TRAUMATIC BRAIN INJURY

A Clinical Approach to Diagnosis and Treatment

Edition 1.0

A Clinical Workbook by

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Chapter 1: An Overview and Introduction

"Adapt or perish, now as ever, is nature's inexorable imperative."

— H.G. Wells

Let's Begin

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, an early hominid learned how to use a bone as a tool, and then as a weapon to kill another hominid. 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 unearthed skulls found with depression fractures of the frontal, temporal, or occipital 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 our socio-economic evolution in the here and now.

In survey of countries that have weathered their own unique social growth over the past two hundred years, we have seen a significant rise in the occurrence of traumatic brain injury from a diversity of causes. In those individuals less than 20 years of age, motor vehicle accidents (mainly DUI related) make up the majority of cases, while those over 65 succumb to overmedication, Frailty Syndrome, and Vitamin D deficiency — which all cause gait instability and falls, the second most common cause for TBI.

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, strokes (hemorrhagic and ischemic), hypoxia, severe hypoglycemia, ionizing radiation, and prolonged surgical procedures can lead to the same pathophysiological pathways and changes in cognition and personality as those produced by direct force trauma to the skull.

Alzheimer's disease (AD) is now being linked to the occurrence of traumatic brain injury. The hallmark of AD has been the accumulation of Amyloid-β and the disruption of microtubules with tau protein disruption which is also being found in TBI. (1) The same critical processes that lead to the loss of executive function and cognitive abilities are the same chemical pathways in both conditions. (2) A 1999, report by the American Journal of Epidemiology acknowledged that those with TBI developed

Alzheimer's disease (AD) at the same rate as those with a history of TBI, but developed it much sooner than statistically anticipated and at an earlier age. (3) Adding to this was a study commissioned by the NFL reported that Alzheimer's disease or similar memory related diseases(dementia) appear to have been diagnosed in the league's former players infinitely more often than in the national population — and at 19 times the normal rate for men ages 30 through 49. (4)

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, neurobehavioral, and psychosocial changes that appear as behavioral issues that can manifest even after a delay of 30 years. (5) 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 cause referred to as the "Stealth Syndrome." (6)

This book and the associated 3-day, TBI Symposium will provide the fundamental knowledge to assist healthcare workers in how to recognize the parameters associated with TBI-releated hormonal dysfunction and how to diagnose and treat the individual. Chapter by chapter, you will find an abundant amount of information that cross-relates and was difficult to avoid redundancy at times. Therefore, I will apologize in advance for these redundancies which, if they were not present, would otherwise lead to a list of once stated facts whose salient points would be lost.

Epidemiology of Non-Combatant 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. (7) 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. (8)

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. (9) A prior CDC evaluation of TBI cases between 2002 and 2006 reported 1.7 million cases per year with 80.7 percent emergency room visits, 16.3 percent hospitalizations, and 3.0 percent deaths. (10) 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 belief, 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 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 percent of TBIs are the result of motor vehicle, bicycle or pedestrian–vehicle accidents. Falls are the second-commonest cause of TBI (20-30 percent of all TBI), being more frequent among the elderly and the very young population. Violence-related incidents account for approximately 20 percent of TBI, almost equally divided into firearm and non-firearm assaults. (11)

Several classification scales are used to rate TBI severity with the post-resuscitation Glasgow Coma Scale (GCS) being the most widely used . The GCS is based on the patient's response (eye opening, verbal and

motor function) to various stimuli. Fifteen is normal with a score of 13–15 considered mild, 9–12 moderate and ≤8 severe TBI. (12) 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. (13, 14) 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. (15) 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). (16)

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 percent 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, it's here now.

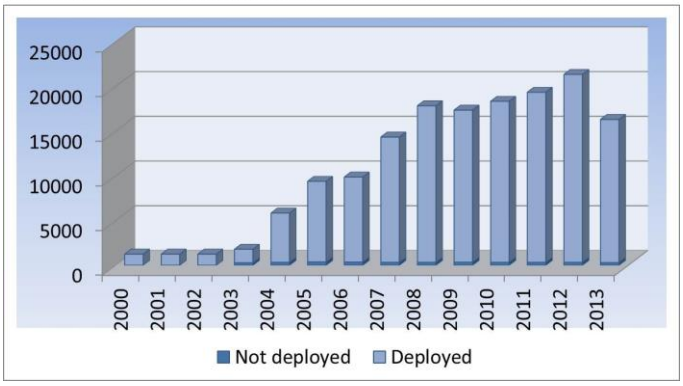
Epidemiology of Combatant Traumatic Brain Injury

Traumatic brain injury (TBI) has been described as the "signature wound" of the conflicts in Iraq and Afghanistan. Improvised explosive devises (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. This micro-impact trauma of repetitive gun fire is a frequently omitted cause of TBI.

