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Abstract Approved: _____
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Affecting an estimated 1.7 million people annually, traumatic brain injury has been labeled a major public health threat. As the leading cause of death and disability in young people, and the signature wound of the wars in Iraq and Afghanistan, the issue is drawing increased media attention. Analyses begin by addressing the relevance of TBI in the context of recent news coverage, followed by the necessity of new TBI research. The aim of the project is to pinpoint means for improving care for patients with TBI. Opinions on expected research trajectories were collected from a series of guided interviews. Interviews prompted and explored the concerns and suggestions of prominent local medical professionals who routinely treat TBI patients. Interviews were interlaced with recently published peer reviewed journal information and related media highlights in a type of modernized literature review. Qualitative data was organized into themes focused on improving public education, diagnosis and treatment/long term outcome predictors for individuals who have sustained TBI. Results point towards areas in need of increased attention and understanding.

Key Words: traumatic brain injury, research, concussion
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Exploring New Avenues of Public Education, Diagnosis and Treatment for Traumatic Brain Injury: Compiling Professional Opinions

By

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I understand that my project will become part of the permanent collection of Oregon State University, University Honors College. My signature below authorizes release of my project to any reader upon request.

Taylor M. Nowlin, Author

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This thesis is dedicated to the full and happy recovery of my good friend Jenna Steele, your perseverance is my inspiration.

Exploring New Avenues of Public Education, Diagnosis and Treatment for Traumatic Brain Injury: Compiling Professional Opinions

Introduction

Once one of the Pittsburgh Steelers' greatest football heroes, Mike Webster retired from the game after 17 years a different man. Severe dementia crippled 6' 1" "Iron Mike", and he saw his business fail and marriage unravel in the chaos and confusion that ensued. Mike Webster's life ended at age 50, but his story was not forgotten. Webster's legacy began a chain of events in the early 2000's that secured the link between football and dementia [10].

In 2011, Dave Duerson, former safety for the Chicago Bears left a note reading, "Please, see that my brain is given to the NFL's brain bank" before ending his own life [32]. Webster and Duerson are among thousands of retired football players, deceased and living, suffering from serious neurological conditions as a direct result of repetitive concussions sustained during their professional careers. The 2013 Frontline Documentary, 'League of Denial: The NFL's Concussion Crisis' tackles the ongoing battle between former players and their families against the National Football League in accountability for this disturbing trend. Studies showing overwhelmingly high death rates from Alzheimer's, Parkinson's and Lou Gehrig's disease, and Chronic Traumatic Encephalopathy (CTE) in former ball players like Mr. Duerson frame the argument for NFL liability [10]. Though still requiring a judge's approval, the NFL has agreed to pay $765 million in settlements to the aggrieved.

At the high school and collegiate levels, it has been estimated that 300,000 sport related traumatic brain injuries (TBIs) are sustained each year in the United States [12].

Second to motor vehicle crashes, sport-related injuries are the second leading cause of traumatic brain injury among people aged 15 to 24 years [12]. The notorious “high-risk” sports include hockey, football, wrestling and boxing, but thousands of annual emergency department visits result from basketball, soccer, and cycling. For young athletes in contact sports, the likelihood of experiencing a concussion in a given season may be as high as 19% [37]. For athletes who have already sustained concussions, further head injuries are not only more likely to occur, but associated with greater risk of long-term consequences. As high school and collegiate sport participation increases, greater numbers of student athletes will likely join the so-called “concussion crisis” [12].

In the last decade, an epidemic of disability and dementia as a result of head trauma has unfolded on the battlefield. Soldiers returning from Iraq and Afghanistan are arriving stateside with lingering problems caused by exposure to multiple blasts. Since 2000, there have been over 300,000 medical diagnosis of TBI in the U.S military [7]. Early on the culture of the military, similar to the NFL, was to “shake it off”, but as increasing numbers of young veterans returned home with significant memory impairments and other debilitating issues, this view shifted. For many veterans, a lack of visible physical injury and delayed onset of symptoms mask accurate diagnosis. “TBI has been referred to as a silent epidemic because the major post-TBI disabilities and neuropsychiatric problems are often not immediately apparent” [8]. Insurgent made improvised explosive devices (IEDs) are often responsible for these injuries, caused by damaging atmospheric pressure waves. The full pathological effects of these reverberations through the human body are not well understood.

Famed sports-figures have familiarized many Americans with the dangers of trauma-induced concussions and blast injuries are considered the signature wound of the wars in Iraq and Afghanistan. But beneath the headlines of NFL football players and war veterans lay deeper issues. These short narratives are pages from a longer story that involves a larger population. Traumatic brain injury, defined as a disturbance in brain function following a jolt or blow to the head, has been labeled a major public health threat by the National Institutes of Health [30]. An estimated 1.7 million people sustain traumatic brain injuries annually, ranging in scope from mild to severe [3]. The serious consequences of this epidemic cannot be overstated. TBI accounts for 50,000 deaths and 275,000 hospitalizations each year [3]. Highlighting the importance of prevention and treatment for TBI is the risk for long-term disability. The Centers for Disease Control and Prevention (CDC) estimates that 2% of the U.S population is living with disabilities caused by TBI [3]. Because half of all TBI events occur in people of working age, these disabilities have a high economic cost [3]. Recent estimates place that price tag at around $76.5 billion annually [3].

Exactly how serious these injuries are is only beginning to be fully understood. The brain is the most complicated organ, acting as a central control center where experiences, memories, and thoughts are stored, sorted, and processed. It governs the function of autonomic nervous system, language and social skills, along with personality, sense of self, perception and awareness. When the brain experiences trauma and is damaged, reactions to the outside world may be permanently and irreparably altered. Neither the complexity of the healthy human brain, or the extent of its response to trauma is fully understood.

