Concussion and Traumatic Encephalopathy

Causes, Diagnosis, and Management

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To the young, who – wide of eye and pure of heart – count on us to know the good.

Contents

The color plates are found between pages 682 and 683.

Guiding Apophthegm

Samuel Clemens, Jeff Victoroff and Erin D. Bigler

When in doubt, tell the truth.

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Preface

Jeff Victoroff

Traumatic brain injury (TBI) is the leading cause of death and disability in people younger than age 45 in the United States … most TBIs are mild.

Nguyen et al., 2016, p. 774 [1]

Typical, clinically attended concussive brain injuries often lead to persistent deleterious brain change. Contrary to the guesses of writers from previous centuries, according to the best analysis of the best empirical evidence, more than 40% of survivors of such concussions still suffer from and/or exhibit neurobehavioral deficits at one year or more post-injury. That fact has global implications for human health.

It is not clear at what moment in history that fact became apparent to the scholarly community. It is not clear to whom credit belongs for that startling observation. In fact, rather than a eureka moment followed by proclamation and universal acclaim, the discovery that typical concussions commonly lead to lasting cerebral dysfunction was initially received with blinking dubiety and even stiff-necked resistance. Thankfully (if somewhat belatedly), the world's neurological community has shaken off the dogged dogma of the 20th century and attended with steadily improving observations and steadily increasing alarm to the empirical evidence that concussions are highly heterogeneous and not reliably benign. That is a paradigm shift.

A concussion is a rattling blow or earthquake-like shaking. To discuss such a blow and its possible effects, one is obliged to specify what is concussed. Sometimes, it is the brain. Sometimes, the blow causes injury. When that occurs, the logical specifier is *concussive brain injury* (CBI). The subject of this book, therefore, is CBI.

CBI is not "mild traumatic brain injury (mTBI)." CBI is not mild anything. It means what it says – comprising the spectrum of brain injuries attributable to inopportune visitation by an abrupt external force that, usually, strikes the hair of the head and causes harm. CBI is the most common type of mammalian TBI. Most mammalian CBIs pass without notice or report, which limits our knowledge to a subset. Those are the typical, clinically attended CBIs that account for about 90% of human emergency room visits after head trauma. Athletic trainers, combat medics, and primary care providers also attend such injuries. Confessing from the outset that one can say little about the huge domain of unreported CBI, one does one's best with the limited available data. The editors of this book feel animated by the thrill of discovery, humbled by the enormity of the problem, and passionate about figuring things out based on first principles. We pledge to do our best.

Many millions of youth in the current generation will suffer CBIs. However, they will be members of the first generation in history to grow up in the new era – an era of scientific revolution about the real effects of blows to the head. This volume is intended to be the first comprehensive textbook of the new era.

Despite centuries of study, some of the most basic questions about CBI remain as opaque as sacred mysteries. What exactly happens in the head? Is that the same from brain to brain? What proportion of concussion survivors suffer brain changes for what time duration, and why them? What does "recovery" mean? Does adaptation to injury carry a hidden cost? Can one CBI cause permanent harm? Is that commonplace or rare? Do one or more CBIs accelerate brain aging, or trigger conventional neurodegeneration, or cause a unique post-concussive dementia? In every concussion survivor or just a few? And what on earth can we do to mitigate the harm of this globally endemic disorder?

Readers are in for a feast. Although our ignorance remains profound and our capacity to intervene remains primitive, a cornucopia of new data and revised conceptualization has grandly enriched the scholarly banquet in just the last ten years. A host of heroic efforts by devoted clinicians and scholars deserves credit for overthrowing the more egregious fallacies of the 20th century. Neuroscientists have graduated from the old "cascade" hypothesis, replacing that thin-slice pathophysiology with a meatier framework that recognizes the interdigitation of force, genetics, and pre-morbid status in a dramatic brain-wide post-concussive melee between scores of degenerative and regenerative factors. Neuroimagers have soundly trounced the "Three-Month Myth," according to which a previous generation of scholars imagined concussion to be self-limited in the overwhelming majority of cases. Neurologists, physiatrists,

and psychiatrists have flung aside the straightjacket of clinical homogenization, recognizing that concussion does not do any one thing, or any five things, but has as many presentations and courses as there are genomes. Neuropsychologists, having discovered that paper-and-pencil tests from the 1960s are invalid and insensitive to the effects of CBI, are boldly reinventing their field, dismissing the localizationist fallacy and seeking concordance with the revelations of functional neuroimaging. Neuropathologists have courageously bucked resistance to follow the trail of breadcrumbs back from degenerate brains to repetitive CBIs. Public policy is finally beginning to be informed by concussion science. This textbook – perhaps better called a brief collaborative essay – summarizes the state of the art and attempts, in so far as possible, to anticipate the trajectory of discovery.