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. (17) The majority of these soldiers are without loss of consciousness or overt physical trauma and are now classified as Post-Traumatic Stress Disorder (18) experiencing symptomatology that parallels that of mild TBI.

In March 4, 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

Chart 1.1: Annual PTSD diagnosed in all branches of the service from 2000 – 2013. Data from the DMSS.



90,000 veterans whose symptoms persist and warrant specialized care." (19)

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 primary blast wave where air filled structures such as the sinuses, ears, lungs, and intestines are most vulnerable leading 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 (diffuse axonal injury).

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. (*20*) 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. (*21*)

Consistent with 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 percent of those injured with TBI that do have one or more hormonal deficiencies by 3 months. (22) Failure to recognize and correct the underlying hormonal deficiencies (insufficiencies) may compound the physical and psychological complications of TBI and interfere with rehabilitation. (23)

The Military's available programs are comprehensive but limited. They might be seeing the literature and acknowledge that there is an association between mTBI and hormonal dysfunction, but they rarely pursue testing as recommended by the American Association of Clinical Endocrinologist and others. (24) 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. (25) The free laboratory testing has been made possible through a privately funded grant from Access Medical Laboratories of Jupiter, Florida and the El-Hosseiny family.

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 consequences of hormonal deficiencies precipitated by traumatic brain injury that led to their depression and ultimate suicides. (26)

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 and off 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, even decades after their last head injury, who will seek medical attention due to altered personality, bouts of anger and rage, and both cognitive and functional impairments. Hopefully, at that time, their medical care will include an initial history of trauma and a TBI

hormonal assessment as opposed to being placed on a psychotropic medication first and ask questions later. Furthermore, if the athlete is found to be hormonaly insufficient, and not necessarily deficient, they will be allowed to have replenishment to raise the levels to a more physiologic one as opposed to being denied a potentially life-saving treatment protocol. (27, 28, 29)

Both the physical and social impacts of sports related TBI have 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. (30)

Consequently, there are many NFL veterans who are still struggling post-career. A 1994 survey from the players' association found a significant numbers of retirees were depressed, fat and managing chronic pain. A 2006 Scripps Howard report found that of 3,850 deceased players, NFL players were 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. (31)

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. (32)

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 percent, and at 12 months, hypopituitarism was present in 30.3 percent. 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. (33) I think there is little else to say here, but more later.

Neuroendocrinology of TBI (Chapter 3)

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. (34) 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. (35, 36, 37, 38, 39)

PTHP 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. (40)

The pituitary gland responds to acute trauma 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 an independent decrease in activity of their target organs. Changes in circulating hormone levels becomes apparent during the first hours or days after trauma, and may persist for the duration of the

acute critical phase of injury. 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 in treatment during this early phase (glucocorticoids, narcotic analgesics or dopaminergic agents). (41)

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), and adrenocorticotropic hormone (ACTH), and posterior pituitary markers such as anti-diuretic hormone (ADH) and vasopressin. (42)

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 establish the presence of a primary hormonal deficiency (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). Therefore, identifying those that are deficient early in the course of injury allows for development of comprehensive treatment protocols. (43)

Our recent understanding of neurosteroids (NS) 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 starting with cholesterol. Pregnenolone, progesterone, allopregnanolone, and DHEA, and their sulfanated active metabolites, are a few of the prominent neurosteroids. Each has important functions to protect nerves from oxidative stress (ROS), reduce inflammatory cytokines, reduce interleukins, promote neuroregeneration, and to regenerate myelin. (44, 45, 46) An interesting finding in the frontal lobes of patients with Alzheimer's disease is a significant deficiency of allopregnanolone (47, 48, 49, 50) which is also found in traumatic brain injury. (51)