Current gaps in knowledge reveal a concerning lack of data on TBI diagnosis, treatment, and long-term outcomes. The main classification tool for assessing injury severity and enrolling patients in clinical trials, called the Glasgow Coma Scale (GCS), has been heavily criticized for its insensitivity to confounding aspects of TBI. Many of the standard protocols for treating patients with TBI have not been rigorously tested through clinical trials [22]. "To date, no medications have been useful in improving outcome. There have been over 200 failed neuroprotective drug trials" [22]. Standards of care for TBI are associated with high failure and mortality rates, leaving sizeable margins for improvement. Perhaps more concerning are the shortage of new research endeavors being designed and funded to better understand these issues. Care for traumatic brain injury is decades behind other leading causes of death in the United States, such as stroke, cardiovascular disease, and cancer [23]. Despite traumatic brain injuries having a comparable prevalence and higher incidence than stroke, they are the subject of one-fifth the clinical trials and one-third fewer new studies [5]. New translational research has the potential to eliminate the discrepancy, while improving patient care and boosting survival rates.

This study uses interviews with local medical professionals to frame a discussion and provide a fresh vantage point on the recent advances and future prospects of TBI research. With a combination of direct quotations from the interviews and peer-reviewed journal information, readers will be both entertained and educated. Written in a style more approachable than the standard literature review, this thesis is designed to present information to the general public, not medical professionals. Difficult concepts are introduced and explained through relatable anecdotes and common language. A large

scope of topics are covered and intentionally formatted to hold interest. The use of local doctors practicing in Oregon as study participants brings the story to the reader's doorstep with names they may recognize. Traumatic brain injuries are both common and concerning, and finding new formats to address them in is necessary to cultivate understanding and awareness.

This thesis begins by discussing the relevance of traumatic brain injuries by analyzing recent media coverage. The focus then shifts to investigating new avenues for traumatic brain injury research through a series of interviews. The opinions and suggestions of the medical professionals interviewed in this qualitative study provide commentary on where the current understanding of TBI lies, and where more effort needs to be put forth. Mild traumatic brain injuries (mTBI), or concussions, which account for approximately 85% of all brain injuries, predominate throughout the discussion, while more severe TBI is addressed to a lesser extent [30]. Three major themes were identified in the responses to the interview questions. Participants mentioned improved public education, diagnosis, and treatment for TBI as fields in need of attention. These three themes will guide a stepwise analysis intended to answer the question, "Where is the field of traumatic brain injury research headed?"

Study Design

A series of interviews with local medical doctors were used to investigate future directions of traumatic brain injury research. Professionals with significant experience in the diagnosis, treatment, and/or research of traumatic brain injury were sought after for their status as community leaders on the subject. A convenience sampling of interviewees was obtained through social networking. Each medical professional was asked an identical list of questions intended to prompt discussions regarding personal experience with TBI, TBI in the media, and the advancement of TBI research. A complete list of interview questions can be seen in Appendix A. Interviews were conducted over the phone or in person and lasted anywhere from 5-20 minutes. Each conversation was recorded using the Super Note recording app for iPhone and later transcribed for the purpose of accurate quotation.

The Oregon State University Institutional Review Board (IRB) approved the project as an exempt study involving research on human subjects on April 4, 2014. Interviews began the following week and were completed by June 6, 2014. In accordance with IRB requirements, participants were informed that study involvement was 100% voluntary and compensation of any kind would not be provided. Verbal consent was granted prior to beginning each interview. Participants were notified that interviews were part of an Undergraduate Honors College Thesis project. Intent to record interviews and publish direct quotations was made clear. All participants were encouraged to withhold perceivably risky or confidential information. A total of eleven interviews were used to construct a response trend analysis. Major themes were identified and sorted into

categories. The study design was not intended to produce statistically relevant or fully representative data. Opinions and suggestions produced by interviews were understood to be samples within a broad spectrum. All abbreviations used in the text are defined in Appendix B. A list of interviewees and their qualifications can be found in Appendix C.

TBI in the Media

Recent media attention is shining a new light on the issue of traumatic brain injury. A CDC study on media coverage of TBI between 2009 and 2011 concluded that in terms of quantity and focus, reporting on TBI related subjects has seen significant growth [33]. The study found that the number of social media and print articles focused primarily on TBI increased from 6% in an earlier analysis to 38.6% between 2009 and 2011[33]. Within the same time span, it showed that 77% of newspapers increased coverage of TBI [33]. As a public health issue, TBI has benefitted from this new level of collective consciousness. Media coverage is a powerful tool that can be used to help the public prevent, recognize, and react to TBI in an appropriate manner. It can be linked to increased research funding, can direct research interests, and should ultimately better patient care. So what are the key issues responsible for bringing TBI to the forefront? A question posed to each interviewee was "Why do you think TBI has developed such a heightened presence in the media over the past few years?" The answers illuminated the relevance of TBI research as topic. Similar to the CDC study, responses suggest that there is an opportunity to strengthen the way TBI is covered in the media [33].

The first response trend dealt with sports concussions. Multiple interviewees cited the erratic behavior, neurodegenerative disease development, and suicides of high profile athletes as main attention grabbers. Retired Critical Care Surgeon and former Head of Salem Emergency Physicians Dr. Floyd Strand recalled boxing legend Muhommad Ali, "[Ali] was one of the most widely known, highly respected and popular athletes of the 20th century… How much of his Parkinson's Disease is from being 'punch drunk' so

many times?" [Telephone]. Sports and Family Medicine Doctor Craig Graham mentioned Canadian hockey stars Brett and Eric Lindros who, "both had to retire from hockey for recurrent concussions" and have since become spokesmen for head injury awareness [Personal]. Senior Associate Athletic Director for Sports Medicine at Oregon State University and Sports Medicine Doctor Doug Aukerman brought the National Football League into the conversation. "I think truly the thing that has really helped bring it to the forefront is some of the NFL brain donation research and the media catching hold of that and making it an issue. If the media doesn't catch hold of it, if somebody doesn't do an expose on the NFL, I don't think it will gain the attraction it does" [Dr. Aukerman, Personal]. Dr. Terry Morrow, Internal Medicine Doctor, observed that attention to concussions in the abovementioned sports even has a "trickle down" effect to sports that receive less media coverage [Telephone].

