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New Developments in Brain Science:
Implications for Victims, Providers and Lawyers

By: Robert Luce

Attachment to "homogeneous" definitions of "mild" traumatic brain injury ignores recent developments in brain science, risks missing targeted treatment opportunities, and can lead to miscarriage of justice for brain injury victims.

1. Classifying Brain Injury as Mild, Moderate and Severe is Outdated and Counterproductive

10.24.13

A. JAMA Viewpoint: The evolution of brain injury science over the last decade has caused most scientists who focus on this field to reject any one size fits all "mechanistic" definition for what has been increasingly understood as a heterogeneous, not a homogeneous condition – in other words, there are an infinite variety of brain injuries depending on the precise pathoanatomical and molecular features of the injury. These definitions do not incorporate newer insights and findings from diagnostic tools such as imaging and biomarkers and therefore do not promote "mechanistic targeting" for clinical trials.

B. This notion that every brain injury is unique and may cause a unique pattern of symptoms is not new. Bryan Jennett, Professor of Neurosurgery at the University of Glasgow and originator of the well-known "Glasgow Coma Scale," said in 1981 that: "Impairment of Consciousness is indicative of diffuse brain damage, but there can also be marked local damage without alteration of consciousness or amnesia."

C. One of the most striking examples was the classic report of the head injury of Phineas Gage, which occurred in Vermont in 1848. Gage, a railroad worker, sustained a severe frontal lobe injury when an explosive charge propelled an iron bar upwards through the lower left side of his face with the point of the bar exiting the top of his skull after passing through the left frontal lobe. Mr. Gage never lost consciousness and was reported to be sitting up and talking with the bar protruding from his skull.

2. Concussion as a Medical Diagnosis

5.27.14

A. Dr. Alhilali, lead author in a paper published in the journal Radiology in April 2014, noted that one of the most important implications of his study is that "[c]oncussion is not just one pathology, but many different injuries with different symptoms. Not every case is the same, and we need to treat every patient differently."

Using the MRI technique known as DTI, "diffusion tensor imaging," (see explanation below) the researchers found that concussed patients with persistent vision and balance problems exhibited damage in the parts of the brain known to be associated with vision and balance.

B. Similarly, a March 2014 paper published in the American Journal of Radiology found that post-concussion patients with persistent sleep-wake cycle disturbances were more likely to have brain anatomy that makes the pineal gland – which produces melatonin – subject to impingement when the brain is exposed to acceleration/deceleration forces.

C. Dr. John Leddy and his team of researchers at the University of Buffalo have identified a substantial subset of concussion patients with disturbed autonomic nervous system function, causing greater sympathetic nervous system activity and lower parasympathetic nervous system activity than controls. "This may explain, " Dr. Leddy's team reports, "why symptoms often reappear or worsen with physical and/or mental exertion."

3. Functional Brain Imaging Helps Explain Post-Concussion Symptoms and Role of Exercise in Healing
12.11.13

Publishing in the *Journal of Head Trauma Rehabilitation* the University of Buffalo team, using functional brain imaging (fMRI), found that post-concussion patients had a hypermetabolic state. "Normal subjects," the authors reported, "use a few specific regions of the brain to accomplish the task whereas the [post-concussion] patients used multiple areas of the brain. Patients' brains were lit up like Christmas trees." This explains, the authors note, why many patients can still accomplish the same tasks, but tire out quickly. The authors also found that patients treated with a program of graded aerobic exercise showed significant improvement in symptoms.

4. Growing Support for Treating TBI as a Chronic Disease
8.27.13

Two recent paper provide additional scientific support for the position statement issued by the BIA in 2009 that "brain injury" should be treated not as a static event from which patients gradually recover over time, but as the beginning of a disease process that can cause symptoms that change over time, in some cases getting worse instead of better, and that can impact multiple organ systems.

5. A New Paradigm for Understanding Incapacitating Post-Concussion Syndrome
5.28.15

McMaster University researchers, publishing in the medical journal *Brain Behavior*, offer strong evidence that one of the underlying mechanism for post-concussion symptoms (headaches,

irritability, depression, sleep disturbance, fatigue, dizziness and memory impairment), as well as similar symptoms found in patients without a history of head injury – such as patients with infections or PTSD – is a systemic inflammatory and immune response producing neuroinflammation. The authors point out that subtle *genetic differences* may influence the extent and persistence of the inflammatory response. This insight may impact treatment going forward, highlighting the potential benefits of anti-inflammatory medications already being explored for treatment of depression and controlled exercise (which is known to reduce pro-inflammatory cytokines.)

6. Link Between TBI and Alzheimers: The Bad News and the Good News
4.30.15

The April 2015 issue of the *Journal of Neuroscience* offers new evidence concerning the link between head injury and later development of Alzheimer's disease-related clinical symptoms. They build on other studies showing a link between neuroinflammation and neuropathology characteristics in both brain injury and Alzheimer's. Using mice genetically altered to made a protein found in Alzheimer's, the authors were able to prevent the development of these symptoms following head injury by administering a drug which blocks overproduction of the molecules that cause neuroinflammation.

7. Neuroendocrine Dysfunction following Traumatic Brain Injury: Could This be a Key to a More Successful Treatment?
5.21.14

In August 2012, the Defense Department recommended screening for neuroendocrine dysfunction in mTBI cases. Because of its vulnerable location in the brain, the pituitary gland is vulnerable to sheer damage. This pea-sized gland located in the center of the skull releases several essential hormones affecting such functions such as growth and metabolism. Deficiencies in key hormones such as Growth Hormone (GH) can cause persistent symptoms commonly seen in mTBI cases, such as fatigue, poor memory, emotional lability, lack of concentration and attention difficulties. According to the Defense Department, there is some evidence that pituitary dysfunction caused by injury *may worsen over the five year period following the injury*. (calling for ongoing screening.) There is some controversy over the tests needed to effectively screen for this condition; for example, whether a standard blood test is adequate.

