this official figure: the number is inflated with regard to concussion, since much of the cost of TBI medical care goes for hospitalization after severe injury; and the number is deflated with regard to concussion given that typical estimates of injury impact fail to consider subtle and long-term brain changes. Bearing those caveats in mind, the United States spends one-tenth of a penny on research for every dollar TBI costs our nation every year. I am not an economist. No gold standard exists for the "right" amount of spending per dollar of cost of an illness to society. Yet (gut instinct), spending 1/1000 of the cost of a disease trying to fight it seems suggestive of inadequate funding.

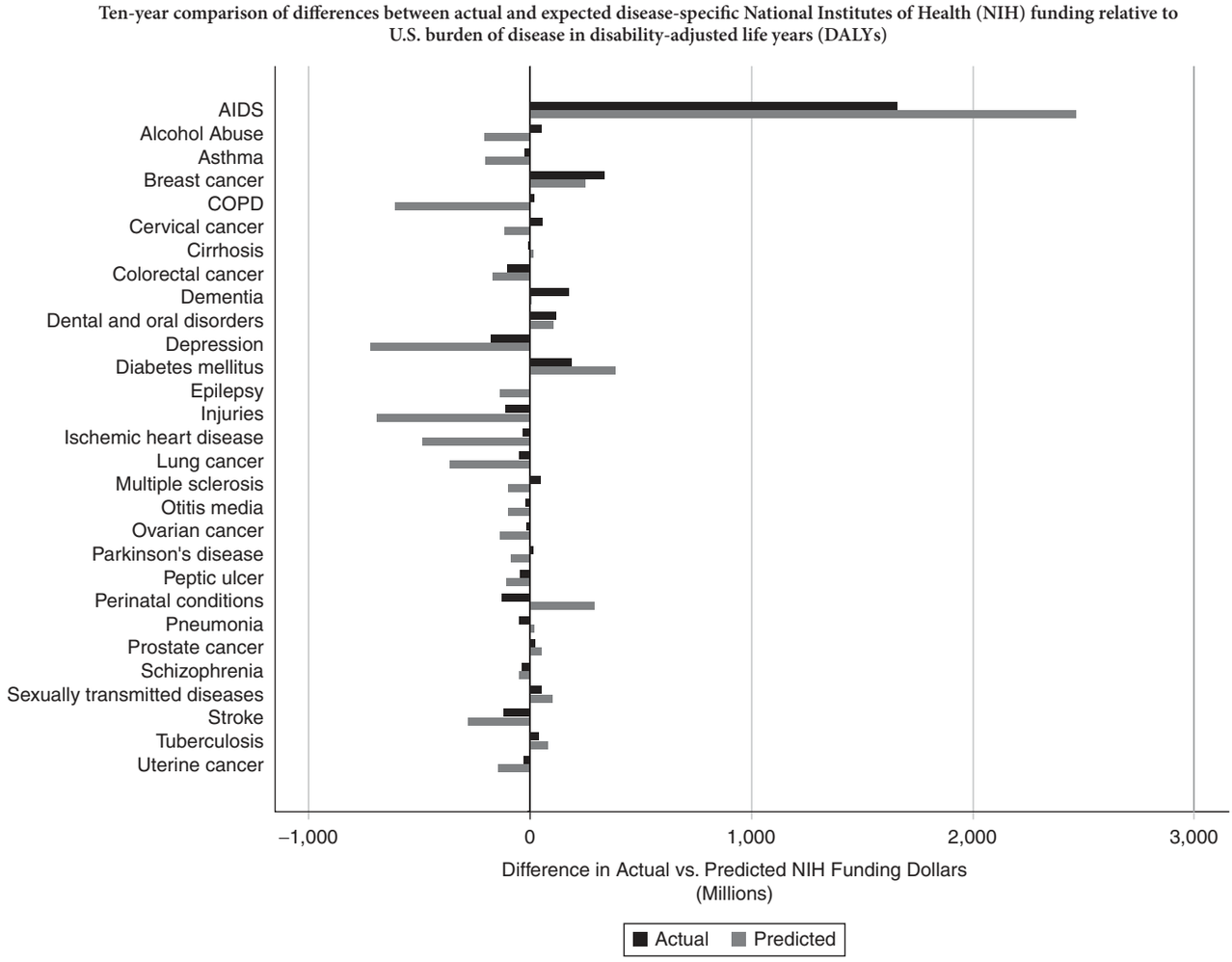

Fig. 4 A comparison of differences between actual and expected funding values as predicted by DALY burden alone in 1996 (light gray) and 2006 (dark gray). Negative values reflect actual funding dollars less than expected and positive values represent actual funding dollars more than expected.