Traumatic brain injuries in the military arose as a second major response trend. Participants expressed familiarity with headlines of high rates of suicide and depression in the military, along with issues of health care compensation for veterans. This level of coverage is warranted, as an estimated 10-20% of returning veterans have incurred mild traumatic brain injuries [29]. Dr. Susan Rowell, Critical Care Surgeon and Principle Investigator of an ongoing multicenter study on TBI at Oregon Health and Science University (OHSU) provided a thorough synopsis on the subject:

> "I think one of the main reasons for [increased media coverage of TBI] is because of the Iraq/Afghan conflict. The Department of Defense (DOD) is well funded and is bringing this to the forefront. Probably the only good thing that's come out of this war is the advancement of trauma care and of medical care because of the money that has poured into research on our injured war fighters… In addition to hemorrhagic shock, TBI is the number one reason that these people die. They have Kevlar vests now, so other than amputation, there's less penetrating torso injury, but the blast injuries have had a major impact, not only in the field and the

> far forward, but in the hospitals when they get flown back here they have chronic disabling sequela of TBI… That's one of the reasons there's a lot of focus and funding going into it" [Telephone].

Many of the participants mentioned society's increasingly cautious approach to TBI due to the increased coverage. Retired Vascular Surgeon and former West Linn High School Team Physician Dr. Clark Burnham commented, "Now with the rise of all the articles in the local newspapers and attention in national magazines, people realize that concussions are a huge deal, even a mild concussion can be a huge deal" [Telephone]. Recounting on his experiences Dr. Bob Sotta, Sports Medicine Doctor Orthopedic Surgeon, said, "I've spanned an era from a lot of information that was empirical information being used as guidelines to a more current era of much more detail and it still remains an issue that's very poorly understood. I think right now we're currently in a wave of over-diagnosis and over-protection but that's more because we don't know how to differentiate the dangerous ones from the ones that are somehow less dangerous" [Telephone]. Until new diagnostic research can accurately characterize the severity of TBI, a cautious diagnostic approach is well warranted. Coming from a similar place, Dr. Aukerman explained, "Where we are now compared to where we were 5-10 years ago is a much more conservative place. Where I think we're going to be in 5 years, is going to be far more conservative than where we are now" [Personal]. This rise in awareness is having a large impact. "There was a 30% increase in the rate of emergency department visits for TBI between 2006 and 2010" [24].

Whether the talk is about concussions in athletics or blast injuries in warzones, more people are tuning into the topic of TBI. As awareness of TBI as a public health issue increases, broadening coverage beyond these select examples would more

accurately represent the issue. More commonplace accidents such as falls or motor vehicle crashes deserve equal coverage, as do issues of prevention. A more careful portrayal of TBI in sports coverage may be advantageous. Contradictory articles mentioning head injuries as ‘just part of the game’ or ‘occupational hazards’ are sometimes seen alongside reports on the long-term consequences of TBI [6]. The importance of accurate portrayal of TBI cannot be overstated, as “media reporting on health issues can also help shape positive health-related attitudes and behaviors” [6]. Alongside media coverage, public education has the power to shape societal views and common knowledge of traumatic brain injuries.

Public Education

Questions two and three on the interview questionnaire prompted study participants to identify workplace inefficiencies, aspects of clinical or research work that deter from level of patient care, pertaining to TBI and provide suggestions for their improvement [Appendix A]. A major theme that arose from these responses addressed a need for better public education on TBI symptom recognition and treatment options.

Study participants discussed the importance of modifying contact sport culture in decreasing the number of concussions that go untreated. Praising resilience despite injury in competitive sports is a common occurrence, but incredibly unsafe with regard to TBI. Interviewees shared concerns about head injuries being viewed as 'just part of the sport' and the failure of communities to comprehend the severity of these injuries. Both Dr. Graham and Dr. Strand mentioned the importance of decreasing social pressures from coaches, parents, and fellow teammates on athletes who have sustained concussions to return to play [Personal, Telephone]. Additional concern was expressed for student athletes themselves. For these young people, purposefully failing to report symptoms in order to avoid losing playing time is worrisome because injured athletes may be reentering the game [Graham, Personal]. "People don't want to be taken out of any competitive event for any reason, if they think they can go, they want to go" [Dr. Sotta, Telephone]. Dr. Jeffrey Leon, Anesthesiologist with Oregon Anesthesiology Group added, "It's a reality… Kids will do anything to play. With that in mind, we're trying to get away from a window where subsequent concussions lead to severe repercussions down the line" [Telephone]. Participants agreed that public education measures should

help athletes recognize the signs of concussion, and encourage them to report symptoms. Hope for earlier interventions to prevent repeat injuries from causing cumulative impairments, namely second impact syndrome, were expressed. In this syndrome, "a concussion sustained while an athlete is still symptomatic from an earlier concussion results in progressive cerebral edema" [16]. In light of these responses, ensuring all players grasp the seriousness of TBI should be considered a main public health goal.