8. Visual Dysfunctions Following Concussion and Other Traumatic Brain Injury
3.25.14

Research recently published by the VA indicates that the percentage of TBI victims with vision problems may be as high as 60% - not surprising since over 50% of the brain in used in visual processing. (The post includes a detailed description of the pathological process by which acceleration/deceleration can damage the brain's visual processing systems.) One of the most

common vision problems following TBI is convergence insufficiency; the ability of the eyes to focus on near objects, maintaining "binocular vision" (thought to depend on the integrative function of the cortical and subcortical areas of the brain.) People with convergence insufficiency may report an array of vision challenges, including blurred vision, double vision (diplopia), eye strain, headaches, loss of concentration, difficulty reading and remembering, and visual fatigue. There is good evidence that vision therapy helps improve vision in many patients.

Another more commonly recognized visual problem following TBI is photophobia (sensitivity to light) which can in turn lead to headaches, eye strain, an fatigue.

9. The "Show Me" Jury Challenge | Proving TBI to a Jury
5.9.13

A. We live in a world of "show me" juries, programmed to believe that most people bringing personal injury claims to trial are trying to get something for nothing.

Among the most common defenses to mTBI claims are the following:

1. The EMT/Police/Medical Records do not document loss of consciousness (or alteration of consciousness) or amnesia – symptoms often found following mTBI and referenced in many standard "mechanistic" definitions. (Most "definitions" include these symptoms in a list calling for "one of more of the following" and including "neurological dysfunction" and "positive imaging findings" on this list.)

2. Conventional imaging, used to determine whether acute intervention is need because the brain is bleeding or swelling, is normal. The inference drawn is that these "normal" results indicate no injury. (We now have imaging more capable of visualizing axonal damage; however this imaging is not commonly used for treatment because if it not needed to detect the conditions requiring immediate intervention, such as swelling or bleeding.)

3. Most mTBI victims get better over a few days or weeks. The inference drawn is that people who do not get better, and especially people who get worse, must be faking, intentionally or unintentionally. (This is inconsistent with the notion that TBI can be a disease process which evolves over time and that certain injuries caused be concussion, as discussed above, can be persistent.)

B. A definition more closely following our current understanding of TBI is the following definition offered by Dr. Barlow at a recent deposition: "A traumatic force that is put on the brain that results in an alteration in the function of the brain."

10. A Surprisingly High Percentage of Uncomplicated MTBIs have Persistent Deficits and Require Ongoing Therapy
6.17.15

The April, 2015 issue of The American Surgeon reports that a surprisingly high percentage of patients with MTBI with "normal" CT results and "normal" Glasgow Coma scores had persistent deficits after neurocognitive testing and would benefit from referral for ongoing therapy. The authors found that whether or not the patient lost consciousness was of no predictive value in determining long term deficits. The authors recommend a change in ER protocols for MTBI patients.

11. Progress on Proving Mild Traumatic Brain Injury Using Biomarkers
6.27.13

In June, 2013 University of Rochester Medical Center researchers published evidence in the *Journal of Neurotrauma* that two protein biomarker predict which patients will experience persistent symptoms following mTBI. This research builds on evidence that injury triggers a chemical cascade, a pathological process that interrupt axonal transport and produces an accumulation of protein products. It supports our understanding that persistent symptoms are not, by definition, "psychological and not physiologic", as defense experts would have us believe.

12. Study Links Tau Protein with Persistent Post-Concussive Symptoms
8.13.15

New research from the National Institute of Health, published in the August, 2015 issue of JAMA *Neurology*, shows that a protein ("Tau") that was until recently linked only to acute symptoms following TBI, may also be responsible for chronic neurological symptoms such as headaches and dizziness found in patients with persistent post-concussion syndrome. The researcher adopt the "disease process" model to explain these finding. "Months to years after the primary injury," Anlys Olivera, Phd, one of the researchers wrote, "there may be a continuation of secondary injuries with residual axonal degeneration and blood-brain barrier disruptions in this population that may contribute to the maintenance of post-concussive symptoms and affect symptom severity."

13. The Verdict is Clear: Diffusion Tensor Imaging Demonstates Damage to the Brain Associated With Mild Traumatic Brain Injury
1.5.15

Damage typically associated with mTBI is in the axons, the microscopic fiber tracts in the white matter of the brain too small to be seen by conventional tools such a MRI and CT. In fact, an individual with a perfectly normal MRI and CT could even be in a coma due to brain injury. Treatment providers have been left to infer injury from clinical symptoms. However, even the most commonly used clinical tools, such as neuropsychological assessment, are generally seen as insensitive to the subtle, but sometimes life-altering, effects of mTBI. Countless peer-reviewed studies over the last several years have shown that "diffusion tensor imaging" (DTI) is a reliable tool to detect damage in these microstructures of the brain. DTI works by measuring the distribution of water through portions of the brain based on the known physics of the flow of

water. Healthy white matter in the brain creates barriers to the flow of water, which therefore moves unequally in all directions (called anistrophic distribution.) However, when the white matter is damaged, the outer membranes are broken down, causing water to flow equally in all directions (called isotrophic distribution.) DTI divides the brain into thousands of voxels and measure the distribution of water through each voxel, providing a score known as "fractional anistrophy" (FA). The FA for each voxel is then compared to the mean FA scores of a group of healthy volunteers. Significant deviations (more than two standard deviations) indicate damage – especially in areas of the brain known to be susceptible to axonal injury through trauma, such as the grey-white matter junctions of the brain.

Since 2006 Defendants in approximately 30 legal cases have sought to exclude evidence of DTI results, but this evidence has been permitted in each case.

14. Study Shows Brain Atrophy Following "Mild" Traumatic Brain Injury
5.30.13

In March 2013, NYU researchers published a study in the *Journal of Radiology* finding a correlation between persistent post-concussive symptoms such as anxiety, depression, fatigue, headache, dizziness and perceived cognitive changes, and global and regional loss of brain volume. Prior studies had shown that progressive atrophy of the brain occurs after "moderate" and "severe" TBIs. This study documents that the same thing can occur after a single concussion.