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 life, years later. 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, after followed new TBI cases for a period of one year, one or multiple hormone deficiencies were found at 56 percent and 36 percent, at 6 and 12 months, respectively. (52)

A more recent article in the Journal of Neurotrauma (2012) addressed the persistency of Pituitary Hormone Deficiency after Traumatic Brain Injury, acknowledging that 69 percent of the patients had at least one pituitary hormone deficiency, where GH deficiency was more prevalent (severe: 40.0 percent; partial: 23.6 percent) than corticotropin (27.3 percent) or thyrotropin (21.8 percent) deficiencies. (53)

Diagnosing the TBI Hormone Dysfunction Syndrome (THDS) can be challenging for the majority of clinicians, as well as for the trained endocrinologists. This is because of the new paradigm in what constitutes a laboratory result as being insufficient or low-normal as well as the controversial of whether-or-not to treat the insufficiency? Many of the hormone tests have reference ranges that are very broad, representing two standard deviations so that the numerical distance from the low-end to the high-end can be immense as in the case of Total Testosterone; 270 ng/ml to 1730 ng/ml. So, if a patient has a result of 280 ng/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 associated complaints and elect not to treat. Fortunately, this is slowly changing and physicians are treating patients with appropriate physiological doses of replenishment hormones to achieve a level that is from the median of the range (50^{th} percentile for age) to the 75^{th} percentile.

Neuropathophysiology of TBI (Chapter 4)

The majority of mild traumatic brain injury (mTBI) cases, if not all, are of the non-penetrating type where the force of the trauma is conveyed to and through the skull (blunt force, blast waves, or ionizing radiation). Nonetheless, there are two phases of injury that occur to the brain: an initial mechanical injury (primary injury) associated with contusion, hemorrhage, edema, ischemia, and axonal shearing, and this is followed with a biochemical-inflammatory assault (secondary injury) associated with expanded neuronal loss resulting from the activation of one or more of the injury cascades — Necrosis, Apoptosis, Autophagy, and Parthanatos. (54, 55)

These events, mechanical and biochemical, can co-exist depending upon the magnitude of damage, but frequently in mTBI, the primary injury is short-lived while the subtle and insidious secondary injury can linger on for years taking its toll cell by cell. It is the impact of these biochemical processes that are most important for understanding the cause-and-effect relationship between TBI and hypothalamic-pituitary dysfunction (HPD) and the disruption of hormonal homeostasis.

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 there is impact upon a region of brain that regulates right and wrong and self-preservation.

Neurons that escaped the initial mechanical trauma(shearing) 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, excytotoxicity, cytokines, and interleukins create an environment of collateral cellular damage as the oxidative stress (OS) increases. This is the non-neuropermissive environment (NPE), that like a pebble dropped in water leads to concentric rings of expanding cell death. Over time, the accruement of dead and dying brain cells leads to the signature changes that have come to represent not only mild traumatic brain injuries but all degrees of neurotrauma. (56)

Compounding the condition, 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 leaking 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, hypoglycemia and further neuronal damage all cause acceleration of oxidative stress and expansion of the involved area. (57)

Although these processes have an overt appearance of a negative net affect upon the brain, 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. Think of it as a back fire in a blazing forest which is set to control the path and extent of the initial fire, but with a complexity that has been orchestrated into the following four types.

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 is now suggesting that its occurrence and progression might be tightly controlled. This is based upon finding signs of organized processes like mitochondrial dysfunction, ATP depletion, increased ROS, cytoskeletal proteolysis by Calpain, and disruption of the cell membrane. It is this loss of cell membrane integrity that precipitates irreversible cell death. (58, 59)

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. (60)

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. (61, 62, 63) 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 into its principle components for reutilization for other cell structures, a form of cannibalization that can also occur during cell starvation where the cell is forced to ingest its own parts (organelles) for survival. (64)