Many state legislatures, sports leagues and organizations have taken initiative on boosting public education of TBI. "Between 2009 and 2013, all 50 states and the District of Columbia passed laws on concussions in sports for youth and/or high school athletes" [28]. Many of the interviewees recognized the importance of these moves. "I think educating the coaches at all levels is a critical issue, and I think it's critical they do it (review the signs and symptoms of concussion) every year. It brings awareness" [Dr. Burnham, Telephone]. Dr. Leon spoke on the benefits of the legislation, "We are already seeing a lot more early evaluation of kids. Coaches and trainers are getting better at identifying head injuries and managing them afterwards" [Telephone]. Dr. James Chesnutt, Medical Director of the OHSU Sports Medicine Program, said "I think our goal as medical professionals and public health people is to figure out how we can present a really cogent argument about what needs to be done and then help people implement that on a local level" [Personal]. Dr. Chesnutt was involved with the passing of two key pieces of Oregon legislature, Jenna's Law and Max's law, which are designed to ensure appropriate medical care for young people in school and club sports. The laws are named after two local high school athletes who suffered life altering secondary impact syndrome. Guidelines such as these impose requirements for recognizing and responding

to possible concussions in athletes. Recent educational campaigns, such as the distribution of the CDC's "Heads Up: Concussion in High School Sports" booklet have increased concussion symptom awareness among the general public. Alongside these campaigns are the multimillion-dollar pledges to advance TBI medical science and new player safety guidelines released by both the NCAA and the NFL. These efforts to improve public awareness have made a visible impact, but there remains more work to be done.

After sustaining a traumatic brain injury many people don't know what to do, and either don't have, or aren't aware of the resources available to them. Dr. Graham and Emergency Medicine Doctor Dr. Gabriel Ledger, talked about helping people differentiate between mild and severe TBI and achieving less unnecessary ER visits for mild TBI and more urgent attention for moderate-severe TBI.

> "For your average kid whose wrestling and gets head butted by another kid, they don't usually need an emergency room visit, but we see a lot of those cases…if the public could make that determination and they could say, okay, maybe that's a concussion, but this is clearly not bleeding on the brain that requires immediate surgery, and therefore you don't usually need to be seen right away by an ER doctor, you can be seen by your primary care doctor the next day" [Dr. Ledger, Telephone].

The availability of medical health professionals as a resource for athletes arose as a part of this discussion. On the importance of having medically trained staff at sporting events, Dr. Sotta commented "there are a lot of times where people get these injuries and there are no medically trained people to assess them" [Telephone]. This is especially a concern in rural school systems and smaller sports programs, where having an on staff athletic trainer (the medical health professional most likely to be present) at every sporting event is not an affordable option. In these cases, remote resources such as a

'concussion hotline' manned by local medical specialists may be helpful for symptom recognition and treatment advice [Dr. Graham, Personal]. Dr. Graham proposed some solutions to the issue, "I think it needs to become more important to have staffed athletic trainers to be used as a resource by doctors, coaches, parents and athletes. Along those lines, concussion clinics for community members would be useful… A concussion hotline, manned by a physician or PA or AT to help make decisions would be a huge asset" [Personal].

Communication online and through social media plays an important role in spreading traumatic brain injuries awareness. Web resources suggested by interviewees include the Centers for Disease Control and Prevention, National Institute of Health, American Academy of Neurology, Brain Injury Association, Inc., Brain Injury Alliance of Oregon, Center for Brain injury Research and Teaching, and the Oregon Concussion Awareness and Management websites. Brain Injury Awareness Month, which takes place in March, is perhaps the most well known campaign that utilizes social media platforms such as Facebook, Instagram, Twitter, and Pinterest to promote understanding of TBI. As science advances understanding of TBI, these outlets may help dissipate new knowledge and ultimately lower the incidence of TBI.

Risk Assessment

Part of developing effective concussion preventative measures through public education depends on increasing knowledge of risk factors. Two of the sports team doctors interviewed brought up the need for future TBI research to identify and characterize these factors. Responses stemmed from the fourth interview question, which

asked, “What questions do you see TBI research investigating and perhaps answering in the coming years?” [Appendix A].

> “The people who get multiple concussions, are they because they have a giant predisposition where they are unable to heal or recover or is there something that makes them at risk? And if there is, is there something we can do to prevent that? I think its either going to be a neurophysiology trait or something where some people are just able to overcome injury and heal quicker than others. So is there a genetic trait where some people just are really adept and really able to heal quickly and others aren’t? Maybe it’s a chemical that we just haven’t identified” [Dr. Aukerman, Personal].

> “A risk stratification section, what findings from research can we get that would tell us who is just at flat out greater risk [for TBI]. If there were a particular way for us to look at all the demographics, be it gender, age or some sort of genetic marker testing… If there’s some way to know out of the gate that risk is much greater, be it a biological factor or a genetic marker that wasn’t too complicated that could be used to assess risk across the board” [Dr. Graham, Personal].

Currently, risk assessment for TBI comes from statistical data on causation and demographics, which are often criticized for being an over-simplification of the true complexity of these cases. CDC data records show that TBI account for one third of injury related deaths in the United States. Of these, falls are the leading cause of TBI, disproportionately affecting young children (ages 0-14) and older adults (65+) [3]. TBI are also the single leading cause of death and disability in young adults [3]. As better injury surveillance systems and risk assessments are developed, public education campaigns focused on injury prevention will have more acutely defined target populations. A quote from one of the interviewees exemplifies the power of this momentum, “We all had our ‘bell rung’ when we played football back in the day, and it used to be nothing. Now, if someone says they got their bell rung, everyone will listen to it because of education” [Dr Burnham, Telephone].