15. The Power of Mindfulness
3.3.14

A recent study in the *Journal of Head Trauma Rehabilitation* found that mindfulness based practices improved symptoms, particularly depression, following TBI. One explanation offered in that these practices help improve acceptance and awareness "thereby minimizing the catastrophic assessment of symptoms associated with TBI and chronic disability."

One of most overwhelming symptoms experienced by victims of brain injury who do not recover fully, is the grief experienced over the loss of "self," the person before the accident with capabilities that did not survive after the accident. Getting beyond this understandable attachment to the past is one of the greatest challenges of recovery. There is growing evidence that "mindfulness" practice such as yoga and meditation can be a useful tool to recapture ones sense of self and thereby reduce the barrier to recovery caused by grief and depression. These practice are designed to increase awareness of the present moment- to increase awareness of thoughts, physical sensations and emotions without filtering them through past experience or fears of the future. Victor Frankl, a neurologist, concentration camp survivor, and author of "Man's Search for Meaning" describes the process as follows; "Between stimulus and response there is a space. In that space is our power to choose our response. In our response lies our growth and freedom." Mindfulness practices are designed to find that space between stimulus and response and choose a new and more productive response.

Classifying TBI as Mild, Moderate or Severe is Outdated and Counterproductive

10.24.13

The August issue of the *Journal of the American Medical Association* (JAMA) includes a "Viewpoint" by two leading neuroscientists promoting the use of an "International Knowledge-Based Approach" to traumatic brain injury (TBI).

One of the causes of the failure of clinical trials to successfully treat TBI, the authors contend, is the common classification of TBIs as "mild, moderate or severe." These classifications do not incorporate newer insights and findings from diagnostic tools such as imaging and biomarkers and therefore do not promote "mechanistic targeting" for clinical trials. The authors support the transition to a more nuanced approach, a precise disease classification model that is based on the precise pathoanatomical and molecular features of the injury.

As discussed in my previous post on "Meta- Analysis," the existing classification approach lumps TBIs into the mild, moderate or severe category based on acute symptoms, such as length of unconsciousness or alteration of consciousness, or Glasgow Coma Scale, and assumes that all injuries with similar symptoms will follow a similar course. In other words, brain injuries are treated as "homogeneous" when we know from research over the last several years that they are very "heterogeneous."

As we have gained more ability to measure brain pathology following injury, it makes more sense to focus on the actual injury, not just the acute symptoms.

One study the authors point to as holding promise for providing a more useful approach is a 2013 study by Yuh, et al, in the *Annals of Neurology* where magnetic imaging uncovered structural abnormalities in approximately 30% of 135 patients with mild TBI and a normal computed tomographic (CT) scan. The presence of these abnormalities predicted an unfavorable outcome at three months. "This study," the author of the Viewpoint say, "represents an important step toward improved stratification of heterogeneous patient subgroups within the population traditionally classified as having mild TBI or concussion."

Another development referred to by the authors has also been discussed in this blog, the newly validated blood-based glial proteomic biomarkers which have been shown to reliably detect the presence and severity of brain injury seen on CT scan.

Progress towards a more nuanced approach to TBI continued with a very recent October 2013 article in the *Journal of Neurotrauma* presenting evidence that there are genetic influences on the outcome following a TBI, impacting the neuroinflammatory processes that contribute to the severity of outcome.

It is time to move beyond the unproductive use of terms like "mild, moderate and severe" and develop an approach that takes advantage of our growing understanding of the brain and its response to trauma.

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Concussion as a Medical Diagnosis

5.27.2014

Different symptom patterns of concussion depend on the precise nature of the damage to the brain. Medical research is increasingly identifying the various ways a concussion can impact the brain and is providing explanations for why different symptoms persist in a subset of people diagnosed with concussion, based on the anatomy and physiology of the brain.

Much of this recent research has benefited from new techniques to "image" the brain, including various MRI techniques such as "diffusion tensor imaging" ("DTI"). In a prior post, I discussed research concerning the subset of concussed patients who experience persistent ocular (vision) and vestibular (balance) problems. A paper published online on April 15, 2014 in the journal Radiology reported that DTI imaging of patients with these symptoms revealed damage in the parts of the brain know to be associated with vision and balance.

Dr. Alhilali, the lead author, noted that one of the implications of the study is that

> "Concussion is not just one pathology, but many different injuries with different symptoms. Not every case is the same, and we need to treat each patient individually."

On the same theme, a study published by Yeager et al in March 2014 in the American Journal of Radiology found that post-concussion patients with persistent sleep-wake disturbances are far more likely to have brain anatomy that makes the pineal gland –which produces melatonin – more likely to be impinged when the brain is subjected to the acceleration/deceleration forces involved with a concussion.

A group of researchers from Buffalo led by Dr. John Leddy have focused on a substantial subset of concussion patients who manifest metabolic and physiological changes in organ systems outside the brain. A common manifestation is higher heart rates at rest and after cognitive and physiological stress. The Buffalo team relies on research showing that concussion can disturb the autonomic nervous system, causing greater sympathetic nervous activity and lower parasympathetic activity, compared to controls.

Concussion can also disturb "autoregulation," the maintenance of cerebral flow at appropriate levels during changes in systemic blood pressure.

> "This may explain," Dr. Leddy's team reports, "why symptoms often reappear or worsen with physical and/or mental exertion. "

Dr. Leddy's team tests patients by subjecting them to a "provocative exercise" test they call the "Buffalo Concussion Treadmill Test." In addition to higher heart rates than would be expected, patients with ongoing symptoms commonly experience a painful tightness in the head when subjected to this exertion. This test is recommended as a tool to determine exercise tolerance levels, permitting gradual return to function in most patients.

Dr. Leddy's team reaches the same conclusion – that concussion is better viewed as a medical problem than as a neuropsychological problem and that the symptoms usually have a medical explanation. This perspective increases the potential for medical solutions, good news for victims of persistent concussion symptoms.