Source: Gillum et al., 2011 [22]. Reproduced under the terms of the Creative Commons Attribution licence, CC-BY

In summary, hope of progress in knowledge about concussion has suffered from: (1) failure to fund research commensurate with the threat to human health; (2) delay in development of technology to objectively assess injury – especially the embarrassing fact that there exists no biologically meaningful outcome measure (see below); and (3) the low priority of research regarding the long-term impact of concussion. The United States – with the most extravagant medical research on Earth – spends a miserly pittance and gets what it pays for.

Thankfully, there are changes in the wind.

It would be unfair and inaccurate for 21st-century scholars to claim that they have been the midwives of a research renaissance. The launch of modern attention to TBI might be dated to 1974, when the NIH began phase I of the Vietnam Head Injury Study – even before computed tomography (CT) scanners were widely available. Phase II began in 1981, by which time MRI scanners had gained a commercial footing [24]. The 1989 U.S. Federal Interagency Head Injury Task Force report set off a sincere effort to determine the incidence of TBIs [25]. In 1992, the U.S. Congress established the Defense and Veterans Brain Injury Program (later renamed the Defense and Veterans Brain Injury Program Centers, DVBIC) – a somewhat disruptive innovation since it bridged the previously disjointed medical operations of the Department of Defense and the Veterans Administration (VA) [26]. Six lead centers went into operation across the nation. Of course, the size of the investment was small and the focus of these early initiatives was on moderate to severe TBI. For instance, the 1996 Traumatic Brain Injury Act authorized just $3 million per year for the CDC and $5 million per year for the Health Resources and Services Administration (HRSA) [27]. And the CDC's 1999 report to Congress on TBI [28] virtually ignored CBI (mTBI).

However, with the new millennium came a gradual escalation in attention to concussion. In 1999 a concussion clinic was established at U.S. Marine Corps Base Camp Pendleton in California. The next year President Clinton signed the TBI Act Amendments of 2000 [29]. For historians of concussion, this was a watershed moment: Section 1302 of those Amendments expanded the study of TBI to include victims of "mild brain injury." Research funding remained very limited; public awareness remained vanishingly low. But mild injury finally appeared on the U.S. federal agenda.

Three social factors have prodded a reassessment of the urgency of funding since that watershed moment at the outset of the 21st century. One is the significant increase in the global incidence of concussion (and global burden of brain injury) due in small part to increased survival after violence and in large part to the enhanced availability of motor vehicles without a safety culture in developing and middle-income countries. Another recent factor increasing the pressure for research has been the high incidence of concussions among warfighters in Iraq and Afghanistan. A third factor is increased awareness that contact sports may cause permanent brain damage. And technical factors have contributed as well. For one, transgenic rodents have been developed that better express human-like neurodegenerative changes. Another factor is that advances in human neuroimaging such as diffusion tensor imaging (DTI) and functional MRI (fMRI) have improved detection of injuries. This enables studies that would have been fruitless using the previous generation of imaging devices. Together, all these factors have inspired, if not a renaissance, at least several tentatively promising initiatives. Table 2 is a partial list of recent programs that raise hope of better research funding, research progress, or both. (Sincere apologies to the rest of the world. U.S. progress is emphasized simply because the story is more familiar to this author.) Note, however, that for all the expressions of concern and all the new money, concussions remained trivialized by many.

Table 2 Milestone 21st-century traumatic brain injury (TBI) research initiatives

- 2002: Common Data Element project
- 2003: International Mission on Prognosis Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT)
- 2007: Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (PH/TBI)
- 2008: Veterans Administration/Department of Defense Evidence Based Workgroup on mTBI/concussion
- 2009: Defense and Veterans Brain Injury Program Centers explored development with NATO of international standards for concussion/mild TBI
- 2011: The International Initiative for Traumatic Brain Injury Research (InTBIR)
- 2012/2013: Head Health Initiative
- 2013: The White House Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative
- 2013: Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) pilot study
- 2014: Department of Defense (DoD)/National Collegiate Athletic Association (NCAA) concussion project
- 2015: DoD and Department of Veterans Affairs (DVA) Chronic Effects of Neurotrauma Consortium (CENC)
- 2018: National Football League (NFL) funding pledged for furtherance of the TRACK-TBI study, the DoD/NCAA study, and a National Institute of Aging (NIA) study

