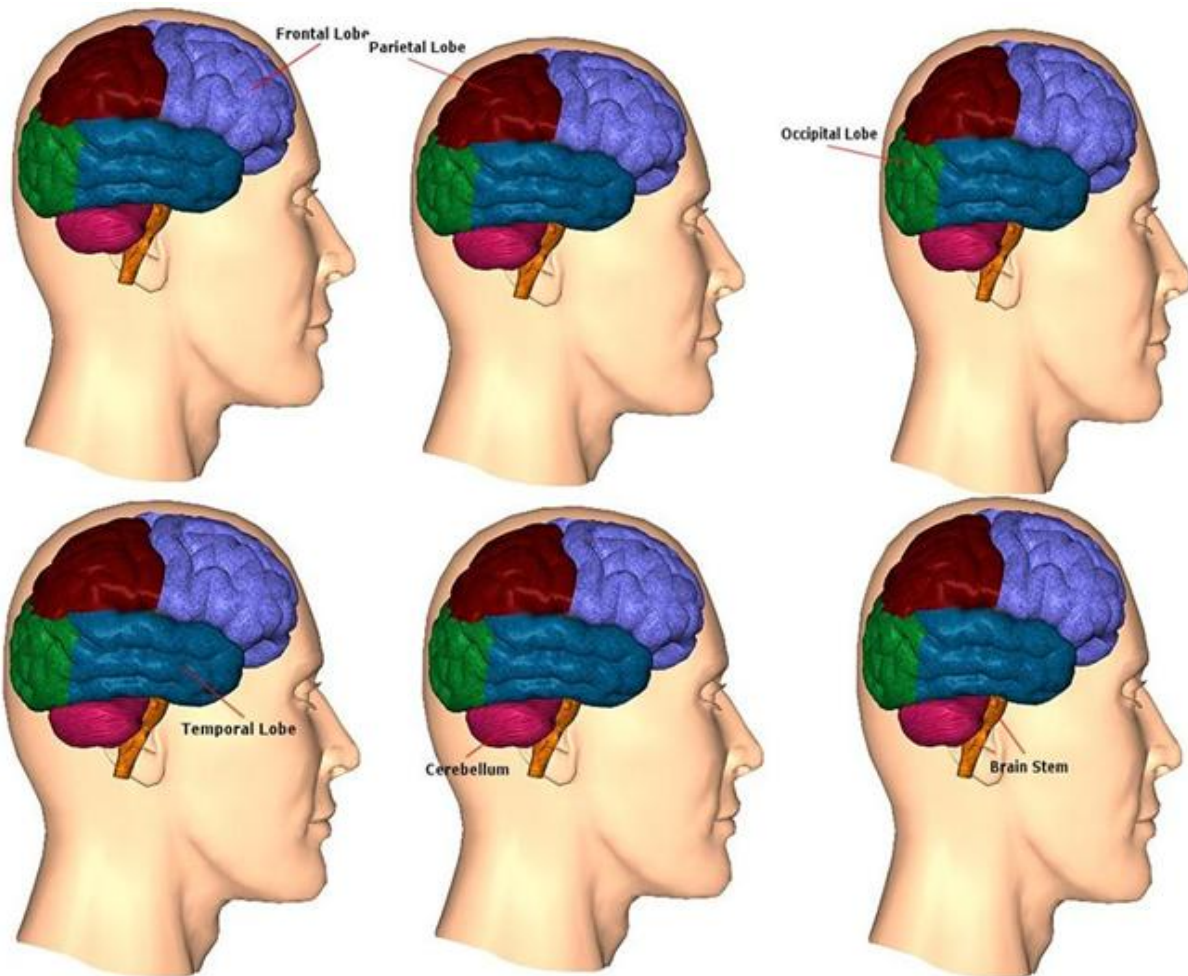


# Traumatic Brain Injury:

A Clinical Approach to Diagnosis  
and Treatment.

By Mark L. Gordon, M.D.



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**Other Books by the Author**

The Clinical Application of Interventional Endocrinology (2007)

The Clinical Application of Interventional Endocrinology; the Handbook (2013)

The Laboratory of Interventional Endocrinology (2014)

Hormones and the Brain (2014)

**Special Thanks\***

It is greatly appreciated that Access Medical Laboratories of Jupiter, Florida have provided the Millennium Health Centers, Inc. with a Grant in 2009 for the evaluation of 100 military veterans with mTBI sustained while in combat. Mr. Ryan El-Hosseiny, CEO, Access Medical Laboratory.

# Dedication

To Private Charles H. Kuhl, of L Company, U.S. 26th Infantry Regiment, who reported to an aid station of C Company, 1st Medical Battalion, on 2 August 1943. At the time, Kuhl had been in the U.S. Army for eight months, and attached to the 1st Infantry Division since the 2nd of June 1943. He was diagnosed with "exhaustion," a diagnosis he had been given three times since the start of the campaign. Arriving at an aid station he was subsequently evacuated to the 15th Evacuation Hospital near Nicosia for further evaluation being started on treatment with sodium amytal. Notes in his medical chart indicated that he was suffering from "psychoneurosis anxiety state, moderately severe – this soldier has been twice before in hospital within ten days. He can't take it at the front, evidently. He is repeatedly returned."

Patton arrived at the hospital the same day, accompanied by a number of medical officers, as part of his tour of the U.S. II Corps troops. He spoke to some patients in the hospital, commending the wounded. He then approached Kuhl, who did not appear to be injured. Kuhl was sitting slouched on a stool midway through a tent ward filled with injured soldiers. When Patton asked Kuhl where he was hurt, Kuhl reportedly shrugged and replied that he was "nervous" rather than wounded, adding "I guess I can't take it." Patton "immediately flared up," slapped Kuhl across the chin with his gloves, then grabbed him by the collar and dragged him to the tent entrance. He shoved him out of the tent with a kick to his backside. Yelling "Don't admit this son-of-a-bitch," Patton demanded that Kuhl immediately be sent back to the front, adding, "You hear me, you gutless bastard? You're going back to the front."

Corpsmen picked up Kuhl and brought him to a ward tent, where it was discovered he had a temperature of 102.2 °F (39.0 °C); he was later diagnosed with Malarial parasites. Speaking later of the incident, Kuhl noted "at the time it happened, [Patton] was pretty well worn out ... I think he was suffering a little battle fatigue himself." Kuhl wrote his parents about the incident, but asked them to "just forget about it." That night, Patton recorded the incident in his diary: "[I met] the only errant coward I have ever seen in this Army. Companies should deal with such men, and if they shirk their duty, they should be tried for cowardice and shot."