What's New?

In-depth epidemiological analysis suggests a much higher incidence of clinically significant CBI than was previously appreciated (see Chapter 2). Critical investigation exposes the dubious validity of much animal research (Chapter 4). Systematic review reveals a much higher than previously recognized rate of persistent post-concussive distress and dysfunction. Moreover, for the first time, biomarkers support the conclusion that prolonged post-concussive psychiatric symptoms must be associated with organic brain damage (Chapters 5 and 10). We need, and do not have, a neuroimaging marker of CBI. That may change shortly, as we adopt machines that permit us to watch a single protein fold (Chapter 6). Recent data show why outcome research will remain mired in fallacy pending adoption of genetic, epistatic, and epigenetic stratification, and why treatments will remain randomly effective pending the discovery of biomarkers with individual predictive validity (Chapter 7). Intriguing evidence suggests that smoked marijuana is the most effective treatment for post-concussive irritability and aggression. The U.S. federal government, however, willfully blocks the urgently needed research (Chapter 10). Neuroscientific advances have overthrown dated theories of aging-related brain change and informed a dramatically new approach to studying the late effects of CBIs, mandating a profound rethinking of "traumatic encephalopathy" (Chapters 11, 13, and 14). As of 2018, for the first time in history, the U.S. Food and Drug Administration has approved a biomarker panel for computed tomography (CT)-positive traumatic brain injury. It is absolutely not a concussion test (Chapter 17). Although research has been heartbreakingly slow to discover efficacious interventions, management of concussed people is beginning to rest on science (Chapters 20, 23, 24–27). Some concussions trigger legal disputes. It is hard for an honest doctor to serve justice in an adversarial system: shadows haunt the cavern where paid experts covene. But federal Rule of Evidence 706 is quietly swinging a light at the edge of that dark place (Chapter 28).

Many survivors of typical, clinically attended concussions feel fine after a week – especially in cases of sport-related concussion. Yet a large proportion of concussion survivors continue to suffer or display neurobehavioral problems for many months or years. Why? In so far as the present parlous state of the science permits, this slender volume has the answer. Readers will be provided with abundant evidence – much of it very recent – that supports what is arguably the first major reconceptualization of concussion in more than a century.

For instance, previous generations conceived of concussion as a transient event and took "recovery" for granted. How would one ever know? Subjective recovery is, of course, highly desirable. So is functional recovery. Neither of these, however, is either reliably measurable or a marker for normalization of brain function. Nor is return of neurofilament light levels to baseline [2]. Nor is the statement, "I'm fine." At the time of this writing, true and complete brain recovery after a typical clinically attended CBI has yet to be demonstrated. Instead of attempting to assess brain recovery – meaning restoration to pre-morbid status with no risk of late effects – most of the old literature discussed results from superficial desktop behavioral assessments or from insensitive bioassays – such as autopsy. Science long ago transcended the assumption of neuropathological omniscience. Although subjecting fragments of dead tissue to chemical manipulations and looking at them was an exciting innovation 125 years ago, the resulting *a posteriori* inferences about the orchestrated dynamic interactions of the ~16 billion adult cortical neurons of at least 17 types [3] are speculative, not probative. One *hopes* that human brains (or some) have the capacity to fully recover after CBI. But, surprising as it may seem, in regard to authentic recovery with no late effects, the jury is out. That recent realization has made CBI a legitimate suspect in the premature aging of tens of millions of brains and galvanized the international quest for better answers.

Although some critical questions remain intractable to the best science, others have recently yielded to the muscular levers of scholarship and technology. Readers will learn, for example:

- why there is a striking mismatch between subjective recovery and biological recovery
- why outcomes vary
- why conventional neuropsychological testing fails to detect indisputable brain dysfunction
- why, despite the supposed protective effects of estrogen, menstruating women are at greater risk for lasting harm
- why "post-concussion syndrome" has been abandoned as a clinical entity
- why determining the late effects of concussion has frustrated neuroscience for more than a century – and how that problem may soon be solved
- why *chronic traumatic encephalopathy* is an extremely common human condition, although a recent academic shanghaiing of that phrase focused attention on a narrowly characterized, dubiously unitary subset of cases
- what evidence-based practices are most likely to help a concussed person in the emergency room – and after.