Forward March

The first step in this forward march: a major impediment to comparing trials of TBI outcome or treatment efficacy has always been the lack of a consensus regarding the best way to measure cognitive, behavioral, and functional outcomes, since results cannot be compared unless metrics are shared. This pressing need drove the National Institute of Neurological Disorders and Stroke (NINDS) Office of Clinical Research to initiate the Common Data Elements (CDE) project. The initial contract was signed in May of 2002 and renewed in 2012 (KAI Research Inc. contract no. N01-NS-7-2372) [30]. Future NINDS-funded research will require the use of the CDEs, or at a minimum be CDE-compatible. Candidly, it is hard to predict the impact of the CDEs. Although the broad aims of the initiative are indisputably vital, the mission statement suggests that we may see a somewhat more pedestrian result: "The primary goal of the NINDS in developing CDEs for clinical research in neurology is to reduce the effort required to train coordinators and create the data collection forms in future studies" [31].

The next big step: in 2003 the U.S. CDC issued its second report to Congress on TBI. The pendulum had swung. For the first time – as mandated by Clinton's 2000 TBI Amendments – concussion was the primary focus. Hence the title: *Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem* [32]. The Introduction of that report warns: "Mild traumatic brain injury or MTBI – also called concussion, minor head injury, minor brain injury, minor head trauma, or minor TBI – is one of the most common neurologic disorders." This report was perhaps something of a wake-up call. Although the risk of lasting dysfunction after a single CBI was far from resolved, policy makers and doctors were put on notice that there might be a risk, and we'd better find out. That very year, the NIH-NINDS funded a multinational, multidisciplinary initiative called the International Mission on Prognosis Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) [33]. The IMPACT study group has collaborating institutes in Antwerp, Edinburgh, Richmond, VA, and Rotterdam. Having obtained access to 11 large data sets from clinical trials, the consortium has been working for more than a decade to improve the design of trials in TBI [34].

The United States and NATO began fighting various conflicts in the Middle East with the invasion of Afghanistan in 2001. That year, the Army cared for 3393 cases of mTBI [35]. TBI soon gained a reputation as the signature injury of the war. By 2007 – a year in which the Army cared for 11,461 mTBI cases – it had become clear that the available knowledge and resources about moderate to severe TBI were not addressing the military's needs because (1) many soldiers suffered from concussion and (2) many soldiers suffered from post-traumatic stress, with or without concomitant TBI. Based on about 300 recommendations from expert panels, in late 2007, the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness established a new umbrella entity, originally called the Post Traumatic Stress Disorder and Traumatic Brain Injury Research Program. In January 2008 the program came under the auspices of the Congressionally Directed Medical Research Programs and the new name became the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury [36]. At the time of this writing, the Defense Centers of Excellence oversee three subsidiary programs: the DVBIC, the Deployment Health Clinical Center, and the National Center for Telehealth and Technology, sharing the mission of "advancing excellence in psychological health and traumatic brain injury prevention and care." The law provided for $151 million for post-traumatic stress disorder (PTSD) research and $150 million for TBI research – a gratifying infusion of resources. However, it is challenging to pluck, from public records, an estimate of spending specifically designated for concussion/mTBI.

Further modest steps on the march occurred in 2008, when (1) the Traumatic Brain Injury Act of 2008 [37] reauthorized funding for the CDC and HRSA, and (2) the DVBIC convened a summer consensus conference on management of concussion in the deployed setting. Soon thereafter, the DVBIC released its clinical practice guideline for mTBI in non-deployed settings [38]. The upshot of that meeting was a 16-page report that distilled the military's judgment at that time: "Almost all people recover completely following a concussion" ([38], p. 9).

In 2009 the effort to improve and standardize the clinical approach to concussion became international, when the U.S. DVBIC explored development with NATO of international standards for concussion/mTBI. The same year, the Minneapolis Veterans Affairs Medical Center also prepared for the VA a "systematic review of the evidence" regarding TBI [39]. On the one hand, it was a sign of progress that that report included a discussion of concussion/mTBI. On the other hand – as Chapter 2 of the present text explains – that 2009 VA review failed to assay the literature. No responsible reviewer could read the published evidence and claim, "approximately 90% of mTBI cases follow a predictable course of recovery and do not experience long-term residual symptoms requiring treatment" ([39],p. 6). Chapters 2, 5, 7, and 10 will provide actual data from systematic reviews and let the reader judge. Equally problematic was the VA's claim that "Psychological factors (e.g., depression, anxiety, or PTSD), compensation and litigation, and negative expectations and beliefs are the strongest risk factors" for post-concussive symptoms" (p. 6). Again, Chapters 2, 5, 7, and 10 of the present text demonstrate that other factors are more important.