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Functional Brain Imaging Helps Explain Post-Concussion Symptoms and Role of Exercise in Healing

12.11.2013

Using functional brain imaging (fMRI) a multidisciplinary team of researchers at the University of Buffalo have documented metabolic and physiologic changes in the brains of patients experiencing post-concussion symptoms. They found improvements in both imaging findings and in patient symptoms following a controlled, progressive aerobic exercise program. The results have been published in both the Journal of Head Trauma Rehabilitation and in Current Sports Medicine Reports and are summarized in UB news releases.

The authors report that following concussion students often report that they can make it through the first couple of classes but end up exhausted and unable to continue through the day. When assessed for cognitive ability their speed and accuracy is often indistinguishable from subjects without concussion, leading to the inaccurate suggestion that the symptoms are psychologic and not physiologic or metabolic. Functional imaging studies of post-concussion patients showed a hypermetabolic state with altered blood flow compared to normal subjects.

> "Normal subjects," the authors report, "used a few specific regions of the brain to accomplish the task whereas the [post-concussion] patients used multiple areas of the brain. Patients' brains were lit up like Christmas trees, reflecting hyperactivity of metabolism."

This explains the experience of many patients–they can still accomplish some of the same tasks, but quickly tire out.

The researchers also found that patients with concussion had less activation in certain areas of the brain compared to normal subjects, such as the cerebellum, which is responsible for balance and coordination and the posterior cingulate, which is often underactive in patients with dementia.

Patients who were treated with a program of graded aerobic exercise showed significant symptom improvements. Many studies have shown that premature return to exercise can interfere with recovery from concussion and that early exposure to the risk of a second concussion should be avoided. Victims of concussion should therefore consult with their physicians to insure that any program of aerobic exercise is advisable and consistent with the parameters used in UB study.

Growing Support for Treating TBI as a Chronic Disease

8.27.13

Two recent peer reviewed papers support the position statement adopted by the Brain Injury Association in 2009 that "Brain Injury" be treated not as static event from which patients gradually recover over time, but as the beginning of a disease process that that can cause symptoms that change over time, in some cases getting worse instead of better, and that can impact multiple organ systems.

The good news is that most people do, in fact, recover. For those who do not, however, the disease model is more consistent with the evolving research. As McCrea, Iverson, McAllister, et. al. noted in their 2009 Integrated Review of Recovery after Mild Traumatic Brain Injury, brain injury science has advanced more in the last few years than in the previous 50, causing us to change the paradigms we have used to understand both the injury and its consequences.

Research Supports Treating TBI as a Chronic Disease

The most recent paper, Traumatic Brain Injury as a Chronic Health Condition, by Corrigan and Hammond, is in the August 2013 issue of the *Archives of Physical Medicine and Rehabilitation*. The paper begins with the premise, based on contemporary research, that "some mild TBIs and most severe injuries" can cause permanent impairments. The usual clinical precept is that these residual effects are static once initial recovery has plateaued. The authors note, however, that data from the TBI Model Systems National Database suggests that change is more common than stability for long-term global outcomes.

The data also indicates that onset of symptoms can be delayed and progressive and that "cognitive deficits, depression, psychosis, and social isolation emerged or reemerged much later after injury." This information has treatment implications – indicating that people may benefit from receiving periodic monitoring of the evolution of the disease process and ongoing treatment for cognitive, motor, psychological or other issues that arise.

Similar observations are made in an August 2010 abstract in the *Journal of Neurotrauma*, by Masel and DeWitt, Traumatic Brain Injury: a Disease Process, not an Event. The authors note that TBI can increase long-term mortality and reduce life expectancy and can be "associated with increased incidences of seizures, sleep disorders, neurodegenerative diseases, neuroendocrine dysregulation and psychiatric diseases, as well as non-neurological disorders such as sexual dysfunction, bladder and bowel incontinence, and systemic metabolic dysregulation that may arise and/or persist from months to years post-injury."

As discussed in other posts, the accelerating research on TBI is providing more and more information on the factors that cause or predict these chronic problems, including such factors as genetics and the existence of focal lesions. The hope is that with better understanding and better ongoing treatment, the consequences of this disease can be minimized.

A New Paradigm for Understanding Incapacitating Post-Concussion Syndrome

5.28.2015

In a study published in April 2015 in the medical journal Brain Behavior and Immunity, a team of Canadian researchers at McMaster University presents a new understanding of the cause of the wide-array of symptoms experienced by some patients following concussion, such as headaches, dizziness, sleep disturbance, fatigue, cognitive impairment and neuropsychiatric symptoms.

This new paradigm helps to explain why the same pattern of symptoms can be found in some non-head injury patients, such a patient who has experienced infections or a patient diagnosed with post-traumatic stress disorder. It also helps to explain why some patients recover and others do not and why pre-accident experience can influence the course of post-accident recovery.

A pattern of symptoms producing neuroinflammation is described as Post-Inflammatory Brain Syndrome (PIBS)

The authors' analysis of the peer-reviewed literature revealed strong evidence that one of the underlying mechanisms for post-concussion symptoms, as well as similar symptoms found in patients without a history of head injury – such as patients with infections or PTSD – is a systemic inflammatory and immune response producing neuroinflammation. The authors suggest that a better term to describe this pattern of symptoms is "post-inflammatory brain syndrome" or PIBS.

Neuroinflammation is inflammation within the nervous system and includes activation of immune cells (particularly microglia) and non-immune cells, as well as increases in inflammatory mediators (including cytokines.) It has long been known that production of cytokines is increased in the brain following concussions. The authors review evidence supporting the conclusion that inflammation plays a role in producing symptoms such as headache, irritability, depression, sleep disturbance, fatigue, dizziness and memory impairment. The authors conclude that "there are many significant reasons to suspect that the generation of cytokines is involved in the etiology of post-concussion syndrome." Patients with polytrauma not including TBI may also experience a systemic inflammatory reaction, explaining why they may have similar symptoms. Increased sensitivity to stress, found in patients with a history of depression, can result in an increased inflammatory response, explaining why a history of depression may increase the likelihood of persistent post-concussion symptoms. The authors also point to evidence that subtle genetic differences may influence the extent and persistence of the inflammatory response.