This is a story about knights, and a few knaves, and a fight to bring scientific rigor to a field long beclouded by lore and sacred cows. The editors submit this text to readers with high hopes

and earnest caveats. Textbooks usually explain and support the status quo. In good conscience, we cannot. Dr. Bigler and I, by evolutionary convergence or serendipity, arrived at pretty much the same conclusion at the same time: the barrier to understanding the immense spectrum of human consequences of CBI was not merely the antiquated 20th-century prejudice that dismissed patients with long-term complaints, not only the frugality of funding agencies and the resulting poverty of data, but something deeper: a systematic misunderstanding of health and neurobehavioral dysfunction that seems to have arrested the development of this field for about two generations. We felt compelled to start fresh – to unfetter the narrative from the tyranny of dated terms of art and seek a straightforward, logical, semantically coherent, scientifically muscular conceptual framework loyal to the commands of the data.

We know our earnest wish to just make sense may trigger cognitive dissonance in some readers. Students may become disoriented. Professors whom we call friends may regret their hearty lunches. And, in the end, overthrowing the illogic of 20th-century neurological nosology may prove impossible – leaving our account a historical outlier. Nonetheless, we both feel ethically compelled to do our darndest, informed by our rustic faith in first principles. The stakes are enormous. We dearly hope that – after an awkward period of outrage and adjustment – the result is human benefit.

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Acknowledgments

First and foremost, I thank my patients who survived concussive brain injuries (CBIs). They shared their life stories, thoughts, and feelings. It was not my professors, not my textbooks, not the grand libraries whose stacks I've haunted that alerted me to the gravity of CBI as a human problem. In fact, those didactic sources delayed insight, because, until very recently, the most ravenous scholar would starve looking for impartial and open-minded academic accounts explaining concussion. There are many reasons we can now share the revelations of the last decade or so. In my own case, the first glimmerings of awareness came in the clinic. Repeated, artless, forthright stories of long-term problems after so-called "mild" injuries finally rang a bell in my own head. I am embarrassed that it took so long before I reached astonishment at the mismatch between textbook minimization of the problem and the troubling human truth. The candor and eloquence of concussion survivors set off the alarm that propelled me from complacence to passionate commitment.

Second, I cherish the collaboration, counsel, support, and friendship of Erin D. Bigler. Readers already know Erin is a towering figure – a neuropsychologist whose empirical and theoretical contributions to the understanding of CBI are legendary. His brilliance, depth of thought, work ethic, and innumerable accomplishments are widely familiar and authentically awe-inspiring. None of that explains our friendship. Those who have been privileged to know him know his most precious quality: Erin is a good man. Outsiders might imagine medicine and psychology to attract thoughtful, wise, and compassionate people. They do. But there is a high ceiling and a low floor. In more than 30 years in academic neurobehavioral practice I have never encountered another professor whose gift of virtue – wholehearted devotion to doing what is right – matches Dr. Bigler's.

Third, I must express the deepest regard for our co-authors. If they did not know what they were getting into from the outset of our collaborative essay project, they gradually came to realize that the editors were shooting for the moon. Erin and I, by evolutionary convergence or serendipity, arrived at pretty much the same conclusion at the same time: the problem with truly understanding the human consequences of CBI transcended the combined effects of low-quality research and puritanical suspicion of patients with persistent distress. The problem seems to have been a widespread failure of imagination, such that symptoms that could not be explained by then-available technology were reflexively attributed to psychogenic illness. Asking our co-authors to rethink the problem from first principles was an outrageous imposition. Academics get no credit for book chapters. Our co-authors, therefore, not only volunteered to beautifully summarize their expert knowledge, but to question the very roots of that knowledge – *pro bono*. They more than ably rose to that challenge, transcending the duties of scholarship and, when required, braving the risk of criticism for daring to doubt the received wisdom. We are most warmly appreciative of their special effort.