In April of 2013, President Obama announced the launch of the White House Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative [40]. The BRAIN initiative quickly received pledges of $300 million from public and private sources, and comprises a collaboration between five agencies: NIH, National Science Foundation, the Defense Advance Research Projects Agency, the Food and Drug Administration, and the Intelligence Advanced Research Projects Activity. Although TBI is only one of the disorders that this initiative will tackle – and although it remains to be seen what attention will be paid to concussion – there is at least some hope that, over the 12-year anticipated lifespan of the project, advances will occur that enhance knowledge regarding the biology, prevention, and treatment of CBI.

Gratifyingly, in the intervening years multiple new research initiatives have begun. For instance, as shown in Table 2, the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) pilot study that began in 2013 has become an NIH-funded multicenter longitudinal project. In 2014 the DoD began collaborating with the National Collegiate Athletic Association (NCAA) to study thousands of young athletes. In 2015, another component of the DoD and Department of Veterans Affairs joined forces in the Chronic Effects of Neurotrauma Consortium (CENC). The longitudinal designs make all these programs especially promising.

Perhaps the most dramatic recent research developments (indeed, something of a passion play) pertain to the interjection of corporate funding. This has, of course, prompted justifiable concerns about corporate motives.

Early in 2013, after the suicide of linebacker Junior Seau, the National Football League (NFL) pledged to support medical research at NIH with $30 million over five years. But in 2015 the League called an extraordinary and unseemly halt when some support was designated for the highly productive Boston University research team. The NFL literally refused to pay its

pledge because the Boston scholars had expressed concerns about the League's ethical behavior [41]. In 2016 the NFL revised its pledge to provide $40 million for medical research, ostensibly to be managed by the Foundation for the National Institutes of Health [42]. Yet a congressional committee found that year that the NFL was improperly steering the money toward a league-connected doctor. The League trimmed its promise to $30 million – but only $12 million was actually provided. The League simply let its contract with NIH lapse in July of 2017, holding on to $18 million.

That broken promise prompted a sharp rebuke from members of the House Committee on Energy and Commerce. Under congressional pressure, in early 2018 the NFL again promised to make good on its gift, pledging $7.65 million to the multicenter NIH/TRACK-TBI project, $7.65 million to the DoD/NCAA longitudinal project, and $2.25 million to the National Institute of Aging [43]. That modest support is welcome. History will judge whether the NFL's principal motive has been compassion, image management, or corporate research and development [44].

These signs are heartening, if somewhat mixed. The new initiatives reflect both increased concern about what concussion does to the human brain and residual loyalty to the belief that the answer is: not much. Yet the field is moving. Readers of this text, in fact, may be witnesses to a historical change in attitudes. Such changes come slowly. Like women's suffrage, school integration, reproductive rights, and many other examples, time is required for large groups to shift their allegiance from one stance to another. That seems to be happening in the domain of concussion. A decade ago, those who were concerned that concussion often causes lasting brain dysfunction were an outsider minority. The tide is turning. The subgroup of victims of concussion with persistent symptoms finally have reason to hope that their distress will not forever be dismissed as psychological frailty or venal self-interest.

What Needs to be Done Right Now?

The present author is not a neurobiologist nor a health care economist (and certainly not a seer). He cannot predict how many dollars of research funding, spent in what way, would prove, after several decades, to have been the wisest investment. He can only express a personal opinion about the most pressing research priorities, and a guess about cost-efficiency. Still, in the course of preparing this collaborative essay, both the editors and authors repeatedly encountered the same knowledge gaps. We do not understand the pathophysiology of CBI beyond the limited domains of inquiry that have been studied (primarily, cerebral blood flow and metabolic changes, readily assayed chemical changes, and currently familiar light microscopic changes) nor beyond the early stage of the process. We do not know the natural history of CBI in any species. We do not understand why outcomes from seemingly identical injuries vary greatly. We have virtually no disease-modifying therapies. And – potentially a matter of urgency given the global aging of the human species – we are only beginning to understand the relationship between CBI and neurodegeneration and how to intervene so that a teenaged CBI victim has a reduced risk from that lifetime sword of Damocles. Filling those knowledge gaps is probably necessary to reduce the accelerating harm that CBI is doing to societies.