This new paradigm may impact future treatment. The authors suggest that anti-inflammatory medications being explored for treatment of depression may be a potential avenue for treatment of post-concussion syndrome. The authors also endorse the potential benefits of exercise, which is known to reduce the levels of pro-inflammatory cytokines. Earlier posts in this blog have reviewed evidence on the benefits of controlled exercise as a treatment for persistent post-concussion syndrome. This new paradigm offers an explanation for why these benefits may occur.

Link between TBI and Alzheimers: The Bad News and the Good News

4.30.2015

The latest issue of the *Journal of Neuroscience* (April 22, 2015) reports on animal research from the University of Kentucky which "adds to an increasing body of knowledge strongly indicating that traumatic brain injury is a contributor to increased susceptibility to Alzheimer's Disease-relevant pathologies, including cognitive dysfunction."

The authors begin by noting that "epidemiological studies have associated increased risk of Alzheimer's disease-related clinical symptoms with a medical history of head injury," but that "little is known about the pathophysiological mechanisms linked to this association." Prior studies, as well as this study, did find that persistent neuroinflammation is one outcome observed in patients *after a single head injury*.

The first conclusion in this study is that

> "a single, comparatively mild, diffuse brain injury administered before onset of age-associated functional deficits and pathology in an AD-relevant mouse model can induce chronic cognitive impairment."

Similar neuroinflammation has also been found to be present early in relevant brain regions during the Alzheimer's disease progression. Animal studies models have linked neuroinflammation to neuropathology and cognitive impairment in both brain injury and Alzheimer's disease.

The authors explored the potential interplay between these two pathologies in hopes of making progress towards a treatment that might interrupt the process that links the two conditions. The results of the study laid a foundation for developing such a treatment. To explore the chain of events that link TBI to dementia, the authors used mice that were genetically altered to make a human protein called amyloid beta, a key player in Alzheimer's disease. The mice were then subjected to a procedure that mimics a mild traumatic brain injury. Some of the mice received a small molecule drug known as MW151, which blocks overproduction of the molecules that cause inflammation in the brain following TBI. The mice that received this treatment no longer showed learning and memory problems, while the mice that didn't receive the drug showed profound learning and memory problems.

The implications of this work regarding a link between TBI and Alzheimers cannot be overstated, as the authors note in a recent story on the research in ScienceDaily:

> "As the signature injury of the Iraq and Afghanistan wars, and with approximately 1.5 million people in the United States each year seeking medical treatment for a traumatic brain injury, the impact of earlier onset of dementia in such a large number of people is simply unthinkable…Adam and Scott's work could have a large impact both socially and economically."

Neuroendocrine Dysfunction following Traumatic Brain Injury: Could This be a Key to More Successful Treatment?

5.21.2014

Recent research has shown that traumatic brain injury, (TBI) including mild traumatic brain injury (mTBI), can damage and cause dysfunction in the pituitary gland, a pea-sized gland located in the center of the skull that releases several essential hormones affecting such functions as growth and metabolism (part of the neuroendocrine system). Researchers have found that a surprisingly high percentage of patients with persistent symptoms following a TBI show evidence of neuroendocrine dysfunction.

It turns out that the anatomy of this gland makes it particularly susceptible to the sheering injuries seen in TBI. The most common dysfunction found after TBI is deficiency in the Growth Hormone (GH), one of the key hormones released by the pituitary gland. The symptoms of GH deficiency overlap with many persistent TBI symptoms including fatigue, poor memory, depression, emotional lability, lack of concentration and attention difficulties. The good news is that most hormonal deficiencies, including GH deficiency, can usually be treated, with a significant improvement in quality of life. The bad news at the moment is that many physicians treating TBI patients with these persistent symptoms are not aware of this research and are not referring their patients to endocrinologists for assessment.

US Defense Department Experts Recommend Screening for Neuroendocrine Dysfunction following Traumatic Brain Injury

The US Defense Department was once again on the cutting edge of this issue when it published clinical recommendations for screening for neuroendocrine dysfunction in mTBI cases in August 2012. These recommendations were developed by a panel of experts relying on current research and are intended to provide guidance to primary care providers. (More detailed training slides are also available.)

It is recommended that all patients experiencing post-concussion symptoms for more than three months should be assessed for neuroendocrine dysfunction (NED). The training materials indicate that approximately 15% of people who suffer a mild traumatic brain injury experience persistent symptoms lasting more than three month and that of this group, between 15% and 30% develop NED. Identifying these patients and treating the NED significantly improves prognosis. The materials also note that NED may develop up to three years after the injury, consistent with the notion discussed in prior blog posts that TBI should be seen as potentially a disease process, not as just an acute injury.

A year after the Defense Department released its clinical guidelines in this area the Journal of Neurotrauma released a five-year prospective investigation of pituitary function after TBI. The study reinforces the defense recommendations, also concluding that

> "screening the pituitary function after TBI for five years is important, especially in patients with mild TBI."

The study also found that in some patients pituitary dysfunction may worsen over the five year period following the injury.

Both the study materials and the defense materials note that in addition to the commonly seen TBI symptoms, hormonal deficiencies may produce physical symptoms, including increased fat mass, especially in the abdominal area, and impaired lipid profile (commonly referred to as a to cholesterol test.) Increased total cholesterol and triglyceride levels are not uncommon.

I recently discussed the importance of assessing vision following a TBI, especially convergence insufficiency, since this condition can also produce many of persistent symptoms associated with a TBI and can often be treated. A neuroendocrine assessment also appears to be a potential key to more successful treatment of persistent symptoms.