Diagnosis

The second prominent theme that arose from the study questionnaire was a need for quicker, more reliable diagnostic measures of TBI. Shockingly, there is no single set of generally endorsed diagnostic criteria for mild, moderate, or severe TBI used today. This shortage has been called, "one of the most significant challenges in both mTBI research and clinical work" [30]. According to a recent World Health Organization (WHO) task force report, there are 38 different definitions of mild traumatic brain injury alone [15]. Interviewees expressed frustration over this lack of standardization. In a statement from the Mayo Clinic, "Timely diagnosis and prompt treatment can help prevent more serious concussion complications, including diffuse brain swelling and severe, permanent neurological dysfunction or death brought on by subsequent concussive injury" [25]. A concept that highlights the need of more timely diagnostics for severe TBI is the so-called 'golden hour'. In his interview, Dr. Leon explained the phrase, "During that evaluation period, patients who are being stabilized and receiving definitive care do better than those who have delayed diagnosis" [Telephone]. There is great need for new traumatic brain injury research to develop rapid and reliable diagnostic criteria for universal use, but it's a multifaceted issue.

Understanding the Heterogeneity of TBI

A major hurdle in the accurate diagnosis of traumatic brain injuries is their diverse presentation, which is often underrepresented in statistical data. Factors contributing to the heterogeneity of TBI include patient history and psychological

makeup, the unique physics and circumstance of injury, manifestation of structural damage, symptom presentation, coping ability, and resiliency to psychiatric distress, among other factors [30]. On this topic, Dr. Sotta noted, "The biggest problem is that we have no way to quantify the injury. There's no objective data and there's huge variability in what any given symptoms might mean and it's not as easy as if you're unconscious for several minutes, that's a bad one, and if you just get your bell rung, that's not a bad one" [Dr. Sotta, Telephone]. Dr. Aukerman also spoke on the complexity of head trauma:

> "There's not a good understanding of the different parts of the brain and how they may present a concussion. So somebody may have the predominant signs or symptoms of headache and memory loss and stuff like that but other people may just have the sensation of not being steady or having motion or other people may have more auditory or sensoneural type issues. Other people may have vestibular or visual issues. They all are very different, and they all respond differently" [Personal].

Catering to individual needs with personalized diagnosis and treatment options requires a thorough understanding of injury progression. Unfortunately, modern science can't completely explain the detailed pathophysiology of these injuries. At the cellular level, very little is known about what happens within the first few hours after a brain injury. Dr. Aukerman spoke on the subject, "So somebody gets a traumatic brain injury, what happens to them without any intervention or treatment, just time? What truly happens, and what is the natural history? I don't think we really know" [Personal]. Developing more satisfying diagnostic tools for traumatic brain injuries will require a more thorough understanding of the natural history of brain trauma. One interview provided commentary on the subject, "There are multiple varieties, different lesions and they each probably have different treatment modalities… Which is why we are looking for different indicators like biomarkers. Likewise, outcome measures are equally crude"

[Dr. Rowell, Telephone]. The biomarkers mentioned, and the development of other new technologies capable of differentiating between TBI of varying severity and causation will depend on the success of further research.

Sport-Related TBI

For high school and college athletics, baseline testing is the most widely implemented methodology for diagnosing TBI. These assessments include cognitive and neuropsychological tests, and use computerized tasks to measure verbal memory, visual design memory, concentration, visual processing speed, and reaction time [26]. "These paradigms have proven sensitive for the detection of sport-related concussion and, when used in conjunction with symptom reporting and clinical assessment, more sensitive in detecting injury and monitoring recovery than symptom reporting alone" [26]. Collecting pre-injury baseline data on athletes provides athletic trainers and sports medicine doctors with a reference point from which to judge the status of athletes following head trauma. Examples of these testing systems include ImPACT, SCAT, the Axon Sports test and the K-D test. Dr. Burnham, introduced the ImPACT program to West Linn, Oregon.

> "Getting it started was hard, it took a fair amount of time, and I had to have other people help me as we gave instructions to get all the athletes covered, but ultimately we did get all the athletes… West Linn is a 6A school, and when we got started, at most there were only 6-10 other 6A schools that did ImPACT testing. Now it's really standard in 5A and 6A schools [throughout Oregon]" [Dr. Burnham, Telephone].

Large margins for improvement exist in these tests, for example the ImPACT program is expensive, and not available in many smaller schools, despite the availability of grant money. If baseline tests aren't taken, students' scores are compared to national averages, which can prove misleading. Repeating the test can lead to increased or

decreased scores due to memory from previous attempts. A few of the interviewees commented on these margins for improvement, clarifying a need for affordability and standardization. “People with higher intellect can fool a lot of these tests, and there’s many variables it doesn’t capture but at least its one method, and over time that method can be further analyzed with real data” [Dr. Sotta, Telephone]. Dr. Graham expressed further concerns, “A brief neurological standardized test that was reliable and reproducible would be great. With ImPACT, if you do it too many times, your scores may be altered” [Personal]. When the interview question was posed, “What questions do you see TBI research investigating and perhaps answering in the coming years?” the responses were consistently thorough and full of concern. It was very clear that baseline testing and symptom monitoring are not sufficient diagnostic tools.

> “For athletes who have experienced head trauma, the number one concern is return to action. We need a better understanding of that point where a bump in the head becomes a concussion. High school and college football clearance isn’t foolproof. Oftentimes athletes are under-diagnosed or over-diagnosed because there isn’t a failsafe method to make that determination. We need a device or system developed to make that diagnosis with a higher level of certainty that doesn’t involve huge amounts of radiation” [Dr. Strand, Telephone].

> “It would be nice if we had a diagnostic test that was based in good science and we could know truly with measuring what we think it was measuring. The things we use now, are all extrapolations and resuming that they are accurate. So biomarkers would be a great thing to have if you could draw a blood test or some type of fluid and we knew that if it was negative, it was truly negative and if it was positive… Well, you don’t really know. But at least you have something that is reassuring as opposed to now, trying to take an extrapolation of a neurocognitive test” [Dr. Aukerman, Personal].

> “We see tons of people in the ER who want to get checked for concussions…There might be cognitive testing you can do like baseline testing, but we don’t do that in the ER and concussions don’t show up on any scans so a lot of times people come to us asking if they’ve had a concussion and generally we say probably, but we don’t really know” [Dr. Ledger, Telephone].