Finally, and the most recent addition to the cell death mechanisms is **Parthanatos** which is initiated by release of mitochondrial apoptosis-inducing factor (AIF) and its translocation to the nucleus. (65) Apoptosis-inducing factor is a mitochondrial flavoprotein contributing to both cell life and death. Under physiological conditions, AIF maintains mitochondrial structure and plays an essential role in oxidative phosphorylation. Conversely, under pathological conditions, AIF enters the nucleus and facilitates poly (ADP-ribose) polymerase-1 (PARP-1)-dependent cell death. (66) In the process, mitochondrial transmembrane potential dissipates, chromatin condenses and large DNA fragmentation are formed. Unlike apoptosis, it does not cause apoptotic body formation or small scale DNA fragmentation. It is worth noting that PARP-1-mediated cell death involves loss of membrane integrity similar to necrosis, yet it does not induce cell swelling. Parthanatos is distinct also from autophagy as it does not involve autophagic vacuoles formation or lysosomal degradation. (67)

Traumatic brain injury in humans results in a pattern of neuronal loss that seems to preference the cortex, hippocampus, cerebellum, and thalamus (hypothalamus). (68) In the acute post-traumatic period, injured neurons appear swollen then become shrunken and eosinophilic with condensation of chromatin. This pattern suggests the presence of both necrotic and apoptotic processes. Under the electron microscope, these degenerating neurons appear swollen, with swollen mitochondria, vacuolated cytoplasm and Pyknotic nuclei, indicative of necrosis. (69) 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. (70)

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. (71) 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. (72)

Neuroradiology of TBI (Chapter 5)

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 thought 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, large areas of 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. (73)

The importance of this technology was clearly defined in the paper by Orson and Handson in 2009 when they showed that 76 percent of non-combatant individuals who sustained a TBI had positive findings with only 14 percent involvement of their pituitary gland. (74) This, in my mind, opened the door to looking beyond the pituitary gland as the poor recipiant of all things bad and turn attention to other areas of the brain. In fact, in this same paper, over 59 percent of findings involved the Hippocampus (memory and the ability to learn new information) and 29 percent diffuse axonial injury (DIA). 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 Tension 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

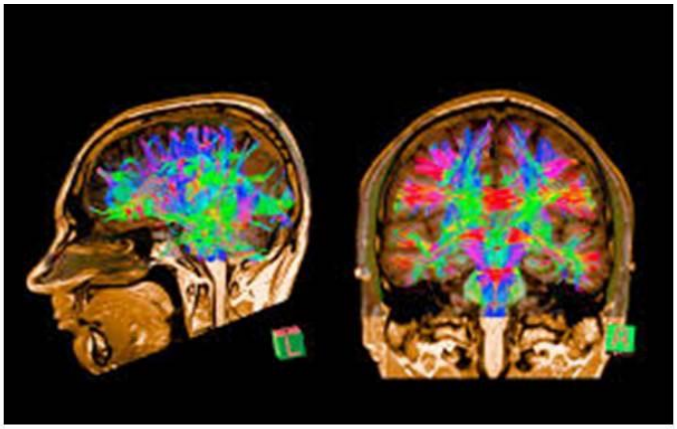


Image 1.1: Diffusion tension imaging MRI or tractography follows the flow of H_2O within the axons of neurons.

functioning that we see as change in the personality and cognitive abilities of the individual. (75)

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. (76)

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

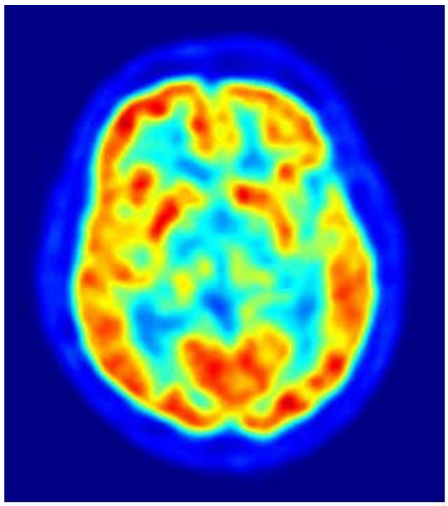


Image 1.2: Functional MRI showing preferential regional blood flow into areas of the brain that are actively being used.