Fourth, I must somehow credit the giants upon whose shoulders we humbly stand, without writing a list as long and considerate of history as the *Mahābhārata*. Two inspirations from the mid 20th century were the neurologist Cyril Courville and the psychologist Hans-Lukas Teuber. Both cried out like voices in the wilderness, urging deeper thought about traumatic brain injuries. More recent figures, sure to become historical, are neurologist Barry D. Jordan (one of our co-authors) and neuropathologist Bennet Ifeakandu Omalu – both heroes for following the data in the face of contention. Journalist Alan Schwarz (a finalist for the Pulitzer Prize in public service) deserves credit for exposing the despicable behavior of the National Football League on the front page of the *New York Times* – an initiative that hugely raised public consciousness of the dangers of repetitive concussions. In the same vein, Peter Landesman is owed credit for multiplying global awareness of the problem, writing and directing the 2015 film *Concussion*. A team of prolific and indefatigable scholars at Boston University will go down in history for taking the sport-related concussions ball and running with it – energetically exploring the hypothesis that repetitive CBIs sometimes cause a special and tragic spectrum of brain changes. Just two members of that deep team are neuropsychologist Robert Stern and neuropathologist Ann McKee. Kevin Guskiewicz, another of our co-authors, is a sports medicine scientist who, for more than two decades, has played a keystone role in advancing the understanding of sport-related CBI. Yet another of our co-authors, Christopher C. Giza, along with his colleague David A. Hovda, revolutionized the understanding of why trauma can become a crisis for a neuron. That work, synthesized with complementary findings regarding inflammation, molecular genetics, protein conformation, and the

connectome, buttresses almost every effort to find an effective early intervention.

These and many other bold individuals have literally fought to get out the truth in the face of tremendous disciplinary and institutional resistance. Not everyone wants it to be known that typical concussions commonly lead to long-term (and possibly permanent) brain damage. This brief collaborative essay may conceivably be regarded as the introduction of a paradigm shift. At the least, it is a heartfelt plea for a long-overdue revolution. It is past time to overthrow the untenable assumptions and insupportable prejudices of 20th-century concussion writing in favor of science, untrammeled by dogma. Our new conceptualization hardly arose *de novo* like an island from a volcano. It is merely the inevitable accretion and synthesis of thousands of novel, careful, open-minded empirical investigations. The original investigators are the soul of today's revolution. The list, really, goes back to Hippocrates – and will hopefully go forward to include a few of our readers.

Finally, we gratefully honor the contributions of Kaylee L. Valverde, Susan Wheatley, and JoAnn Petrie, Ph.D. Erin and I are old guys. We are eager to keep up with neurobiology and imaging technologies, but our understanding of clerical technology peaked with the IBM Selectric. To make this book happen, we turned to experts. These authorities mastered EndNote and other digital magic that has (according to early reports) facilitated coherent scientific documentation. Their energetic and thoughtful support enabled us to deliver a text enhanced with citations and figures that credit our sources and offer our readers direct access to data that will hopefully benefit humanity for generations to come.

Jeff Victoroff

The first acknowledgment goes to patients and research participants who have sustained a concussive brain injury (CBI). They are the inspiration behind all of my research and clinical work with traumatic brain injury (TBI). It was 1975 when I conducted my first neuropsychological exam of a pre-teen with a history of concussion, who was experiencing persisting symptoms. Understanding concussion from a mid-20th-century perspective emphasized its benign nature and inconsequentiality. So why was this child still having problems? Computed axial tomograms or CAT scans – the original acronym – had just been introduced as an initial triage assessment for "closed head injury," as it was referred to then. By today's standards the original CAT scans were laboriously slow and the images based on enormous voxel sizes, as large as a cubic centimeter. Nonetheless it was incredibly exciting to be able to visualize the brain in the living patient, regardless of how crude the image might be.

As reflected in the medical records, the first child I saw had been hit by a car while riding his bike, experienced a brief loss of consciousness as witnessed by family members, but this child had a negative CAT scan and routine skull films when evaluated in the emergency department. Note this was before the universal adoption of the Glasgow Coma Scale (GCS) rating system, so there was no GCS recorded. The child was observed overnight and then discharged. I did not see the child until several months post-injury when there were issues of poor concentration, attention, and memory, particularly notable in terms of diminished academic performance at school, along with what the parents reported as moodiness, poor impulse control, and impulsivity. None of these symptoms/problems had been observed before the injury, but he was also a pre-teen and pubescent. Neuropsychological tests reflected relatively intact cognitive performance and, given the conventional clinical wisdom of the day, as already stated, it was just assumed that over time things would be OK.