Basic Research

Two methodological issues deserve attention. First, as laboratory rodents age, they exhibit little of the deposition of pathological proteins most associated with human neurodegeneration: β-amyloid, hyperphosphorylated tau, and α-synuclein. Transgenic animals have helped overcome this barrier. Such animals have been widely used for more than a decade in basic Alzheimer's disease (AD) and Parkinson's disease research [45–51]. One especially useful model is the 3xTg-AD mouse, which expresses both amyloid precursor protein and tau. And since APOE genotype moderates the human brain's response to injury, the availability of APOE-ε4 transgenic rodents can facilitate modeling of gene–environment interaction [52]. In fact, since 1999 several TBI studies have employed transgenic animals capable of modeling neurodegeneration in TBI research – including a 3xTg-AD experiment [53–55]. If the goal is to determine the relationship between CBI and brain aging or neurodegeneration, the time has perhaps come to say, "Please employ appropriate transgenic models. Do not sacrifice the wrong animal to little purpose."

A second methodological issue: controversy exists about the ideal apparatus for experimental TBI. This issue will be further discussed in Chapters 1 and 2. By far the most popular laboratory tactic has been the fluid percussion injury model, in which a piece of a rodent's skull is removed so that the concussive blow is applied directly to the brain or dura. Yet observers of TBI for almost 1000 years have pointed out that the essence of this injury is force transmitted through – and presumably diffused by – the skull. At the risk of alienating superb local colleagues whose fluid percussion injury work has provided exceptional insights, the present author would ask for experimentalists to review the validity of conclusions made regarding creatures with skulls based on studying creatures without skulls.

Despite literally thousands of publications reporting experimental concussion, primarily using rodents as subjects, it is astonishing that so few laboratories follow their subjects for more than a month. Perhaps this disabling research weakness derives from the old assumption that the effects of CBI are transient. Now that most biologists are aware of evidence suggesting a risk of lasting or permanent brain damage, we need skillful investigators to discover the natural history of CBI. That means subjecting animals to graded injuries and assessing outcomes throughout the remainder of their lives. Without such longitudinal information, it is impossible to determine: (1) the spectrum (which seems to be broad) of natural histories after a given impact; (2) how single or repetitive CBIs interact with aging and environment to effect neurodegeneration; or (3) what interventions, if any, mitigate that effect. The author strongly urges neurobiologists to consider under what circumstances short-term outcome studies justify animal sacrifice. Yes, housing and studying rodents for two to four years is expensive. Yet the most compelling CBI question for human societies seems to be: what are the long-term effects? The importance of answering this question requires a new focus on life course outcome studies.

Translational Research: The Hope for Biomarkers

The most compelling single research gap, in the opinion of many TBI authorities, is that no biomarker exists for TBI. Unless injuries are visible on scalp examination or with neuroimaging, we cannot even conclude whether the head was struck. A biomarker could "mark" many aspects of a particular case of CBI, from confirming that a force impacted the patient's brain to determining the occurrence and amount of neuronal death to predicting functional outcome. Forensic stakeholders are naturally eager for a marker of severity. Table 3 lists several candidates [56–62].

With regard to biomarkers, readers must be wary. For instance, in February of 2018 the U.S. Food and Drug Administration (FDA) announced with considerable fanfare its approval of a two-element commercial blood test for "concussion" [63]. It is nothing of the sort. The approved test analyzes blood levels of ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein drawn shortly after a traumatic exposure. Research (not yet published as this volume goes to press) purportedly found that elevations of these markers were 99.5% sensitive for CT scan positivity – that is, visible "lesions." If replicated, that would make the test truly valuable for detecting the 1% of patients most likely to have such imaging findings – an advance in emergency assessment protocols that might spare many patients' exposure to radiation. Yet a typical clinically attended CBI, by definition, shows no gross bleeding on CT. Typical CBIs, in fact, rarely trigger these biomarker elevations, making the test virtually useless for the diagnosis of concussion.