The Laboratory of TBI (Chapter 6)

In Ireland Dr. Amar Agha, in Italy Drs. Ambrosio and Amaretti, in Serbia Dr. Popovic, and here in the United States Drs. Ronald Swerdloff and Daniel Kelly, have published, as a group, thousands of articles discussing the relationship between TBI and hormonal dysfunction. In 2007, on ESPN Outside the Lines, Dr. Dan Kelly and I were on the January 21st program discussing the relationship between hormone deficiencies and sports related TBI. So, it would make sense by now, almost 10 years after the fact, that everyone would have an idea as to the ideal hormonal panel to use in the evaluation of anyone with TBI. Right? NOT YET!

The Millennium-TBI panel (3624) consists of 26 specific tests that allows for both direct and indirect assessment of the neurosteroid and neuroactive steroid pools. In the initial assessment of the patient it is important to determine if any of the hormonal deficiencies are of a primary nature with failure of the peripheral glands or of a central origin due to damage to the HP axis. The findings of low tetraiodothyronine (T4) and elevated thyroid stimulating hormone (TSH) is a classical pattern of Primary Hypothyroidism while a finding of low TSH and a low T4 would be more suggestive of a central or Tertiary Hypothyroidism. Furthermore, having a normal TSH, low-normal T4, normal T3 and a high level of rT3 would indicate a Low T3 Syndrome with impact on mood with predilection for depression, poor sense of well-being, fatigue, diminished cognition, dry skin and brittle hair.

Without the full compliment of testing you will be left with insufficient data points to make an accurate assessment of deficiency to formulate an optimal treatment protocol. The end result might be some improvement, but not optimal.

Biomarkers of TBI

The search for a viable biomarker for traumatic brain injury, which can identify the presence and progression of neurotrauma and be predictive of outcome, 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

Creatine Kinase	**CK**	Special energy requirements of different neuronal and glial cell types.
Glial Fibrillary Acidic Protein	**AFAP**	Intermediate filaments form networks that provide support and strength to cells.
Lactate Dehydrogenase	**LDH**	Marker for brain aging/damage
Myelin Basic Protein	**MBP**	Comprises about 20% of the myelin sheath in neuronal axons.
Neuron-Specific Enolase	**NSE**	Rapidly detected in serum after TBI. Elevated in brain tumors.
* S-100 Proteins (19 types)	**S-100 β**	S 100β is detected in TBI patients.
Spinal Fluid IL-6	**SPIL-6**	Inflammatory cytokine.
Serum Cleaved Tau Protein	**CLT**	Microtubule protein.
Caspase -3	**Cap3**	Messenger of Death.
α II-Spectrin	**AIIS**	In CSF 24-72 hrs post-TBI.
* Neurofilament 68 Protein	**NF-68**	Information on the pathophysiology of dendritic and axonal damage after TBI.

Table 1.1: These are bio-markers of proteolytic damage to brain that are found in the cerebral spinal fluid within hours to days of neurotrauma.

indolent damage to the brain.

Table 1.1 is a short listing of the most prominent biomarkers of TBI that are actively under evaluation. Unfortunately, many are only obtainable from the cerebral spinal fluid and not present in the peripheral circulation to any usable extent.

Neuropsychiatry in TBI (Chapter 7)

In this 2002 study, patients who had suffered traumatic brain injury were evaluated to determine the occurrence of psychiatric disorders during a 30-year follow-up period. Of the 60 patients, 29 (48.3 percent) had had an Axis I disorder that began after traumatic brain injury, and 37 (61.7 percent) had an Axis I disorder during their lifetimes. In this study, the most common disorders associated with post-traumatic brain injury were major depression (26.7 percent), alcohol abuse or dependence (11.7 percent), panic disorder (8.3 percent), specific phobia (8.3 percent), and psychotic disorders (6.7 percent). Fourteen patients (23.3 percent) had at least one personality disorder. The most prevalent individual disorders were avoidant (15.0 percent), paranoid (8.3 percent), and schizoid (6.7 percent) personality disorders. Nine patients (15.0 percent) had DSM-III-R organic personality syndrome. (77)

A 2009 Australian study commented on 100 post TBI patients, “Post-injury, 65 percent received a diagnosis, of which major depression became the most common (45 percent), followed by anxiety (38 percent) and substance use disorder (21 percent). Frequency of depression, generalized anxiety disorder, post-traumatic stress disorder, panic disorder, and phobias rose from pre-injury to post-injury. More than two-thirds of post-injury depression and anxiety cases were novel and showed poor resolution rates.” They concluded: “A high frequency of post-injury psychiatric disorders was evident up to 5.5 years post-injury, with many novel cases of depression and anxiety. Individuals with TBI should be screened for

psychiatric disorders at various time points post- injury without reliance on history of psychiatric problems to predict who is at risk, so that appropriate intervention can be offered." (78) The high rate of psychiatric disorders found in this study emphasizes the importance of psychiatric follow-up after traumatic brain injury.