> "I think that our current tests that we use on the sidelines are pretty good, but they're not accurate or sensitive enough and so we can't pick up all the concussions and sometimes it's hard to document our findings and then use all those down the road to compare with rehabilitation outcomes. So that may be the major issue is just accuracy and then longitudinal follow up" [Dr. Chesnutt, Personal].

New Diagnostic Tools

Comprehending diagnostic tools for TBI requires some understanding of what they are measuring. The severity of TBI can depend on several factors, primarily the nature of the causative event and the force of the impact. Tissue injury for any degree of TBI may be focal- from penetrating injuries like gunshot wounds, diffuse- from acceleration injuries like car accidents, or may have aspects of both. The damaging agent itself may cause a closed or penetrating injury, based on whether or not it breaks the skull and enters brain tissue. Hemorrhaging, or bleeding, is a common result of either type of damage. For patients with closed injuries, excessive hemorrhaging (which may form pools called hematomas) and bruising (called contusions) is often observed. "Typically, mild TBI causes no gross pathology, such as hemorrhage…but instead causes rapid-onset neurophysiological and neurological dysfunction that resolves in a fairly short period of time. However, approximately 15% of individuals with mild TBI develop persistent cognitive dysfunction" [39]. Frequently what puts patients at greatest risk is diffuse axonal injury, a medical term which describes a loss of communication between brain cells (neurons) by damaging their connections to one another (axons). For patients with penetrating injuries, the trajectory of the projectile that pierced the brain may leave a trail of inflammation and tissue injury, and create opportunity for infection. Being able to

visualize and quantify the extent of macro and microscopic damage is the challenge of diagnostic tests.

Evaluating diverse TBI requires a wide array of diagnostic tools. Standard assessment of TBI uses a clinical tool called the Glasgow Coma Scale (GCS), which is a scoring system that assigns patients a number from 3 to 15 based on the severity of their injuries. Eye opening, verbal, and motor response scores are summed to provide an overall score, with 3-8 describing severe TBI (deep coma or death), 9-13 describing moderate TBI, and 13-15 describing mild TBI (concussed state) [3]. GCS scores are one grading system for TBI, but like baseline testing for mTBI, many different scales are currently in use. The American Congress of Rehabilitation Medicine (ACRM), and the World Health Organization (WHO) have also published criteria [30]. A more precise way to classify traumatic brain injuries is an ongoing subject of new research, and one that many of the interviewees shared great interest in. "We have to clarify the diagnosis with diagnostic criteria… The biomarkers can be really important. They can be chemical or physical or anything about your body that we can measure that can be helpful. So balance is one… There's also chemical tests that may be useful, others could be eye tracking issues" [Dr. Chesnutt, Personal].

Many interviewees were concerned by the fact that the GCS scoring system divides patients into broad, insensitive categories. Also, "While the GCS has proven its utility in the clinical management and prognosis of severe TBI patients, it cannot provide information about the pathophysiological mechanisms responsible for a patients neurological deficits" [17]. Adding to the commentary, Dr. Rowell said,

> "I think the biggest limitation is no gold standard for diagnosis and for outcome. So we use GCS to enroll patients in clinical trials and for treatment decisions, and

> it's well established that GCS is unable to detect the presence of structural injury early, so if you're drunk, if you're in shock, if you have medications or some other reason for being unconscious, then GCS will not show that… Which is why were looking for better indicators like biomarkers" [Dr. Rowell, Telephone].

Alongside quantifying injury severity with GCS scores, Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) scans are routinely used to visualize TBI-related pathology. CT scans are the preferred test in emergency settings because they are quick, accurate, and widely available, but MRI can provide more detailed pictures. The problem is that CT/MRI "has not proven specifically informative about likelihood or type of persistent cognitive or emotional impairments" and negative findings "do not rule out long-term complaints and functional declines" [30]. Interviews yielded many predictions on the subject, including "I see new imaging contributing to further exploring the mechanisms involved in brain injury" [Dr. Rowell, Telephone]. In the last decade, there has been increased interest in new imaging technologies able to "detect microscopic damage to brain tissue and to link patient brain structure and function to objectively measured or subjectively reported complaints" [30]. Dr. Rowell commented on some of the recently published data,

> "There are a lot of new imaging modalities, especially for mild and moderate TBI. It's fascinating actually, if you see some of the studies for mild TBI. So I'm talking about when you get knocked down on the football field, you get up and continue to play, and then you do functional MRI and look at those MRI's versus somebody who has not had that injury, and there are significant differences in different tracts and pathways and there is a very high rate of neurodegenerative disease…So they're just now starting to figure out what the link between those is" [Telephone].

More sensitive imaging techniques such as Functional MRI (fMRI), as mentioned, Diffuse Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), Arterial Spin

Labeling (ASL), Magnetoencephalography (MEG) have been the subject of recent studies [38].

In addition to new imaging modalities, biomarkers for TBI are in high demand. "The absence of clinically validated brain injury diagnostic markers as an internal indicator of tissue damage with the ability to measure changes in the cellular, biochemical and molecular events during the injury response has been identified as a major limiting factor to diagnostic and therapeutic development for brain injury" [17]. Biomarkers capable of indicating traumatic brain injury must be specific to the brain, present in the bloodstream in measurable amounts, and indicate injury pathology. Most biomarkers are found in the cerebrospinal fluid at heightened amounts following injury, and enter the bloodstream when the blood brain barrier is damaged. The expectation is for these markers to help physicians not only diagnose intracranial pathology, but inform injury management and therapeutic approaches. Currently, there are no blood based diagnostic tests to detect biomarkers, but many new candidates are currently under investigation. The most promising include lactate dehydrogenas (LDH), glial fibrillary acid protein (GFAP), neuron specific enolase (NSE) and S100-B [17]. Other biomarkers of brain injury include inflammatory proteins (IL-6, IL-8, IL-10), tau proteins, amyloid precursor protein (APP), and myelin basic protein (MBP) [39]. The practical success of these biomarkers will depend on their capacity for measurement. The development of sensitive assays using antibodies or other means will need to be both cost effective and user friendly.