Table 3 Candidate blood biomarkers for concussive brain injury

Neuronal/axonal markers
Neuron-specific enolase (NSE)
Ubiquitin c-terminal hydrolase (UCH-L1)
Alphall-spectrin breakdown products (SBDPs)
Hyperphosphorylated neurofilaments-heavy (NF-H)
Serum neurofilament-light protein (NF-L)
Glial markers
S100 beta (S100β)
Glial fibrillary acidic protein (GFAP)
Myelin basic protein (MBP)
Growth factors
Brain-derived neurotrophic factor (BDNF)
Nerve growth factor (NGF)
Transforming growth factor-beta (TGF-β)
Inflammatory markers
Interleukins (IL-) 1, 6, 8, 10, 12
Interferon-gamma(IFN-γ)
Tumor necrosis factor(TNF)-α
Kallikrein-6 (Klk6)
Soluble Fas (sFAS); soluble vascular adhesion molecule (sVCAM-1); soluble intracellular adhesion molecule (sICAM-1)
Genomic biomarkers
APOE-ε4
Val^{158}Met polymorphism in COMT gene
5HT transporter 5-HTTLPR gene polymorphisms
Others
Heart-fatty acidic binding protein (H-FABP)
Creatine kinase BB
Soluble cellular prion protein (PrPC)
Cortisol
Cleaved tau
Micro-RNAs (e.g., microRNA let-7i)

Note that Table 3 excludes cerebrospinal fluid markers as well as a host of alternatives, including structural and functional neuroimaging markers (e.g., diffusion tensor imaging, or proton magnetic resonance spectroscopy), electrophysiological markers (e.g., event-related potentials, eye movement analysis, and postural stability measures.

Yet is it realistic to expect a single measure of harm in a neurological condition that reportedly up- and down-regulates ~1000 genes in a matter of minutes? One can certainly settle on arbitrary operational differentiations. For example, some authorities have urged a dichotomy between "uncomplicated" concussion (with a normal CT scan) and "complicated" concussion (with CT abnormalities). Yet the phrase "CT abnormalities" includes such a wide range of radiological findings (e.g., atrophy, ventriculomegaly, calcification, hemorrhage, dysgenesis) that it hardly distinguishes any physiopathological subtype. There might be a little practical value in discriminating between concussions with and without intracranial bleeding. But – apart from providing attorneys with a simplistic classification – it is not clear how patients benefit from testing whether one aspect of their unique and complex findings fits some such arbitrary metric of "severity." Clinicians could surely eschew this kind of actuarial rhetoric, as we do with pneumonia, and just describe what's wrong. The Glasgow Coma Scale was not intended to measure injury severity but to assist clinicians in tracking changes in consciousness. One would rather know what happened to the patient, her vital signs, what she can do now, and whether she might profit from a neurosurgical intervention than know some intern's one-word title for the severity of her injury.

Indeed, can one ordinally rank the severity of ten injuries if each injury alters neurobiology in many ways, resulting in complex and individually unique profiles, such that if we assay five, or ten, or 100 chemicals or cognitive functions, every patient's brain exhibits its private Himalaya of peaks and valleys? The brain does more than one thing. It is not a liver, kidney, or thyroid. We seem unlikely to find any single clinically meaningful cerebral equivalent of a thyroid-stimulating hormone level. Moreover, new facets of basic cell biology are still being (and will forever be) unearthed. To what degree is the harmful effect of CBI due to entatic heme ligation changes in cytochrome c due to dissociation of the Met80 ligand from this "respiratory" protein, converting it to an apoptosis-enabling peroxidase? If a scholar cannot answer that question, why would he or she claim to understand concussion? Basic research suggests that we are just beginning to discover the vast number of neurobiological changes common at various time points after a CBI.

Given this conundrum, no single biomarker is likely to satisfy. The biotech companies currently racing for the golden apple will not find it.

Instead, one anticipates the discovery of multiple markers that assay various aspects of injury that may be somewhat dissociable in duration and degree, for instance, CBF changes, metabolic changes, transmission dysfunction, mitochondrial dysfunction, generation of reactive oxygen species, axonal dysfunction and connectivity changes, circuit compromise, inflammation, apoptosis, reactive gliosis, and cell death, all predicting any number of dissociable clinical outcome variables from somatic distress to cognitive deficits to psychiatric problems to late degenerative change. As Kobeissy et al. put the issue, "Many studies suggest that because of the brain's complexity and the heterogeneous nature of brain injury, the measurement of a single biomarker cannot be used to assess TBI evaluation such as diagnosis, prognosis, and management" ([55],p. S103).