This brings us to the recent office case of Bill who 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 a hospitalization. At 36 years of age, and after nearly tens years of self-medication with alcohol Bill was interred for evaluation and treatment for severe depression. Once he was detoxified from the alcohol addiction, he was treated with a number of SSRIs, that did not fully resolve his depression (treatment resistant depression). Ultimately, Bill's psychiatrist placed him on three medications and acknowledged and accepted the persistence of mild depression.

Five years later, at age 41, and after being on psychotropic medication for 5 years, Bill became aware of traumatic brain injury causing hormonal deficiencies that can be causative of depression and substance abuse. Bill came to our offices in Los Angeles from Boston, at which time he had our TBI-panel performed. In review of his TBI intake forms, there was a suggestion of testosterone deficiency.

Bill was given a 60mg injection of our blended testosterone and sent home with instruction to call in one week to review any response to this "Provocative testing". 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 1st 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, was emotionally stable, had a new girlfriend, had a return of his libido, and was working out harder in the gym with improved recovery.

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. (79) Unfortunately, each section contains a clinical case where every single patient is ultimately placed on one or more psychotropic medications foregoing any laboratory assessment for hormonal homeostasis. This is in light of the thousands of articles showing the correlation between changes in psychoneurobehavior and hormone dysfunctioning. (80L)

Women with anorexia and low testosterone levels were found to be the most resistant to traditional treatment with antidepressants. After low-dose replacement testosterone therapy the Anorexic patients' cerebral metabolism increased in the posterior cingulate, subgenual anterior cingulate, premotor cortex, right caudate and right parietal lobes as compared to the control group of Anorectic patients with improvement in their depression. (81)

For whatever reason, we seem to be focusing in on only the superficial aspects of psychological conditions without going after the cause (neurochemical); 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, replacement is all that is needed. Medicine has become shortsighted in the quest for health and wellness vying for a quick fix rather than a potential cure.

PTSD versus mTBI

I believe that the use of the term PTSD is a misnomer and should be replaced with the more accurate term; mTBI. The use of PTSD implies that there is a psychological or emotional propensity that is precipitated by a non-physical trauma or a trauma that does not create an overt or enduring physical injury. (82)

Looking at the work by Kessler and Gelea; approximately 7.7 million Americans suffer from PTSD, with the most common causes of PTSD in the civilian sector being motor vehicle crashes and assaults. (83, 84) These are both conditions that involve acceleration-deceleration type injuries and the possibility of blunt trauma. The underlying biomechanical forces that are involved are commonly seen in all levels of TBI. The fact that there is a delay in the on-set of neuropsychological symptomatology should not dispel the presence of TBI, as causative, over PTSD since delays in the onset of symptoms have been recorded up to 17 years post TBI and frequently appear as Alzheimer's Disease .(85)

A 2009 article looking at the use of functional neuroimaging techniques to distinguish between TBI and PTSD did not convince me that these differences were exclusively associated with PTSD or TBI. It may be that a particular pattern of neurotrama generates the patterns that they are promoting or that these patterns were pre-morbid to the event that caused the PTSD. Either way, the symptomatology is the same and the beneficial results that the Millennium has achieved in both PTSD and mTBI are the same. (86)

Supplementation for TBI (Chapter 8)

The use of supplementation concurrent to hormonal replenishment is necessary in order to reverse the non-neuropermissive environment (inflammatory) that was precipitated by the secondary phase of neurotrauma. (87) Additionally, supplementation must be used to counter any side-effects associated with treatment, such as diminution of pregnenolone and DHEA from down-regulation caused by testosterone.