Visual Dysfunctions following Concussion and other Traumatic Brain Injuries

3.25.2014

Recent literature has highlighted the prevalence of dysfunctions in vision following traumatic brain injuries of all levels of severity (including concussion.) Research published by the Veterans Administration (VA) in 2012 indicates that the percentage of TBI victims with vision problems could be as high as 60%. They explain that this prevalence is not surprising, since over 50% of the brain is involved in visual processing. Alvarez et. al. explain how visual and other symptoms occur when the brain is subjected to "acceleration/deceleration" forces:

> TBI may be associated with diffuse axonal injury (DAI), which may occur with or without a focal blunt force to the head.28, 29 Trauma of acceleration / deceleration may lead to damage to the white matter and superficial layers of the brain. This damage may then extend inward within the brain, depending upon the extent of acceleration / deceleration forces. Initially, the injury disrupts the cytoskeletal network and axonal membranes of white matter and the surrounding cerebral vasculature.30–33 Secondary damage may occur due to ischemia and a cytotoxic cascade, including altered calcium homeostasis and oxygen depletion, leading to cell death.30–33The recovery from TBI may be determined by the severity of these secondary injuries.32, 33 Some brain regions may be more at risk for mechanical injury during trauma than others.34 Given the presumed diffuse damage of TBI, it is not surprising that TBI manifests in a diverse array of motor, sensory, cognitive and / or emotional symptoms and disabilities, both short and long-term.[1]

One of the more common vision problems after traumatic brain injury is "convergence insufficiency." Convergence is the simultaneous inward movement of both eyes toward each other, usually in an effort to maintain single binocular vision when viewing an object. It is part of the near-vision complex of the brain and depends on the integrative function of the cortical and subcortical areas, which is often compromised by traumatic brain injury.

As the VA research report notes, patients with convergence insufficiency report an array of vision challenges, including blurred vision, diplopia (double vision), eye strain, headaches, loss of concentration, having to read and/or reread slowly, difficulty in remembering what was read and visual fatigue. Needless to say these symptoms may adversely affect daily activities such as schoolwork and employment tasks, as well as the overall quality of life. They can also lead to inadequate progress in other rehabilitative services, such as cognitive therapy.

Another very common vision problem following TBI is "photophobia" (heightened sensitivity to bright light.) This can also lead to other symptoms including headaches, eye strain and fatigue and can severely limit day-to-day functioning.

There is good news concerning treatment of vision issues following TBI, especially convergence insufficiency. The January 2014 issue of NeuroRehabilitation reported the findings of

[1] Concurrent vision dysfunctions in convergence insufficiency with traumatic brain injury. Optom Vis Sci. 2012 Dec;89(12):1740-51.

Thiagarajan et. al. that ocular-motor based vision rehabilitation had a strong positive effect on oculomotor control, reading rate and overall reading ability. This ocular motor learning effect suggests considerable residual neuroplasticity and good potential for improvement of these symptoms. Treatment for photophobia remains less clear.

TBI victims who experience any of the symptoms associated with vision defects are encouraged to seek assessment and treatment.

The “Show Me” Jury Challenge | Proving TBI to a jury

5.9.13

We live in a world of “show me” juries, programmed to believe that most people bringing personal injury claims to trial are trying to get something for nothing. They want to be convincingly shown that a real injury exists—that the injured person can prove a brain injury or other debilitating condition.

Proving a Mild Traumatic Brain Injury to a Jury

For example, some brain injuries produce bleeding in the brain that clearly shows up on conventional diagnostic images like CT scans—computerized tomography that combines a series of X-ray views taken from many different angles and processed by a computer to create cross-sectional images of the bones and soft tissues inside your body—and/or MRIs—magnetic resonance imaging that uses a magnetic field and radio waves to create detailed images of the organs and tissues within your body—or, that produce visible neurological signs like seizures, visual problems, speech problems, or motor problems.

Proving a brain injury to a jury where visible evidence is available is not difficult. However, we know that many mild traumatic brain injuries are “invisible” to these standard tests, yet are serious enough to greatly impact quality of life. In these cases, the challenge is to help the jury understand those long-term consequences, even when the injury is not visible.

For example, let’s say that the injured person can still walk and talk and at first blush appears normal. In fact, many people with brain injuries find, after getting over the immediate trauma of physical injuries in an accident, that they “just don’t feel like themselves.” They have problems like insomnia, fatigue, and dizziness, ringing in the ears, nausea, irritability, poor concentration, light sensitivity, or loss of smell or taste. So, while they can still function, it takes that much longer to get anything done and by mid-afternoon they are spent.

Sometimes these problems get worse instead of better—sometimes they go away and sometimes they do not. However, when conventional MRIs and CT Scans are normal but the injured is not, friends, family and employers get frustrated that things are not improving and question whether or not the injured person is even trying. Depression begins to set in, making everything even worse.

Making Progress in Proving “Invisible” Brain Injuries

I presented this scenario in an article titled, “Proving a “Mild” Traumatic Brain Injury: A complex but not Longer Impossible Task,” which was first published in the Spring 2012 issue of the Vermont Bar Journal and more recently distributed by “The Research Network on Law and Neuroscience,” a program operated by faculty of the Vanderbilt University and supported by the John D. and Catherine T. MacArthur Foundation. The article outlines three areas of development that have made proving a brain injury (to a jury) a little easier than in the past.

1. Research on brain-injuries-and-veterans conducted by the Department of Defense
2. Research on brain-injuries-and-athletes conducted by the Center for the Study of Traumatic Encephalopathy (and other groups)

3. Ongoing study conducted by the Centers for Disease Control and Prevention (CDC), and publications issued by the CDC that address many common misperceptions concerning TBI, especially “mild” TBI

As a result of these scientific developments, we are learning new ways to diagnose the injury, and the public is exposed to learning more about the severe consequences an “invisible” injury can cause.

The future holds great promise for those who are struggling with invisible, debilitating brain injuries. I will be closely monitoring the progress of these studies and will report on this blog the new developments and how we can use them to the benefit of those who suffer from “invisible” brain injuries—in both their treatment and the courtroom. Meanwhile, feel free to contact me directly with your questions.