I also dedicate this book to all the patients of the Millennium:

I am who I am because of all of you who have challenged me to find an alternative approach to wellness. And, all of you who trusted the literature that I read finding answers that had already been discovered and ignored for years before I dusted the cobwebs off. Not always an issue of selecting the right pill but more so in listening to what you had to share. Not always about treating the numbers in a lab test but accepting that we are not all made equally.

Pushing the envelope on interpretation of standard labs in a non-standard manner and treating to replenish the chemicals, hormones, and minerals that were found to be less than optimal. Redefining the use of the terms - deficiency and insufficiency – with healthy and non-healthy.

For all these reasons and more, I dedicate this book to you.

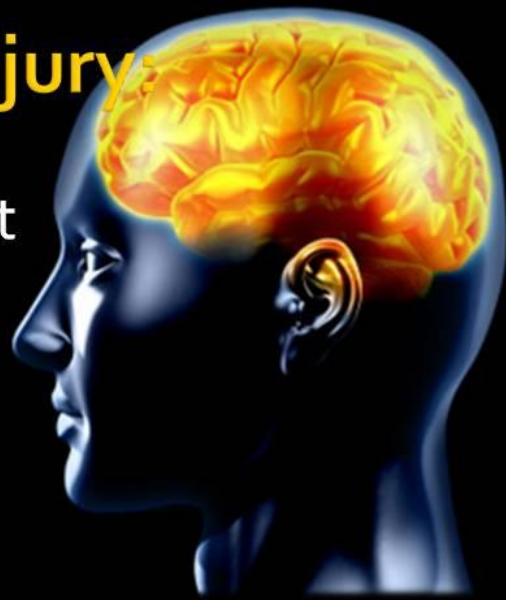
# Forward

by

# **Traumatic Brain Injury:**

## **A Clinical Approach to Diagnosis and Treatment**

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### **Chapter 1: An Overview and Introduction**

Traumatic brain injury (TBI) is nothing new having been developed in the rising of man and the socialization of war. In the time of Australopithecus, as depicted by Stanley Kubrick's 2001; A Space Odyssey, a pre-homo sapien learns about weaponry by confronting a neighbor with a leg bone of some large animal; wielding it like a club. Archeological records represented by skulls and not friable papyrus, tell us the stories of traumatic brain injury before there were stories to tell.

It is unlikely that those skulls discovered with depression fractures of the frontal, temporal, or parietal bones were the result of a motor vehicle accident, an improvised explosive device, or a slip-and-fall, and all-of-which have now become the hallmark of socio-economic evolution, in the here and now.

In survey of countries that have weathered this socio-economical growth over the past two hundred years, we see a significant rise in the occurrence of traumatic brain injury from a diversity of causes; those individuals less than 20 years of age, motor vehicle accidents (mainly DUI related) make up the majority of cases while those over 65 years of age, succumbing to over-medication, Frailty Syndrome, Vitamin D deficiency all causing gait instability and falls as a close second.

The landscape between 20 and 65 years of age is filled with assaults, slip-and-falls, sports injuries, motor vehicle accidents, blast trauma, occupational, and recreational injuries as causative factors.

Although not perceived literally as a trauma, any intracranial vascular event (hemorrhagic or ischemic) or hypoxia, can lead to the same pathophysiological consequences as those produced by direct force trauma to the skull. It appears that a diversity of causes can trigger the same pathways of destruction.

Taking things one step further, we can also add to this group of precipitating factors Alzheimer's disease since the critical process that leads to the loss of executive function and cognitive abilities are the same chemical pathways that are initiated by the accumulation of Amyloid- $\beta$ , stroke, ionizing radiation, and traumatic brain injury.

The core of this book, chapter by chapter, is about the overwhelming number of individuals who have sustained a mild traumatic brain injury (mTBI) and don't even know that it has occurred. They are the ones who develop progressive cognitive and psychosocial changes that appear as behavioral issues that can manifest even after a delay of 30 years (1). These are the individuals that have forgotten the injury and therefore, instead of looking beyond the superficial presentation of their apparent "illness", are placed on psychotropic medications to mask the underlying causes referred to as the "Stealth Syndrome".

This book and the associated TBI Symposium will provide the fundamental knowledge for interested physicians to learn how to recognize the presence of this condition and how to diagnose and treat the individual.

This first chapter is a composite over-view of what the rest of the book has to offer you. It is in fact, the beginning of my story to you.....

## **Epidemiology of Non-Combatant Traumatic Brain Injury**

Traumatic brain injury (TBI) is a major cause of traumatic death and disability. In individuals younger than 45 years of age, injury is the primary cause of death in the United States and other developing nations (2). The general incidence of TBI in developed countries is approximately 200 per 100,000 population at risk. This estimate is skewed since the statistics are based upon those patients with TBI that are hospitalized while the majority of those sustaining a TBI never seek medical attention (3).

Based upon a 2010 report looking at only the United States; a brain injury occurs every 7 seconds and results in death every 5 minutes; representing about 4.5 million brain injuries and 53,000 deaths a year (4). A prior CDC evaluation of TBI cases between 2002 and 2006, reported 1.7 million cases per year with 80.7% emergency room visits, 16.3% hospitalizations, and 3.0% deaths (5). But again, this only took into account those individuals who ended up in the medical system immediately after sustaining their TBI while the majority were lost or delayed from inclusion.

Contrary to general believe, the majority of TBI cases are mild in nature and therefore, the bulk of the injured never seek medical attention, that is, until the subtle behavioral and neuropsychological changes start occurring forcing medical assessment. By that time, the association between the mild TBI(mTBI) and symptomatology is lost. Unfortunately, this creates erroneous data by underestimating the frequency of mild forms of TBI and overestimating the proportion of moderate to severe TBIs.

Approximately 50% of TBIs are the result of motor vehicle, bicycle or pedestrian–vehicle accidents. Falls are the second-commonest cause of TBI (20–30% of all TBI), being more frequent among the elderly and the very young population. Violence-related incidents account for approximately 20% of TBI, almost equally divided into firearm and non-firearm assaults (6).

Several classifications for TBI severity are reported in the literature. The post-resuscitation Glasgow Coma Scale (GCS) is the most widely used clinical classification of TBI severity. The GCS is based on the patient's response (eye opening, verbal and motor function) to various stimuli. A score of 13–15 is considered mild, 9–12 moderate and  $\leq 8$  severe TBI (7). Clinical severity of TBI is also defined by duration of loss of consciousness (LOC), loss of memory for events immediately before or after the accident (post-traumatic amnesia) and identified intracranial lesion (8, 9). Radiological findings by computed tomography (CT) may be helpful in TBI severity evaluation, and the most used radiological scale is the Marshall's CT classification of TBI (10). Functional outcome after TBI is usually evaluated by the Glasgow Outcome Scale (GOS), a descriptive and easy to use scale, describing five outcome categories (death, vegetative, severely disabled, moderately disabled, and good recovery) (11).