So yes, we need biomarkers. Several are promising. But it remains to be seen whether any single chemical measure will reveal the health of a brain better than any single chemical test would reveal the health of an ocean.

Clinical Research to Determine the Risk Factors of Worse Outcome and Traumatic Encephalopathy, and the Modifiable Factors That Protect the Brain

We really must determine the outcomes of CBI. Whether or not one embraces the current concepts of *post-concussive syndrome* or *traumatic encephalopathy*, we need to know who is at the highest risk for distressing or disabling outcomes that persist and for later neurodegeneration. We really need to know who among our children may be at elevated risk. Let's say our research firmly established that a girl who suffered a single concussion playing soccer at age 11 would then have a 17% higher risk of lifetime depression and 1.4 times the normal risk of being demented when she reached age 75. However, if she developed hypertension and it was not properly treated, she'd have a 40% higher risk of depression and 2.8 times the risk of dementia. And if her genotype included one or two APOEε4 alleles, suffering that CBI would make her 16% less likely to graduate from college, 24% more likely to attempt suicide, 42% more likely to divorce, and have 4.7 times the risk of early-onset dementia. On the other hand, if she takes five days of cognitive rest immediately after her injury, or if she exercises in middle age, or if she takes fish oil after menopause, her dementia risk falls significantly toward normal. Might she, her parents, or her pediatrician want to know these things? Might that knowledge influence some life choices, either on the day of soccer sign-ups or later?

These figures are plucked from the air. The author has no way to know if they are too high or too low, or if these putative risk and protective factors will turn out to be important. Nobody does.

The self-evident first step is to launch a multicenter, population-based, prospective long-term longitudinal study. In other words: get to know a large number of young people before CBI. Follow them for the rest of their lives. Determine whether experiencing one or more CBIs has any effect, and whether some people are more vulnerable than others, and whether life choices such as education, the Mediterranean diet, or aerobic exercise might mitigate their risk. This is the one research design that offers a reasonable hope of answering our many questions about cause and effect, and mediating and moderating factors, in scientifically rigorous way.

The Framingham Heart Study [64] – the world's great wellspring of discovery about the natural history of cardiovascular disease, a joint project of the National Heart, Lung, and Blood Institute and Boston University that began in 1948 – was a superb model. Hans-Lukas Teuber urged NINDS to launch a Framingham-like CBI project in 1968 [6]. The present author publicly implored NIH to do the same in 2013. Instead, they cut funding for the Framingham by 40%.

Although no authentic population-based prospective longitudinal study has yet to be funded, at least three exceptionally promising large-scale long-term initiatives are finally under way. One is called "A National Study on the Effects of Concussion in Collegiate Athletes and US Military Service Academy Members: The NCAA–DoD Concussion Assessment, Research and Education (CARE) Consortium" [65]. The second is the NINDS-funded multicenter TRACK-TBI study [66]. Both of these studies include an element of longitudinal follow-up. The third study is called the "Chronic Effects of Neurotrauma Consortium (CENC) multi-centre observational study" [67]. Although this last study is limited to military subjects and will be skewed by a focus on blast injuries, it is the sole prospective longitudinal initiative. The availability of substantial pre-morbid health data makes this 25-year project unique: the investigators will be able to assess injury-related change. All three studies will hopefully yield significant, even fundamental, advances.

In the meantime, even though cross-sectional studies are infuriatingly feebler, a well-designed study of older adults would be a low-risk, high-pay-off investment. Say we recruit 5000 65-year-olds with an unambiguous medical record of CBI and 5000 without. One might compare the two cohorts in any number of ways: neuropsychological testing, psychiatric assessment, neuroimaging, other biomarkers. In fact, we are rapidly approaching the point of having simple tests that detect early-warning signs of neurodegeneration. A big enough sample would allow us control for all manner of potential confounding variables, from contentment on the job to APOE genotype to waist size. Compared with the small-scale preliminary work that's been funded to date, even a study as cheap and dirty as this would be absolutely revelatory.

For these reasons, forgive the redundancy, but the present author must implore those with the resources to step forward. CBI has no angel. It needs one quite desperately. Pending the arrival of our angel – the funder who will some day appear on a spirited Palomino to actualize the first and only high-quality long-term prospective longitudinal studies of concussion employing valid biomarkers in human history – every authority is free to guess what that research will reveal. To guess at the unknown is an irresistible human need. But we uncompromisingly eschew the popular practice of publishing guesses masquerading as knowledge.