A Surprisingly High Percentage of Uncomplicated MTBIs have Persistent Deficits and Require Ongoing Therapy

6.17.2015

The April, 2015 issue of The American Surgeon reports on a retrospective study of 395 patients admitted to the ER following concussions (MTBI, or mild traumatic brain injury). The patients had "normal" Glascow Coma scores of 15 and normal CT scans and therefore met discharge criteria. The study found that a surprisingly high percentage of these patients (27%) had persistent deficits after neurocognitive testing and benefitted from referral for ongoing therapy. The study is authored by Hartwell et. al. and entitled "You Cannot Go Home: Routine Concussion Evaluation is Not Enough."

The authors report that in their Columbus, Ohio medical centers this study has led to "a heightened awareness of persistent MTBI symptoms" and to routine early neurocognitive screening of MTBI patients in the acute setting. The authors found no predictors of persistent symptoms that could be used in the ER setting other than neurocognitive testing – whether or not the patient had lost consciousness was of no predictive value. This study builds on prior authority, referenced in the report, that "up to 15 to 40 percent of patients will experience symptoms and report persistent deficits for a year or longer." For these patients, early identification and early intervention is important to improve long term outcomes.

As previously discussed in this blog, there has been controversy in the past concerning whether or not persistent symptoms following concussion are physiological or only psychological. Scientific developments over the last several years (as also discussed in this blog) have left very little doubt that in a substantial subset of patients, a concussion leads to changes in the brain and that these changes can cause symptoms that persist and in some cases get worse over time. This new report highlights the importance of changing ER protocols to recognize this understanding, identify patients with neurocognitive deficits and provide appropriate early intervention.

Progress on Proving Mild Traumatic Brain Injury Using Biomarkers

6.27.2013

Concussion, or mild traumatic brain injury (TBI), typically produces no gross pathology, such as hemorrhage or abnormalities, that can be seen on conventional CT scans of the brain. It does cause rapid-onset neurophysiological and neurological dysfunction that in most patients resolves spontaneously over a fairly short period of time. Studies have shown, however, that approximately 15% of individuals with mild TBI develop persistent cognitive dysfunction and other symptoms. Researchers are starting to make progress on proving mild traumatic brain injury using the biomarkers that underlie such symptoms.

We know that mild TBI can be caused either by an impact to the head inducing rotational acceleration of the brain, or rapid rotational acceleration of the head without impact. Mild TBI without impact is commonly seen in restrained drivers during a motor vehicle impact. At a neurophysiological level, these mechanical and inertial forces result in stretching of white matter axons, leading to diffuse axonal injury (Nature Reviews Neurology 9, 201-210 (April 2013) | doi:10.1038/nrneurol.2013.9). This injury triggers a chemical cascade, a pathological process that interrupts axonal transport and produces an accumulation of protein products.

Scientists have been actively engaged in the discovery of biomarkers for TBI in the last decade, research based on our awareness that TBI produces pathological changes in the chemistry of the brain. This research is very exciting because it will likely lead to the use of blood tests to both diagnose traumatic brain injury and to determine the likely severity of the consequences. The "invisible injury" will be made more visible. A number of review articles have captured the pros and cons of various potential markers, typically focused on the proteins that accumulate following injury.

On June 18, 2013, researchers at the University of Rochester Medical Center in upstate New York announced the results of study which produced significant evidence to support the development of an effective blood test.

The study, published in Journal of Neurotrauma, showed that a combination of two protein biomarkers, S100B and ApoA-1, significantly increased the correct diagnosis of mild TBI. The study further showed that one of the biomarkers, S100B, was effective at predicting which patients would likely have abnormal CT scans. This could lead to reduced use of CT scan, since this diagnostic tool only shows abnormalities in a small percentage of TBI cases.

We are seeing more exciting research on diagnosing and proving mild traumatic brain injury, a product of funding that has resulted from heightened awareness of the long-term health consequences of traumatic brain injury.

Study Links Tau Protein with Persistent Post-Concussive Symptoms

8.13.2015

Research from the National Institute of Health, published in the August 3, 2015 issue of JAMA Neurology, shows that a protein that was until recently linked only to acute symptoms following traumatic brain injury, may also be responsible for chronic neurological symptoms, such as headache and dizziness, found in patients diagnosed with persistent post-concussion syndrome.

Tau is a protein known to play a significant role in the development of Alzheimer's disease and Parkinson's disease. Using ultra-sensitive technology, the researchers measured levels of tau in the blood months and years after injury. These levels correlated with the severity of post-concussive symptoms. If these findings are further confirmed, this could be the first biomarker that is sensitive and specific to ongoing TBI symptoms.

The researchers adopt the current "disease process" model to explain these findings. "Months to years after the primary brain injury," Anlys Olivera, Phd, one of researchers wrote, "there may be a continuation of secondary injuries with residual axonal degeneration and blood-brain barrier disruptions in this population that may contribute to the maintenance of post-concussive disorder symptoms and affect symptom severity."

Tau protein is not only a marker of brain injury, it can contribute to secondary injury processes such as inflammation. This research may help with the development of therapies to prevent the aggregation of tau and the consequences of this aggregation.

The Verdict is Clear: Diffusion Tensor Imaging Demonstrates Damage to the Brain Associated with Mild Traumatic Brain Injury

1.5.2015

The weight of scientific evidence demonstrates that "diffusion tensor imaging" is an effective tool for demonstrating damage to the white matter of the brain associated with mild traumatic brain injury.

The damage typically associated with mild traumatic brain injury (mTBI) is in the axons, the microscopic fiber tracts in the white matter of the brain too small to be seen by conventional tools such as MRI and CT. In fact an individual with a perfectly normal MRI and CT could even be in a coma due to a brain injury. Treatment providers have been left to infer injury from clinical symptoms. However, even the most commonly used clinical tools, such as neuropsychological assessment, are generally seen as insensitive to the subtle, but sometimes life altering, effects of mTBIs.