Given all these excellent resources to assess those with TBI, it still does not equate out to effective care when you consider that almost 66% of those who need help fail to make it into the medical system. Those that do, the system fails them in limiting diagnoses and treatment to antiquated superficial markers of injury instead of looking deeper into the new science of Traumatic Brain Injury. But, its here now.

## Epidemiology of Combatant Traumatic Brain Injury

Traumatic brain injury (TBI) has been described as the “signature wound” of the conflicts in Iraq and Afghanistan. Improvised explosive devices (IED), mortars, tank cannons, hand grenades, and even repetitive fire from an M-16 or M-4 Carbine, can produce the mechanical factors predisposing a soldier to mTBI.

Of the total 178,876 TBI cases since 2000, 137,328 have been mild, 30,893 have been moderate, 1,891 have been severe, 3,175 have been penetrating, and 5,589 have not been classifiable but all are suffering the sequela of brain trauma with psychological, physiological, and physical impairment (12).

In March 2009, USA TODAY’s caption read “360,000 Veterans May Have Traumatic Brain Injury.” The story followed with; “WASHINGTON — Pentagon officials estimated for the first time Wednesday that up to 360,000 Iraq and Afghanistan veterans may have suffered brain injuries. Among them are 45,000 to 90,000 veterans whose symptoms persist and warrant specialized care.”

Although these numbers are vast they could have been larger if not for the modern body armor worn by soldiers that greatly enhanced chances of surviving mechanisms that are responsible for the mortality and morbidity seen in combat. Blast injuries can cause brain damage with significant long-term and often delayed neurological consequences.

Blast injury can be a complex clinical syndrome or “polytrauma” caused by the combination of four blast effects; primary, secondary, tertiary and quaternary blast mechanisms. Air filled structures such as the sinuses, ears, lungs, and intestines are most vulnerable to the primary blast wave. This can lead to bleeding, alteration of ventilatory mechanisms with hypoxia, and tissue damage. The blast wave can cause a sudden rotation of the brain leading to shearing forces that can sever cerebral capillary and long axons responsible for intra-lobular communication.

Individuals exposed to a blast frequently manifest loss of memory for events before and after the explosion; confusion, headache, impaired sense of reality, and reduced decision-making ability. Patients with brain injuries acquired in explosions often develop sudden, unexpected brain swelling and cerebral vasospasm despite continuous monitoring. However, the first symptoms of blast-induced neurotrauma (BINT) may occur months or even years after the initial event, and are therefore categorized as secondary brain injuries. The broad variety of symptoms includes weight loss, hormone imbalance, chronic fatigue, headache, and problems in memory, speech and balance. These changes are often debilitating, interfering with daily activities. Because BINT in blast victims is underestimated, valuable time is often lost for preventive therapy and/or timely rehabilitation (13).

As is the case in the civilian population, laboratory assessment for hormonal disruption is infrequently performed over the course of the individual’s rehabilitation for their physical trauma. An initial or baseline level is rarely obtained thereby missing the 56% of those injured with TBI that do have one or more hormonal deficiencies by 3 months. (14) Failure to recognize and correct the underlying hormonal deficiencies (insufficiencies) may compound the physical and psychological complications of TBI and interfere with rehabilitation (15).

The Military’s programs available are comprehensive but limited. They see the literature and acknowledge that there is an association between mTBI and hormonal dysfunction but rarely pursue testing as recommended by the AACE and others (XX). Since 2009, the Millennium Health Centers, Inc has offered a free laboratory assessment for military personnel that have sustained a mTBI\* with a Glasgow Coma Score of 13-15.



## Epidemiology of Sports-related Traumatic Brain Injury

Andre Waters was not the first, Dave Duerson was not the second, and nor will Junior Seau be the last to succumb to the secondary psychological and physical consequences of hormonal insufficiency and deficiencies precipitated by traumatic brain injury that led to their suicide.

Their suffering and ultimate sacrifice has shaken the very fiber of the sports world, not only in football but in all contact sports, awakening us to the need for better protection, assessment, restrictions, and treatment for those who have sustained a TBI on the field. Presently, a player can be taken out of a game if their bench-side evaluation (after a suspected TBI) shows any sign of impaired brain functioning. Injured players will no longer have their jerseys just brushed off and be sent back into the game, they will be restricted from playing until their neurological evaluation has normalized.

Nonetheless, there will be many players from all sports that over time, sometimes up to a decade after their last head injury, will start presenting to their physicians with altered personality, bouts of anger and rage, cognitive, and functional impairments. Hopefully, at that time, they will have hormonal assessment first as opposed to being placed on a psychotropic medication. Furthermore, if the athlete is found to be hormone insufficient and not necessarily deficient they will be allowed to have the appropriate hormones available for replenishment and on-going treatment instead of being denied this potentially lifesaving treatment. (16, 17, 18)

The impact of sports related TBI has become a political bailiwick with congressional hearings and threats of banning football and all contact sports. Head injuries suffered by the likes of Patrice Bergeron, Pierre-Marc Bouchard and Marc Savard have raised awareness to new heights, so much so that the NHL instituted in the 2010 season; **Rule 48**, banning blindside hits to the head. This was seen as a way to reduce the public health risks and the consequential financial burden on insurance companies, families and the team leagues.

Consequently, there are many NFL veterans who are still struggling post-career. A 1994 survey from the players' association found that significant numbers were depressed, fat and managing chronic pain. A 2006 Scripps Howard report found that of 3,850 deceased players that NFL players are more than twice as likely as Major League Baseball players to have died before their 50th birthday. Frequently, their much heavier bodies failed in retirement.

What about our children? Football accounts for nearly two-thirds of the estimated 62,816 TBIs incurred in high school sports each year, according to a 1999 survey published in the Journal of American Medical Association.

Traumatic brain injury (TBI) has been associated with hypopituitarism in general and GH deficiency (GHD) in particular; the consequences of this on growth and development are likely to be critical in children and adolescents in the so-called "transition phase". At 3 months, hypopituitarism was present in 34.6%, and at 12 months, hypopituitarism was present in 30.3%. Growth hormone deficiency (GHD) and secondary hypogonadism were the most common acquired pituitary deficits in this age group. These results show the high risk of TBI-induced hypopituitarism also in the transition age. Thus it is recommended that pediatric endocrinologists follow-up pituitary function of children and adolescents after brain injuries. (19) I think there is little else to say here, more later.