An increase in generation of reactive oxygen species (ROS) occurs as a by-product of damage to the cellular energy management system involving mitochondria. The loss of a competent cell surface ion exchange mechanism (ion-gated flux) allows for the random influx of calcium, chloride, and potassium leading to the precipitation of apoptosis or parthanatos. In an attempt to compensate for the loss of energy to regulate the ion-gate, mitochondria increase their production of ATP with an increase in oxidative stress. Free radicals foster inflammation creating a non-neuropermissive environment that does not foster the ability of cells to repair. Therefore, supplements with the ability to scavenge free radicals as well as to decrease inflammation can yield a more neuropermissive environment for cellular recovery. (88)

As a consequence of TBI initiated cellular depletion of ATP reserves, there is a reduced in ubiquitous mitochondrial creatine kinase (uMtCK), an enzyme implicated in the energetic regulation of Ca2+-pumps and in the maintenance of Ca2+-homeostasis. It is when Ca2+ levels increase in the cytosol that irreversible cell death mechanisms are initiated (Caspase-3, the messenger of death). The use of Omega-3 fatty acids supplements normalized the levels of uMtCK after traumatic brain lesions and helps the cell to maintain calcium balance. (89)

Oxidative stress due to the production of ROS, NO, peroxyl, and nitryls along with blood by-products such as *heme*, damages the cell membrane's composition of lipids generating an increased concentration of harmful the end products. Peroxidation appears to be important in atherosclerosis and in worsening the initial tissue injury caused by ischemic or traumatic brain injury. Oxidative stress can damage many biological molecules such as proteins and DNA, and are often more significant targets of injury than are lipids, as well as the finding that lipid peroxidation often occurs late in the injury process. (90)

N-acetyl cysteine (NAC) has been available for about 40 years as Mucomyst being used for pulmonary issues and also as the antidote for acute acetaminophen toxicity, in the emergency room. An impressive group of recent articles (17,500) found that NAC has both antioxidant and anti-inflammatory benefits in TBI. Michael Hoffer, et al 2013, used NAC in an active theater of war (Iraq and Afghanistan) study on mild and moderate TBI cases produced by blast injury. The studies clearly showed that initiation of treatment with NAC within 24 hours of injury led to better outcome in terms of headache, confusion, memory loss, and sleep issues. (91, 92)

Remember nothing is free. When we replenish levels of testosterone we do at the risk of precipitating a negative feedback loop that causes a decrease in the migration of cholesterol into the inner membranes of mitochondria where it is converted to pregnenolone. This appears to be set in motion by the level of lutenizing hormone(LH) which is down-regulated by supplementation with testosterone. Therefore, it is imperative to supplement with all the neuroactive steroids diminished by treatment with testosterone or estrogens for that matter. Otherwise, you diminish the magnitude and speed of a healthy response by the patient; testosterone decreases endogenous pregnenolone and DHEA pathways causing a transient increase in cholesterol.

Treatment for TBI (Chapter 9)

I wish there was something cryptic I could say about this section, which deals with treatment of mTBI based upon laboratory confirmed hormonal disruption, but there isn't. Insufficiencies are generally looked at as being within the "normal" reference ranges, and therefore, they are never considered to be causative or participating in the clinical presentation of the patient. We need to reassess our thinking about what represents healthy hormonal levels based upon individual responses and not what an acceptable numbers looks like on paper. Treatment must be tailored to the patient with the goal of optimizing all hormones based upon functional outcome. What? You think this is unprofessional and not the way medicine should be practiced? Let's see. What are the objective laboratory tests that a psychiatrist performs prior to loading the patient up with medication? There are none! The psychiatrist starts the patient on treatment empirically and monitors their response (subjective at best).

As far as objective results for the treatment of TBI, a 2002 review article entitled "Outcome Measures for Clinical Trials in Neuro-Trauma", clearly indicated that dozens of medication trials 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. (93) Not a single article addressed the associated hormonal deficiencies or insufficiencies.