> "Not only are new systems for diagnosing TBI highly sought after: EEG, biomarkers, enzymes released after injury, but so are ways to measure and interpret these novel sources of diagnostic information. "We currently don't have any good way to measure these biomarkers, however within a year we're going to

> survey a testing biomarker handheld and point secure biomarker tests, in the field and in the emergency department, they just need to be validated with trials" [Dr. Rowell, Telephone].

Biomarkers hold great potential, but further research is needed before they become established as a common part of clinical practice.

Treatment and Long Term Outcomes

An estimated 10 million people worldwide are either hospitalized or killed due to TBI each year [17]. This represents 150-300 people per 100,000 [21]. Though prevalence varies between countries, the severity of TBI as a public health threat is undeniable. Yet there is not a single proven treatment for promoting recovery from brain injury. Currently, physicians manage medical symptoms and rely on rehabilitation to help restore cognitive and motor functions. Finally, TBI-centered clinical trials have, "shown limited success in providing an evidence base for the introduction of successful new therapies into clinical practice" [20].

When asked about the questions he saw TBI research investigating in the future, Dr. Strand responded, "We need better treatment options for traumatic brain injuries, and to manage these injuries we need to better understand how the brain functions, and how it heals. Healing brain injuries is a very slow process" [Telephone]. Responding to the same prompt, Dr. Morrow expressed, "I think the primary focus needs to be how best to treat young people" [Telephone]. Similarly, Dr. Burnham mentioned, "It's the treatment of these injuries that's critical. For those aligned for people that who suffer from TBI, there will be ways to neurologically stimulate them after injury, and that's going to be a whole field in itself" [Telephone].

Multiple factors play a role in the development of new treatments for TBI. Appropriate research infrastructure, funding and resources all need to be available. IRB approval needs to be granted, community consultation measures must be taken, the risk/benefit ratio must be favorable for each patient and researchers must have access to a

representative population for study. The shortage of novel therapeutic interventions reaching clinical practice can be attributed to, "the extremely short temporal window for intervention, failure of many candidate drugs to cross the blood-brain barrier, ethical and regulatory obstacles associated with research in subjects who cannot provide consent, and difficulty in subject recruiting" [20]. The full complexity of what it takes to coordinate a successful clinical trial on TBI patients is impossible to delineate without going into more depth, but suffice to say it is an incredibly cumbersome process with a shortage of funding opportunities. In order to improve clinical practice and improve patient care, "more large scale and standardized research across different cognitive domains" [20].

The scarcity of new trials clarifies the need for increased funding for TBI and better data sharing between physician scientists. The National Institute of Neurologic Disorders and Stroke (NINDS) has played a huge role in promoting information sharing with the Common Data Elements Project. Dr. Rowell explained the initiative,

> "They [NINDS] are working very hard to establish a common way to report data, and to establish a repository of not only biomarkers, but also imaging and genetics so that there's more opportunity for collaboration and other investigators to use this stuff. [Referring to her own work] This study cost 8.5 million dollars, it's hard to do a study like this, so if we put this up to the repository and published these data in the common data elements format…other investigators can utilize this and publish it and expand brain injury research" [Telephone].

Treatments

Currently, multiple guidelines on how to manage concussions have been published to date. Three of the most popular are The Cantu guidelines, the Colorado Medical Society guidelines, and the American Academy of Neurology guidelines. Further concussion treatment recommendations have been produced by the 1st (Vienna), 2nd

(Prague) and 3rd (Zurich) International Symposia on concussion in sport. Common elements of these protocols include physical and mental rest following injury until symptoms have completely disappeared, and incorporate gradual return to normal activity levels.

For more severe TBI, there are many different stages of treatment, and once more, no universally endorsed guidelines exist. Immediate treatment for TBI involves stabilization and injury assessment. Because little can be done to reverse the damage caused by the initial physical insult (primary injury), the focus quickly turns to preventing injuries that may ensue in the following hours (secondary injury). Because secondary injury is the leading cause of in-hospital deaths after TBI, it serves as the main focus of resuscitation efforts [13]. The last decade of research has shared this focus, especially with regard to minimizing inflammation [20]. One therapeutic intervention currently being studied is Progesterone, which along with its metabolite allopregnanolone, "have been shown to reduce the expression of inflammatory cytokines in the acute stages of brain injury" [20]. Though strides such as the Progesterone trial are being made to eliminate the shortage of therapeutic interventions, there are currently no effective pharmacological treatments for TBI [17].

For severe TBI injury management depends on the restoration and maintenance of adequate tissue metabolism by ensuring sufficient delivery of fuel, typically oxygen and glucose, to meet cellular metabolic demands [22]. Fine adjustments in medications, body temperature, and body placement have proven essential for patient survival and long-term success. Drugs such as sedatives, paralytic agents, and analgesics are often administered to help control pain and seizures. Intravenous (IV) fluids such as hypertonic saline and

mannitol are given to correct low blood pressure and act as diuretics (fluid loss lowers pressure in the brain). For patients with low GCS scores, intubation and mechanical ventilation are often necessitated to maintain a safe breathing rate and provide a secure airway. These measures help to maintain adequate blood oxygen saturation, which reduces the risk for secondary injury. Surgical interventions may also be warranted. In the last 25 years, carefully monitoring the intracranial pressure (ICP) and cerebral perfusion pressure (CPP) has caused a significant decrease in morbidity and mortality for TBI patients. ICP the amount of force on the cranium exerted by the blood, soft brain tissue, and cerebrospinal fluid. The cerebral perfusion pressure (CPP) measures the amount of blood flow reaching the brain despite this increase in pressure.