## **Pain Alternatives, Solutions and Treatment Medical Team (P.A.S.T.)**

How many medications are you on? “Eighteen (18)! Three are narcotics and then there is one that is a stimulant to counter the side effects of the three narcotics so I can at least get up and go to the bathroom. Otherwise, I’m so out of it I pee in my bed. Then there are the two muscle relaxers and the three for my depression. Funny thing is, I’m still depressed. Then because of the stimulant I can’t sleep at night so they have me take a couple of sleep pills (Trazodone and Ambien) that make me so groggy in the morning I can’t wake up and take a stimulant medication.”

If you think that encounter was made up, consider spending some time at PAST headquarters in Clifton, New Jersey and you will hear this conversation over and over again. When you walk away you will become a true believer in how these notable professional sports retirees were led down a medication pathway instead of addressing the underlying cause to their pain and altered mental status.

PAST is an organization and program developed by the compassionate Dr. William Focazio, a gastroenterologist by training and a saint to boys who enter his sanctuary.

In explaining PAST, Dr. Focazio stated that, “.. many of the retired athletes that come to his organization have expended their time-limited medical insurance policies graciously given to them upon retirement by their relative sports team. After about 5 years when the progression of their underlying injuries blossom into a limiting disability many have no medical coverage left. Without coverage, their medical treatment is more palliative than curative using an endless number of oral medications instead of corrective surgery or indicated hormonal replenishment.”

“By the time they make it to PAST our first duty is to detoxify them from their personal pharmacopeia. Our Neuropsychiatrist and Neurologist evaluates them and provide a program for detoxification. Concurrently, the retiree is evaluated by one of our orthopedists to see if there is justification for surgical intervention as a means of stopping their pain and retuning them to physical functioning and a healthy life style with the least number of pills”, explains Dr. Focazio.

If they have a history of concussion(s) with or without loss of consciousness, they are evaluated by our Interventional Endocrinologist for hormone dysfunction that plagues many players. It is the deficiency (and insufficiency) of specific brain generated hormones that can cause outbursts of anger, depression, fatigue, cognitive impairment, physical degradation, and suicidal tendencies.

Replenishment of those hormones found to be low (or low-normal) can return the individual to a higher level of functioning and quality of life. Thousands of medical articles attest to the finding of hormonal insufficiency and deficiency in TBI as well as documented beneficial affects when replacement therapy is used to return levels to optimum and physiological.

PAST is a non-profit organization with a team of specialized physicians that provide services to those who cannot afford it. If you are a physician with a desire to help and become a recognized member of the PAST Medical Team; please contact them through their website.

## Neuropathophysiology of Traumatic Brain Injury

Regardless of the type of non-penetrating trauma that is conveyed to and through the skull (blunt force, blast waves, or ionizing radiation), there are two phases of damage that occur to the brain; an initial mechanical injury (1°- primary) associated with contusion, hemorrhage, edema, ischemia, and diffuse axonal injury (DAI), and a neuro- or biochemical assault (2°- secondary) associated with neuronal loss resulting from the activation of one or more of the known terminal cascades - Necrosis, Apoptosis, and Autophagy.

These events, mechanical and biochemical, can co-exist depending upon the magnitude of injury but frequently, in mild traumatic brain injury (mTBI), the primary injury is short-lived while the subtle and insidious secondary injury can linger on for years taking its toll piece by piece. It is the impact of these biochemical processes that is most important for understanding the cause-and-effect relationships between TBI and Hypothalamic-Pituitary Dysfunction (HPD).

The primary impact is frequently followed by the development of vasogenic and cytotoxic edema and impairment of energy metabolism (ATP and mitochondrial loss). This sets in motion a cascade of biochemical events both extra- and intracellular causing an indolent progression to cellular death. That is indolent until either a critical mass of cells are lost or there is impact upon a region of brain that matters (frontal lobe and executive functions).

Neurons that escaped the initial mechanical trauma are exposed to a secondary mechanism that few cells can escape. At the immediate area of contusion and also remotely, neurons that succumbed to the initial trauma release an array of physiological cellular components into the intracellular space that accumulates to toxic levels. Nitric Oxide (NO), Reactive Oxygen Species (ROS), glutamate, cytokines, and interleukins create an environment of collateral cellular damage as the oxidative stress (OS) increases. The end result is a concentric ring of expanding cell death. It is by this process that over time, the accrual of dying brain cells leads to the signature changes that have come to represent not only mild traumatic brain injuries but all degrees of neurotrauma. (20)

Furthermore, capillaries that are torn leak red blood cells and plasma into the environment only to be degraded to a more reactive hemoglobin/iron (OS). As damage includes blood vessels there is the loss of the autoregulatory function of the cerebral vasculature with intravascular fluids leak into the white and gray matter spaces causing edema. Owing to the edema, the intracranial pressure (ICP) increases and the brain is crushed against the unyielding cranium increasing the risk for uncal herniation, as well as, further diminution of vascular blood flow, cerebral spinal fluid circulation and death. The ensuing ischemia, hypoxia, and further neuronal damage all cause acceleration of oxidative stress and expansion of the involved area(s).

We look at these processes as having an overt negative net affect upon the brain but in fact, we are learning that the ultimate goal of these neurochemical cascades is to help preserve and limit damage to the brain and its neurons.

**Necrosis** may be the only process that does not stand out as a bad-good mechanism to help cells survive like Apoptosis and Autophagy. In necrosis, which has classically been regarded as uncontrolled cell death, recent research suggests that its occurrence and progression might be tightly controlled. This is based upon finding signs of organized processes like mitochondrial dysfunction, ATP depletion, increased Reactive Oxygen Species (ROS), cytoskeletal proteolysis by Calpain, and disruption of the cell membrane. It is this loss of cell membrane integrity that precipitates irreversible cell death (21, 22).

**Apoptosis**, or programmed cell death, has always implied that the cell dies in an organized and programmed manner, which is heralded by condensation of nuclear chromatin with DNA fragmentation,

cell shrinkage, and the formation of apoptosomes that are subsequently cleared by phagocytosis. In this process, an organized removal of an irreversible damaged cell ensues in a surgical manner. The process of Apoptosis is focused on the containment of intracellular components that can trigger inflammatory responses that if allowed to float freely into contiguous cell spaces will precipitate collateral damage. Contrary to Necrosis, in Apoptosis there is little collateral inflammation and no significant release of chemotactic agents that would bring the immune defense system into play. This is more of a quiet process that saves the surrounding cells and their morphology from a potential logarithmic process of destruction. (23)

Finally, **Autophagy** also called the type 2, non-apoptotic cell death mechanism, differs from apoptosis in that it doesn't necessarily terminate in cell death. On the contrary, Autophagy is probably the most cell protective mechanism against cell execution (24, 25, 26). In the event that damage occurs to a cytoplasmic organelle, which brings with it the risk of leakage of its content into the cytoplasm, autophagy would encapsulate it in an autophagosome. Once engulfed, the organelle would be processed with lysozymes digesting it to its principle components for reutilization for other cell structures. Cannibalization of this nature can also occur in cell starvation where the cell is forced to ingest its own parts for survival. (27)

Traumatic brain injury in humans results in a pattern of neuronal loss that includes the cortex, hippocampus, cerebellum and thalamus (hypothalamus). In the acute post-traumatic period, injured neurons appear swollen then become shrunken and eosinophilic with condensation of chromatin. Suggestive patterns of both necrotic and apoptotic processes. Under the electron microscope, these degenerating neurons appear swollen, with swollen mitochondria, vacuolated cytoplasm and Pyknotic nuclei, suggestive of necrosis (28, 29, 30).