In recent years scientists have developed and refined a new magnetic resonance (MR) sequence, known as "diffusion tensor imaging," (DTI) which has proven to reliably detect damage in these microstructures of the brain. DTI works by measuring the distribution of water through portions of the brain and is based on the known physics of the flow of water. Healthy white matter in the brain creates barriers to the flow of water, which therefore moves unequally in all directions (called "anistropic distribution.") However, when the white matter is damaged, the outer membranes are broken down, causing water to flow equally in all directions, (called "isotrophic distribution.") DTI divides the brain into thousands of voxels and measures the distribution of water through each voxel, providing a score known as "fractional anistrophy" (FA). The FA for each voxel is then compared to the mean FA scores of a group of healthy volunteers. Significant deviations (more than two standard deviations) indicate damage, especially in areas of the brain known to be susceptible to axonal injury through trauma.

Needless to say, insurers and defendants have aggressively objected to DTI evidence of brain injury, since it provides additional "objective evidence" contradicting the theme used by the defense in almost every case: that because the majority of people appear to recover quickly from mTBI, those with persistent symptoms must be malingering (or suffering from some "psychological" problem.)

Diffusion Tensor Imaging and Traumatic Brain Injury

Prior posts in this blog have highlighted the increasingly compelling scientific evidence demonstrating that mTBI does, in fact, result in lasting sequelae in a substantial minority of patients and that these sequelae have a microstructural neuropathological origin. Having a tool that effectively measures this microstructural damage is a game changer, which understandably accounts for the defense objections to this evidence. Since 2006, defendants in 24 pending legal cases have sought to exclude this evidence. In each of those cases, the defense has lost and the evidence has been permitted, based on the overwhelming consensus in the peer reviewed literature that when used in conjunction with clinical information, DTI is, in fact, highly effective in demonstrating damage to the white matter of the brain associated with mTBI.

An excellent history of the attacks on using this technology, and the response to those attacks in

the peer reviewed literature and in the courts, can be found in a recent article published by Dr. Manley Kilgore and attorney Dorothy Clay Sims in Brain Injury Professional, a publication of the North American Brain Injury Society. The article is titled "The Use of Diffusion Tensor Imaging to Assist in the Diagnosis of Traumatic Brain Injury." The most recent peer reviewed discussion of the issue can be found in an article recently published in AJOB Neuroscience by Dr. Michael Lipton, Albert Einstein College of Medicine, and Dr. Erin Bigler, Brigham Young University, titled "Clarifying the Robust Foundation for and Appropriate Use of DTI in mTBI Patients." Summaries of the peer-reviewed literature and affidavits of leading neuroscientists supporting the use of DTI can be found in the pleadings in the 24 court cases where this evidence has been permitted over defense objections.

Insurers and defendants will likely continue to deny the reality of persistent postconcussion symptoms and oppose use of scientific evidence demonstrating the physiological basis for these symptoms. The question must, however, be asked, "At what point is the evidence so clear that this strategy amounts to bad faith?"

Study Shows Brain Atrophy following “Mild” Traumatic Brain Injury

5.30.2013

Further evidence that the term “mild” should never be used in connection with brain injury can be found in a study published in the March 2013 issue of the Journal Radiology.

In the study, NYU medical school researchers measured changes in global and regional brain volume over a one year period in 30 patients with “mild” traumatic brain injuries and typical post-injury symptoms including anxiety, depression and fatigue, and other symptoms such as headache, dizziness and perceived cognitive problems.

The study demonstrated that after a single concussive episode there was measurable atrophy, or decrease in mass of the brain, one year after injury. It is well known that progressive atrophy of the brain occurs after “moderate” and “severe” TBIs. This study documents that the same thing can occur after a single concussion.

The study further found that the changes in brain volume correlated with performance on neurocognitive tests involving memory, anxiety and other postconcussive symptoms. This study is important because it provides concrete evidence that persistent symptoms following a “mild” TBI can have a tangible chronic pathophysiologic origin.

Not surprisingly, the study found significant intersubject variability in brain changes.

The Power of Mindfulness

3.3.2014

I travel between two worlds that may appear far apart – by day I am a trial lawyer with a focus on traumatic brain injury; nights and weekends I am a yoga teacher. I increasingly find that these worlds are very close together.

As a brain injury lawyer I work with people struggling to recover from the loss of sense of self so often caused by brain injury as well as associated depression and chronic pain. Many of my clients have reported meaningful increases in the quality of their lives following injury through "mindfulness" practices such as yoga and meditation. Practices such as yoga are designed to increase awareness of the present moment, to increase awareness of our thoughts, emotions and physical sensations without filtering them through past experience or fears of the future – to recapture our sense of ourselves.

Although these "mindfulness" practices have been around for hundreds of years, growing "mind-body" scientific research is demonstrating how effective mindfulness practices can be in treating depression and chronic pain and improving the quality of life following injury. A powerful endorsement of mindfulness practice can be found in a recent TBI blog post by Jaisa Sulit, a neurological-rehabilitation occupational therapist, who sustained a spinal cord injury in a motorcycle accident. She describes the role mindfulness practice played in her recovery, including coping with pain without prescription drugs and accepting and caring for her post-injury body.

Sulit quotes Victor Frankl, a neurologist and concentration camp survivor and author of "Man's Search for Meaning."

> "Between stimulus and response," says Frankl, "there is a space. In that space is our power to choose our response. In our response lies our growth and our freedom."

We can't reverse the injuries that have occurred, suggests Frankl, but we can take control of our response – by learning to be in the present moment, listening to the mind and body, and mindfully choosing how to respond. Abraham Maslow, a well-known psychologist, suggests that learning to be in the present moment is not only important to recovery from injury, it is "a major component of mental health."

A recent study in the Journal of Head Trauma Rehabilitation supports the effectiveness of mindfulness-based practice on improving symptoms, including depression, following traumatic brain injury. One explanation offered is that these practices help improve acceptance and awareness "thereby minimizing the catastrophic assessment of symptoms" associated with TBI and chronic disability.

A February, 2014 article in the Journal of Clinical Psychology reports that mindfulness practice shows promise as a tool to reduce dependency on prescription opioid medications to control chronic pain. Many people with a serious injury find that they have lost control of their lives to the medical specialists, insurance companies and lawyers who become involved following the injury. Mindfulness practice is a way to recapture that control.