While true that the majority of cases of CBI do seem to run a "benign" course, the fact that I was seeing cases with persisting symptoms/problems, as above, was troubling. Animal models of CBI were being developed showing more definitive neuropathology – the brain was being injured, detectable at the microscopic level, even with so-called "mild" injury, but not necessarily at the behavioral level. Then in the 1980s, magnetic resonance imaging (MRI) rapidly ascended as the neuroimaging choice for examining the chronic effects of TBI. I remember a CBI case that had a negative CT scan yet when the original proton density MRI sequence was run, this patient's scan showed multiple scattered "hypointense" foci. As we now know, these abnormalities reflect petechial hemorrhages from shear injury, eventually shown to be hemosiderin deposition.

This was a remarkable discovery, because now there was something "objective" to relate to the symptoms/complaints of the CBI patient. Neuroimaging techniques and technologies to investigate CBI improved steadily and dramatically during the end of the 20th and beginning of the 21st century.

In 1975 I also started teaching psychology and neuroscience courses. On all of my syllabi I had Albert Einstein's famous quote of "looking deep into nature, and then you will understand everything better." But in the 1980s I also started including the following statement, credited to Jeremiah Ostriker, a physicist who championed the theory of dark matter: "In young scientific fields if you say all the accepted positions are wrong, you'll seldom be wrong." Now this was a hard, physical science professor speaking about physics and astronomy, referring to them as still being "young." The first international societies involving neuroscience and neuropsychology were being established at about this same time frame – early 1970s. So, if one rejects the prevailing theory, especially in "young" fields – using Ostriker's axiom – one would likely not be wrong.

With the rapidly improving new advances in neuroimaging we now had hard evidence that, at least some individuals who sustained CBI had demonstrable, underlying evidence of physical neuropathology. This began the quest for examining neuroimaging correlates of CBI and listening to what patients were saying about symptoms/problems they were experiencing.

It also became evident to me that, while neuroimaging technology was improving at an incredibly rapid pace, neuropsychology was not. Neuroscience likewise was exponentially adding new discoveries, especially in the interface of cognitive neuroscience with neuroimaging. One of the neuroscience textbooks I used was titled *The Neuron: Cell and Molecular Biology*. In the preface to the third edition, I.B. Levitan and L.K. Kaczmarek

lament the fact that statements in the first two editions were "completely inaccurate." They go on to explain:

It is not that we are acknowledging any major errors of scientific fact in the past editions (although time will certainly show that some of what we now believe about the functioning of the brain is wrong). Rather, the arrival of a new millennium has made nonsense of most of the statements that began "Earlier in this century" [1, p. vii].

All of this became my mantra for exploring CBI. Look deep into nature, reject prevailing theories because they are likely incorrect, embrace new technology and insights that will guide discovery, and establish an improved scientific foundation for the effects of CBI. These views have guided not only my research and clinical work, but also the vision of this book.

I still have my notes from those beginning lectures involved in teaching clinical neuropsychology. What is troubling is that the core aspects of traditional assessment in neuropsychology have not changed in 50 years – the training lecture I gave in 1975 could be given today, basically unaltered. Yes, we have the fourth or fifth edition of a particular test now, but the foundations of that test have not changed. In this 21st-century, information explosion world we now live in, the neuropsychology of concussion has been stagnant, mostly tied to traditional clinical assessment measures that have not advanced the field. Past neuropsychological approaches to understanding CBI have been mostly frozen by its restricted use of conventional techniques. As such, this book rejects many past and prevailing thoughts about CBI that have come out of neuropsychology. It does so because to move a field beyond conventional thought means that those concepts need to be challenged. What is written about in this text provides numerous opportunities for establishing new, testable hypotheses about CBI. We may be entirely wrong about some of what we say about CBI – if so, demonstrate it with the appropriate research study and design, and prove us wrong.

I thank Dr. Victoroff for approaching me to collaborate with him on this project. We had kindred ideas about CBI that we have brought out in this text.

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Reference

1. Levitan IB, Kaczmarek LK. *The Neuron: Cell and Molecular Biology,* 3rd edn. Oxford: Oxford University Press, 2002.