In the delayed or chronic post-traumatic period, there is a progressive but indolent process of neuronal degeneration that differs in the pattern seen in the acute phase, reflecting the apoptotic component of post-traumatic brain injury (31).

Knowledge of the different biochemical cascades associated with each of the above processes has led researchers to develop compounds that can interrupt the progression of neuronal destruction and cognitive impairment (32). Though, it might take 3 to 5 years or longer before we see any of them in our local pharmacies. Until that time, we can use prescriptive and alternative products that are available but are not being utilized due to the lack of awareness and skills in how to use them.

Continued reading of this book might help to fill in many of those blank lines...

## **The Neuroradiology of Traumatic Brain Injury**

It was November 2006; I had just given my classical lecture, Traumatic Brain Injury – The Hormone Dysfunction Syndrome, to about 400 attendees of the ACAM symposium focusing on neurological illnesses. As I walked off the stage and down the side aisle, a voice from behind called out “I got it, I got it”. I turned around and asked in a demanding manner “What do you got?” The doctor repeated herself and said, “I got it. I got it.” Again, “What do you have?”

She introduced herself as a Neuroradiologist who reviews the CTs and MRIs of patients who have sustained anywhere from a mild to severe TBI. She explained that she rarely sees any structural abnormalities in those patients with mTBI even months or years post-trauma even though the patients are being studied for progressive functional impairment. She added that almost all of the moderate to severe TBI cases have recognizable contusions of the brain, diffuse axonal injury, and if not frank intracerebral bleeding (subdural hematomas), punctuate areas of intracerebral bleeds.

This is the paradigm that is finally changing due to advancements in radiologic technology and the unraveling of the biochemical mechanisms that activate both apoptosis and autophagy creating the telltale micro-calcified scars. In the past, these microscopic remnants of injury were missed due to the smaller Tesla coils (magnetic strength) but now with a 3.0 Tesla coil the resolution can identify these micro-calcifications which are found within neuronal tissue representing scarring precipitated by axonal damage (DAI), microhemorrhages, and necrosis (33).

The importance of this technology was clearly defined in the paper by Orson and Handson in 2009 when they showed that 76% of non-combatant individuals who sustained a TBI had positive findings with only 14% involvement of their pituitary gland (77). This, in my mind, opened the door to looking beyond the pituitary gland as the poor recipient of all things bad and turn attention to other areas of the brain. In fact, in this same paper, over 59% of findings involved the Hippocampus (memory and the ability to learn new information) and 29% diffuse axonal injury (DAI). Together, these describe the foundation for the majority of symptoms experienced by patients with mTBI and above.

Using newer software enhancements to this MRI technology (DTI-MRI) allows for images to be formed that look at the directional flow of water within neurons from the bodies down the microtubules into the axons. Diffusion Tensor Imaging (DTI) or Tractography can delineate the course and continuity of long axonal connections between one or more cerebral hemispheres. Traumatic or neurochemical (necrosis, apoptosis or autophagy) damage to these neuronal conduits can be seen as though they were cut wires. It is in these areas where there is loss of continuity and connectivity that produces the alterations in brain functioning that we see as change in the personality and cognitive abilities of the individual (34).

The functional MRI (fMRI) is another neuroimaging technique that can display patterns of brain activity based upon increases and decreases in regional blood flow (hemodynamic). After sustaining a TBI, there can be a significant redistribution of the hemodynamics reflecting the changes in blood flow with alterations in both glucose and oxygen utilization.(35)

There are a number of other technologies like SPECT, PET, and Fusion scans that will be discussed in detail in Chapter 5.

## Neuroendocrinology of Traumatic Brain Injury

Post-traumatic hypopituitarism (PTHP) was first recognized and described in 1918 by Cyran, but at that time it was thought to be a rare occurrence (36). More recently, TBI has been recognized as a frequent cause of hypothalamic–pituitary dysfunction and impairment, contributing to a delayed or diminished capacity for recovery in many TBI patients (37-42).

Hypothalamic-pituitary dysfunction following a traumatic event can be divided into an acute phase; during which there are transient alterations in the production of pituitary hormones such that they are either increased or diminished and a delayed phase; when those alterations in hormones fail to return to normal regulatory production as a result of permanent damage at the pituitary and/or hypothalamic levels.

The pituitary gland responds to acute traumatic events with two secretory patterns: adrenocorticotropin (ACTH), prolactin (PRL) and growth hormone (GH) levels increase, while luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyrotropin (TSH) levels may either decrease or remain unchanged, associated with a decreased activity of their target organ. Changes in the circulating hormone levels become apparent during the first hours or days after trauma, and may persist for the duration of the acute critical illness. These alterations represent part of the acute adaptive response to the injury, and may be influenced by the type of injury and pharmacological therapy used to treat the critical illness (glucocorticoids, narcotic analgesics or dopaminergic agents) (43).

Accepting the premise that trauma to the brain leads to a progressive disruption of hypothalamic control of hormonal production by both the anterior and posterior pituitary glands, would make it reasonable to test for the adequacy of production of those central hormones directly regulated by the Hypothalamus. This would include anterior pituitary hormone markers such as thyroid stimulating hormone (TSH), growth hormone (GH), adrenocorticotrophic hormone (ACTH), and posterior pituitary markers such as prolactin, anti-diuretic hormone (ADH), luteinizing hormone (LH), and follicle stimulating hormone (FSH). (44)

In addition to those hormones, we need to look at IGF-1, IGFBP-3, fT3, fT4, rT3, free testosterone, total testosterone, dihydrotestosterone (DHT), DHEA-s, estradiol (E2), estrone (E1), progesterone, pregnenolone, and cortisol. These are used to assess the patient for primary hormonal deficiencies (peripheral failure) that could pre-date the impact of TBI. Additionally, all these hormones have beneficial affects on the central nervous system as either Neurosteroids(NS) or Neuroactive Steroids(NAS).