Along the spectrum from moderate to severe TBI, interviewees expressed a desire to see further research efforts produce better treatment options. Referring to concussions, "Right now we really don't have any universal guidelines so we're probably over-treating some and under-treating others because we just don't really know where they are on the severity scale" [Dr. Sotta, Telephone].

Long Term Outcomes

There is insufficient understanding of the factors that impact outcomes following traumatic brain injuries. For patients or loved ones of those who have experienced TBI the fact that, "the field is not yet in a position to authoritatively recommend a minimum core set of instruments that provide a necessary yet sufficient evaluation of functioning after TBI" is frustrating [36]. Many of the interviewees shared concerns about this shortage. Dr. Chesnutt expressed, "Coming up with really good rehabilitation protocols

or treatments in general, because we don't really have very good treatments right now at all… Then taking and connecting all this data to outcomes data" [Personal]. With regard to mTBI, Dr. Morrow stated, "I think we need to know if there's more long term sequela than we appreciated in the past" [Telephone]. Dr. Peggy Eurman, Internal Medicine Doctor shared this view, "For the patients, it would be nice to have an algorithm, a timeline as opposed to a guess, of when it's safe to go back to sports, or when the symptoms are expected to get better" [Telephone]. Clinical trials that follow patients years after their initial injury are the solution to this data shortage. In the words of Dr. Sotta, "Some of the real information that we need takes 20-30 years of patients post-injury and then analyzing them to be able to answer… There's always going to be gaps and we have to fall back on what we do know, and apply that to the best of our ability and the best of the patients interests" [Telephone].

Conclusion

In a 2013 talk recorded at TED studios neuroscientist Dr. Stuart Firestein, also a professor at Columbia University, described the best scientists not as individuals who know the most facts, but who ask the best questions. His witty and provocative talk outlined real scientific work not as the scientific method, but as "farting around…in the dark". To an amused live audience he encouraged a generation of 'citizen scientists' to cast aside the idea that knowledge leads to discovery, insisting instead that ignorance does. The idea behind his proposal that pushing the envelope in science requires exploring the unknown [11]. This was the concept I had in mind while writing the interview questions for this thesis. I chose to direct the conversation towards new avenues of traumatic brain injury research to explore discovery-yielding ideations. I chose to reach out to the professional community involved in TBI prevention, treatment, and research knowing their opinions would be received with the most respect and influence. The purpose of this study was to explore a new format for discussing and cultivating awareness for TBI. Eleven interviewees were courteous enough to share their opinions with me, and I hope to have displayed them in a way that readers find both interesting and informative.

Recent media attention has highlighted the timeliness of traumatic brain injury research as an important field of study, especially on the battlefield and sports fields. To the general public TBI is a significant public health threat, and as such it demands our attention. Although the hype has raised the profile of traumatic brain injury in select populations, only new research will advance current understanding of these injuries. The

three major response themes addressed in this thesis call for improved public education, diagnostic tools and treatment/long term outcome predictors for TBI. The commentary presented in this thesis frames a powerful claim of increased attention for these issues.

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Appendices

Appendix A

Interview Questionnaire

1. Can you describe your involvement with TBI (diagnosis/treatment/research)?

2. What are some of the most common setbacks/inefficiencies you experience within standard care guidelines for TBI patients?

3. What are some suggestions you have to improve these setbacks that would make your work more efficient and would benefit others in your occupation?

4. What questions do you see TBI research investigating and perhaps answering in the coming years?

5. Why do you think TBI has developed such a heightened presence in the media over the past few years?

Appendix B

Abbreviations and Definitions

CDC	Centers for Disease Control and Prevention
CPP	Cerebral Perfusion Pressure
CT	Computed Tomography
CTE	Chronic Traumatic Encephalopathy
GCS	Glasgow Coma Score
ICP	Intracranial Pressure
IED	Improvised Explosive Device
ImPACT	Immideate Post-Concussion Assessment and Cognitive Testing
K-D Test	King-Devick Test
MRI	Magnetic Resonance Imaging
mTBI	Mild Traumatic Brain Injury
NFL	National Football League
NIH	National Institutes of Health
OHSU	Oregon Health and Science University
SCAT	Sport Concussion Assessment Tool
TBI	Traumatic Brain Injury
WHO	World Health Organization

Appendix C

Interviewees

Dr. Doug Aukerman, Sports Medicine at Good Samaritan Health Systems and Senior Associate Athletic Director for Sports Medicine at Oregon State University Athletics.

Dr. Clark Burnham, Vascular Surgeon and West Linn High School Team Physician, retired.

Dr. James Chesnutt, Orthopedic and Rehabilitative Medicine at Oregon Health and Science University, Medical Director of the OHSU Sports Medicine Program.

Dr. Peggy Eurman, Internal Medicine Doctor at Kaiser Permanente Mt. Talbert Medical Office.

Dr. Craig Graham, Family Medicine and Sports Medicine at Good Samaritan Health and Team Physician Oregon State University Athletics.

Dr. Gabriel Ledger, Emergency Medicine Doctor at Good Samaritan Health.

Dr. Jeffrey Leon, Anesthesiologist with Oregon Anesthesiology Group.

Dr. Terry Morrow, Internal Medicine Doctor at Kaiser Permanente Mt. Talbert Medical Office.

Dr. Susan Rowell, Critical Care Surgeon at Oregon Health and Science University.

Dr, Bob Sotta, Sports Medicine Doctor and Orthopedic Surgeon in Private Practice.

Dr. Floyd Strand, Critical Care Surgeon at Salem Hospital and Head of Salem Emergency Physicians, retired.