Our understanding of Neurosteroids is mind boggling. These steroid hormones were once thought to pass into the brain through the blood-brain-barrier(BBB) having been produced in the periphery. Today, science shows us that these hormones are regionally manufactured de novo in the brain. Pregnenolone, allopregnanolone(tetrahydroprogesterone), progesterone, allopregesterone, and DHEA-s to name a few. All with important functions to protect nerves from oxidative stress (ROS), reduce inflammatory cytokines, interleukins, and to regenerate myelin.(45-55) An interesting finding in the frontal lobe of patients with Alzheimer's disease is a lack or deficiency of Allopregnanolone.(56).

Neuroactive steroids are those hormones produced in the periphery, which penetrate the BBB and enter the cerebral circulation to participate in the same protective processes as the NS. Many of the NAS are the same as the NS and are therefore, additive.

So, the issue becomes when is the best time to assess the potential of neurotrauma related hormone dysfunction? The answer comes as no surprise in being as soon as possible after the head trauma. Unfortunately, as indicated above, most individuals with head trauma fail to seek medical attention until subtle or overt symptoms start to creep into their lives. The initial testing, if early, will represent the

baseline hormonal levels with follow-up hormone panels at 3 months, 6 months, and 12 months from the date of the initial testing (injury). In a 2006 study by Schneider and Schneider, they followed new TBI cases for a year taking blood at 6 months and 12 months finding a 56% and 36%, respectively of one or multiple hormone deficiencies(57).

A more recent article in the Journal of Neurotrauma (2012), addressed the persistency of Pituitary Hormone Deficiency after Traumatic Brain Injury acknowledging that 69% of the patients had at least one pituitary hormone deficiency, where GH deficiency was more prevalent (severe: 40.0%; partial: 23.6%) than corticotropin (27.3%) or thyrotropin (21.8%) deficiencies.(58)

Diagnosing TBI Hormone Dysfunction Syndrome (THDS) can be challenging for the majority of clinicians, as well as, for the trained endocrinologists. This is because the general consensus for what constitutes a laboratory result as being insufficient or deficient is controversial as is the question of whether-or-not to treat the insufficiency? Many of the hormonal test results have ranges that are broad, representing two standard deviations so the numerical distance from the low-end to the high-end can be immense as in the case of Total Testosterone; 270ng/ml to 1730ng/ml. So if a patient has a result of 280ng/ml is that deficient, insufficient, or normal?

The majority, if not all, of traditional physicians would call that “within the normal range” and not address the myriad of patient complaints and elect not to treat. Fortunately, this is slowly changing and physicians are treating patients with appropriate physiological doses to achieve a level that is the median of the range (50th percentile for age).

## **Biomarkers of Traumatic Brain Injury**

The search for a viable marker for Traumatic Brain Injury, which can identify the progression of neurotrauma leading to the eventuality of functional compromise, is under intense scrutiny. The goal here is to identify a reliable marker that is only present after TBI, is detectable in a peripheral blood sample, and can reflect the intensity of damage based upon the magnitude of the results. Additionally, this ideal marker would also reflect improvement or resolution in the bio-chemical processes that precipitate the indolent damage to the brain.

The following list of markers under investigation is by far complete but extensive in the range of functions that are being evaluated as stable markers of TBI. A number of these markers are discussed in detail in the corresponding chapter and needless to say, the list of potential markers is growing rapidly.

### **TBI Biomarkers**

Protein biomarkers of TBI

S100B

Glial fibrillary acidic protein

Neuron-specific enolase

Myelin basic protein

Fatty acid binding proteins

Proteolytic breakdown products

Phosphorylated neurofilament

Ubiquitin C-terminal hydrolase

Tau Protein

### **Inflammatory Markers**

Interleukin-1

Tumor necrosis factor alpha

Interleukin-6

Anti-inflammatory cytokines

Chemokines

### **Small Molecule Biomarkers**

#### **Lipid Metabolites as Biomarkers**

F2-isoprostane

4-Hydroxynonenal

### **Biomarkers for Secondary Pathologies**



Intracranial pressure

Blood brain barrier compromise

Secondary ischemia

Post-traumatic epilepsy

**Biomarkers for Predicting Outcome**

## Neuropsychiatry and Traumatic Brain Injury

Patients who had suffered traumatic brain injury were evaluated to determine the occurrence of psychiatric disorders during a 30-year follow-up; of the 60 patients, 29 (48.3%) had had an Axis I disorder that began after traumatic brain injury, and 37 (61.7%) had an Axis I disorder during their lifetimes. (60)

In this study, the most common disorders post-traumatic brain injury were major depression (26.7%), alcohol abuse or dependence (11.7%), panic disorder (8.3%), specific phobia (8.3%), and psychotic disorders (6.7%). Fourteen patients (23.3%) had at least one personality disorder. The most prevalent individual disorders were avoidant (15.0%), paranoid (8.3%), and schizoid (6.7%) personality disorders. Nine patients (15.0%) had DSM-III-R organic personality syndrome. The results suggest that traumatic brain injury may cause decades-lasting vulnerability to psychiatric illness in some individuals. (60)

Traumatic brain injury seems to make patients particularly susceptible to depressive episodes, delusional disorder, and personality disturbances. The high rate of psychiatric disorders found in this study emphasizes the importance of psychiatric follow-up after traumatic brain injury. (60)

This study was published in 2002 and at that time the correlation between hormonal insufficiencies and causative factors for cognitive and emotional changes were still not appreciated let alone treated. Fortunately, at the writing of this book there seems to be an increased appreciation for the association between hormonal dysfunction and TBI although, it is still a rare occurrence that a treatment protocol will be started to address it. (60)

This brings me to a case of a 41 year old male who we'll call Bill. Bill played rugby between the ages of 18 and 22 during which time he sustained 5 significant head traumas with loss of consciousness on three separate occasions and one which precipitated hospitalization. At 36 years of age, and after a slow progression of depression, self-medicated with alcohol for ten plus years, Bill was interred for evaluation and treatment for severe depression. Once he was detoxified from the alcohol addiction, he was started on a number of SSRIs which failed one after another to control his depression. The psychiatrist eventually placed him on three times the usual dose of one medication acknowledging the persistent mild depression as acceptable.

At age 41, and after being on psychotropic medication for 5 years, Bill read about our approach to TBI with assessment and replenishment of hormones. The article on TBI causing a hormonal dysfunction syndrome contained many of the elements that he was experiencing. He flew in from Boston to start his evaluation. After lengthy documentation of his history, a TBI Blood Panel was drawn, and he was given a Testosterone provocative challenge test while waiting for the lab confirmation of his deficiency.

Bill was sent home with instruction to call in one week to review his response to the provocative testing and to review his laboratory results. At the time Bill informed me of an appointment he had scheduled with an Orthopedist to discuss his chronic right shoulder pain and "turf toe" (frozen left 1<sup>st</sup> toe). His appointment was two days after our initial appointment.

On that Thursday, Bill called the office and when we spoke he asked me to remind him why he went to the Orthopedist. When I jokingly reminded him that it was for his shoulder pain and frozen toe, he said that he awoke that morning and the shoulder pain was gone and the toe was moving. He also, stated that he slept the night of his injection better than he had in years. He also noted a rise in his libido and a calming of his depression.

Making this long story short, after 2 months on hormone replenishment treatment (self administering a shot of testosterone once a week), Bill started working with his psychiatrist to taper him off of the anti-depressants. At 6 months, not only did Bill's depression abate but he was off his SSRIs, had mental

clarity, slept very well, emotionally was stable, had a new girlfriend, had a return of his libido, and was working out harder in the gym with improved recovery.

I can go on with these anecdotal cases for months. The impact of hormonal replenishment in patients with and without TBI who have neuropsychiatric, cognitive, and physical issues frequently subside or abate within a few weeks of starting treatment.

A recently published book by Springer (2011), entitled; *Acquired Brain Injury - an Integrative Neuro-Rehabilitation Approach*, provides a comprehensive dissertation on Neuropsychiatry and Traumatic Brain Injury. The chapter brilliantly written by Dr. Angela Scicutella discusses the clinical manifestations, assessment, and treatment for an array of psychological complexes (depression, mania, anxiety, psychosis, agitation, arousal and attention, dementia, and sexual dysfunction) that are acknowledged as being associated with traumatic brain injury. Unfortunately, each section contains an educational case where the patient is inevitably placed on psychotropic medications. (61)

Of significant concern while reading this modern text book of psychiatric intervention was, not a single word was offered discussing the impact of TBI on hypothalamic-pituitary dysfunction. This is in light of thousands of articles published over the past 30 years addressing initially, the presence of hypopituitarism in survivors of TBI, and then the association of hormonal deficiencies and their impact on psychological functioning ( both emotional and cognitive).

For whatever reason, we seem to be focusing in on only the superficial aspects of psychological maladies without going after the cause (biochemical). A patient presents with depression put them on an antidepressant and increase the dosing until the symptoms resolve. I was unaware that humans can have an antidepressant deficiency and therefore, replacing them is all that is needed. Medicine has become shortsighted in the quest for health and wellness.

## **Treatment for Traumatic Brain Injury**

I wish there was something cryptic I could say about this section (Chapter 8), which deals with treatment of mTBI with laboratory confirmed hormonal insufficiencies, but there isn't. Insufficiencies are generally looked at as being within the normal reference ranges and therefore, they are never considered for being brought up to the median physiologic level; and there lies the major issue. We need to reassess our thinking about what is healthy in each individual patient and not what numbers look most acceptable on paper. Treatment must be tailored for each patient with the goal of optimizing all hormone levels. This should include the lesser hormones as well as the major ones.

We know from a 2002 review article about our insufficiencies in ; "Outcome Measures for Clinical Trials in Neuro-Trauma" that dozens of studies were stopped prematurely due to their failure to improve the condition of patients with mild to severe TBI. The medications and procedures that were being evaluated did not work at best and many worsened the patients' condition.(62)

More recently, (2009) a review of the benefits of "cooling" in TBI concluded, "... our present knowledge on the use of active cooling in TBI patients has not been shown to be effective for outcome after TBI..."(63)

In light of these and hundreds of other articles addressing the lack of beneficial affects, these treatments continue to be used while the literature promoting the positive outcomes from the use of Growth hormone, IGF-1, Testosterone, DHEA-s and DHT on neuropsychiatric, cognitive, and physical sequelae are ignored. (64,65,66,67,68,69,70,71)

A major reason why the hormonal literature is being ignored is because the studies that have been performed, over the past twenty years were looking at the benefits of replacement of a single hormone such as testosterone; growth hormone, estrogen, progesterone, DHEA, Vitamin D, and Thyroid, have not yielded significant results. In fact the results at times were contrary to the expectations or there were no results at all. Why would that happen? A good guess would be that there is a level of hormonal synergy that is being omitted. (72,73,74,75)

In 1993, Drs. Marc Blackman and Mitchell Harman looked at this issue of synergy in both genders. In the males replenished with just testosterone or growth hormone alone, had lower beneficial effects than when testosterone and growth hormone were used concurrently. The same happened in the females when they were replenished with only growth hormone or only estrogen and progesterone (Progestin). When they were given all replenishment hormones concurrently, the responses confirmed the synergy.(76)

Additionally, in order to prescribe medication such as growth hormone, an Insulin Challenge Test must be performed. Furthermore, to avoid dissenting criticism by your state boards, the patient's laboratory levels must fit into the standards of care in order to provide legitimate treatment protocols. What this means is that we can't practice medicine to the fullest.

Nonetheless, when treating cases of mTBI we must replenish all hormones to at least the median physiologic levels. Then, add secondary hormones that can be lost, such as Pregnenolone and DHEA, when using testosterone. This will maintain optimal levels of NAS and NS and provide for added protection against oxidative stress and promote remyelination of damaged neurons. The addition of specific antioxidant regimens by oral or IV routes is encouraged along with a number of potential Nootropin products (L-Dyprenyl, amantadine, and neurotransmitter precursor amino acids (NPAA)).

Knowing the mechanisms behind the subtle progression of nerve damage can only help us to provide a means of diminishing their long-term affect on brain functioning so that we may maintain who we are for a longer period of uninterrupted quality of life.

## **Medical-Legal Issues relative to Traumatic Brain Injury**

This topic is really a composition of a number of legal issues that arise in the treatment of patients with traumatic brain injury.

Just as important as the “who to blame” for the traumatic brain injury, is the understanding of the legal ramifications of providing treatment. As of the date of this writing, there is no approved diagnostic code for using growth hormone in patients with TBI. Of all the thousands of medications listed in the physician’s desk reference, only recombinant human growth hormone (rhGH) has the restriction of “no off label” use! Therefore, we must prove that there is a state of Adult Growth Hormone Deficiency with an approved challenge test. The safest and apparently most reliable one is the Glucagon Challenge test. This can be performed in the office within 3 hours and the results will justify your use of growth hormone. Otherwise, you are breaking federal guidelines and can be subject to both DEA and State Medical Board challenge; another kind of challenge testing that you mostly fail!

The benefit of GH replenishment is in its ability to up-regulate the serum level of IGF-I that has been shown to help in the repair of neurons, dendrites, axons, microtubules, and stabilization of tau proteins.

As an alternative, the use of a clinically proven growth hormone secretagogue – Secretropin, can initially be used and monitored for its ability to raise GH/IGF-I production in the patient. A three month trial is suggested before a Glucagon Challenge test.

Some years ago, I called and spoke to an attorney that specialized in cases of Traumatic Brain Injury. I shared with him what I was doing in regards to testing and treating with hormones. At some point in the one sided conversation he interrupted me and said, “I’m afraid of you!” When I asked him why he said that he replied, “you mean that if you find that the patient is hormonally out of balance and replace the hormones they can get better?” I replied, “Yes”. He said, “.. that is then a problem since my remuneration is based upon the level of persistent damage that the patient has and if you improve the level of injury, payout for the damages decreases.” He went on to say, “how about waiting until the case is closed and then treat the patient.” I had nothing nice to say in response so I just hung up.

In cases that are litigated or anticipated to be litigated, we as physicians must learn how to best protect the patients’ case by providing some additional testing along with the standards of clinical medical care. A comprehensive past medical history, a specific history of the presenting injury, as well as, prior injuries, a comprehensive physical examination, appropriate standard laboratory testing with a TBI blood panel, and a Cognitive-Emotional questionnaire. If there are issues of neuropsychobehavior a referral to a neuropsychologist to perform appropriate testing is suggested. These tests can also be used as rulers of improvement when the patient undergoes hormonal replenishment.

## **ImPACT to Assess mild Traumatic Brain Injuries (mTBI)**

ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing) is the first, most-widely used, and most scientifically validated computerized concussion evaluation system established for Traumatic Brain injury.

Developed in the early 1990's by Drs. Mark Lovell and Joseph Maroon, ImPACT is a 20-minute test that has become a standard tool used in comprehensive clinical management of concussions for athletes of all ages. ImPACT Applications, Inc. was co-founded by Mark Lovell, PhD, Joseph Maroon, MD, and Michael Collins, PhD.

Given the inherent difficulties in concussion management, it is important to manage concussions on an individualized basis and to implement baseline testing and/or post-injury neurocognitive testing. This type of concussion assessment can help to objectively evaluate the concussed athlete's post-injury condition and track recovery for safe return to play, thus preventing the cumulative effects of concussion. In fact, neurocognitive testing has recently been called the "cornerstone" of proper concussion management by an international panel of sports medicine experts.

ImPACT can be administered by an athletic trainer, school nurse, athletic director, team doctor or psychologist, provided that they have completed training in the administration of the test. Post-concussion care and the management of concussion should only be administered by a trained medical professional. ImPACT assists doctors in making return-to-play decisions and should **never** be used as a stand-alone tool.

ImPACT is the most widely used computer-based testing program in the world and is implemented effectively across high school, collegiate, and professional levels of sport participation.

The test battery consists of a near infinite number of alternate forms by randomly varying the stimulus array for each administration. This feature was built in to the program to minimize the "practice effects" that have limited the usefulness of more traditional neurocognitive tests.

ImPACT takes approximately 20 minutes to complete. The program measures multiple aspects of cognitive functioning in athletes, including; attention span, working memory, sustained and selective attention time, response variability, non-verbal problem solving and reaction time.

## Conclusion

Regardless of the etiology precipitating a traumatic brain injury – motor vehicle accident while under the influence of alcohol, improvised explosive device, or any given Sunday, the biochemical processes or the secondary phase of neurotrauma that are initiated at the moment of a TBI all cascade to the same end-points; necrosis, apoptosis, and autophagia. The major difference is the extent of physical destruction of brain matter ascribed to the primary insult thereby, creating the conditional status of the TBI from minimal to severe.

As you delve into the chapters of this book you will learn about clinical neurology and how to use the TBI Locator<sup>™</sup> to define the areas of the brain that are involved in the neurotrauma associated with mTBI. Understanding where the injuries might be by evaluation of neuro-cognitive deficits by the bedside, can help improve your understanding of the pathophysiology that is underlying any alteration in the personality and cognitive abilities of the injured.

The results of the TBI Locator<sup>™</sup> may also assist in the prediction of the out come of neuroradiologic procedures that are used to further define the area(s) of damage. The use of post-acute phase neuroradiographic assessment has been simplified so that we can assess glucose up-take with a PET Scan showing areas of hypo- or hyper-metabolism, regional blood flow with a fMRI looking at the iron in the hemoglobin molecule, or following the course of long axons with Tractography produced by the DTI-MRI looking at water in the axons. These are but a few radiologic techniques that can help delineate the areas and extent of neurotrauma.

The secondary insult of TBI, the biochemistry that triggers Caspase 3 – the messenger of cell death, BAX, and BCl2 products all lead to death of cells in the region of the trauma as well as in remote areas of the brain. There appears to be areas of the brain that are overly sensitive to ROS and by-products of necrosis and increasing levels of glutamate. These areas of preferential neuronal loss are found in the Cortex, Hippocampus, Cerebellum, and Thalamus (Hypothalamus).(78)

Involvement of the Hippocampus alters acute and long term memory and the ability to learn and store new information but, it is the involvement of the Hypothalamus that interests us the most. Damage to the Hypothalamus not only alters thermal control of the body but affects the ability to regulate all of our hormones. Within the hypothalamus are cell-sensors for the levels of circulating hormones. Damage to this mechanism can lead to initial hormone insufficiencies that can progress to frank deficiencies. Failure of the Hypothalamic-Pituitary Axis is at the core of this books and the foundation for our approach to the diagnosis and treatment of TBI with Hormone Dysfunction syndrome.

Without adequate levels of hormones in the brain, whether neurosteroids produced regionally or neuroactive steroids passing through the blood brain barrier from the periphery, central hormonal deficiencies can be causative for the progression of the secondary phase of neurotrauma and the failure of the brain to heal itself. We have seen the literature attesting to the regeneration of a diverse population of nerve cells under the influence of IGF-I and II, and DHEA-s along with the protection from oxidative stress from pregnanolone, progesterone, and estrogens. (79-DD)

The perinatal histories of 46 children with idiopathic hypopituitarism were assessed in order to define the relationship between perinatal insult and the development of hypopituitarism. Compared to normal control siblings, the pregnancies resulting in hypopituitary children were complicated by a significantly higher incidence of vaginal bleeding at various times during gestation (13 pregnancies). Twenty-four percent of the hypopituitary children were delivered by breech, three times the incidence of control siblings and seven times the incidence of breech delivery in the general population. Prolonged or unusually short labors were more common in the hypopituitary children (13 patients), as were signs of intrapartum distress and asphyxia (10 patients). At the time of the study, 19 hypopituitary children had neurologic abnormalities; of these, 15 had histories of significant perinatal insult. The findings in this study suggest that, in many cases, perinatal insults may cause hypopituitarism. (last)

\*Access Medical Laboratory Grant 2009 for TBI; for the evaluation of 100 non-duty, discharged, male individuals with mTBI sustained while in combat. Jupiter, Florida, Mr. Ryan El-Hosseiny, CEO, Access Medical Laboratory.



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