Another prominent treatment modality is hypothermia or cooling during which an unconscious patient with severe TBI has their body temperature decreased to 32–35°C (89.6-95°F) in order to protect neurons from ischemia and hypoxia caused by cerebral edema. Unfortunately, the attached 2009 review, published their assessment of the benefits of "cooling" in TBI stating "…our present knowledge on the use of active cooling in TBI patients has not been shown to be effective for outcome after TBI…." (94)

In light of these and hundreds of other articles addressing the lack of beneficial affects, hypothermic 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. (95, 96, 97, 98, 99, 100, 101, 102)

It is my opinion that the major reason why hormone treatment protocols are being ignored is because the literature has been weak in supporting the benefits from their use. This arises from the flawed perception that monotherapy for TBI is all you need. A greater understanding of the importance of neurosteroids in neuroendocrinology and the impact of TBI on their production will lead to more complete treatment with greater beneficial outcomes for the patients. The growing science on neurosteroids is clearly showing that they are responsible for the integration, modulation, and maintenance of neuronal functioning, protection and repair. Failure to address the need for optimal neurosteroids in treatment can only mean failure to the patient's abilities for recovery. (103, 104, 105, 106)

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 Nutropin products (L-Dyprenyl, amantadine, and neurotransmitter precursor amino acids). (107)

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

Conclusion

Traumatic brain injury is rapidly become the number one cause of functional disability worldwide. Anywhere from 100 – 250 persons per 100,000 population are succumbing to the progressive development of symptoms that can create hordes of socially dependent individuals.

Mild traumatic brain injury (mTBI) and not post-traumatic stress disorder (PTSD) is associated with a physical component that leads to the interruption of both cellular connectivity and functional neurochemistry. The disruption of cellular membranes precipitated by blunt trauma, penetrating projectiles, motor vehicle accidents, any given Sunday, radiation, chemotherapy, ischemic strokes, hypoxia, blast trauma, repetitive gun fire, and starvation leads to the loss of cell integrity. As the gradient of cellular damage unfolds anyone of the neurochemical processes of the secondary phase of neurotrauma; necrosis, apoptosis, autophagy, and parthanatos, will regulate the ultimate outcome in both cognitive and emotional functioning.

Movement of the brain against the various ridges and bony protuberances of the anterior (frontal) and middle (temporal) fossae is particularly injurious to the temporal and frontal poles and the ventral anterior, medial, and lateral temporal cortices, and the frontal cortices. Acceleration or deceleration injuries are maximal on axonal projections and small blood vessels within and from the brain stem, the parasagittal white matter of the cerebrum, the corpus callosum, the gray-white junctions of the cerebral cortex, and especially at gray-white junctions in the ventral and anterior frontal and temporal lobes. This pattern of injury is associated with an almost predictable group of neurobehavioral conditions that can include depression, anxiety, altered executive functions, rage, aggression, mood disorders and suicide.

Lateral and rotational forces add further injury to the central areas of the brain that includes the pituitary gland, hypothalamus, thalamus, hippocampus, amygdala, optic chiasma, and olfactory bulbs. This accounts for the development of hyposmia or anosmia, hypogeusia or ageusia, hypothalamic-pituitary dysfunction with loss of hormonal homeostasis, faltering memory, and fatigue.

The acute use of neuroradiologic studies is to detect skull fracture, subdural hematoma, intracerebral bleeding, and cerebral edema. In the post-acute phase the use of MRI, DTI-MRI, PET or SPECT scans can help determine the impact on structural and functional integrity. Scarring, cavitation, diffuse axonal injury, altered cerebral blood flow can all be identified and followed for improvement based upon treatment.

Ideally, treatment will be based upon the performance of a comprehensive laboratory assessment that will look at the continuation of hormonal homeostasis predicated by a normal HP axis. In the event that damage impaired the brain's ability to maintain optimal hormonal production, replenishment of those hormones would be mandated to avoid the consequences of neurobehavioral and physiologic dysfunctioning. Furthermore, to avoid missing a patient that has a relative hormonal deficiency or insufficiency, we will need to apply the new interpretive paradigm in which the median of the range is used instead of the ineffective "reference range."

Neurobehavioral conditions have been found in association with the presence of neurosteroid and neuroactive steroid alterations. Both groups of steroids have been found to modulate communication between neurons in all centers of the brain maintaining optimal functioning. Disruption of healthy neuronal communication involving shearing of neurons and loss of hormonal modulation can account for the many psychobehavioral changes witnessed in the post-TBI period. The traditional approach using SSRI's has obviously failed to provide recovery since the majority of individuals are on combination therapies due to treatment resistant depression (TRD); a telltale sign of an underlying hormonal deficiency.

Supporting the neurosteroids' ability to promote recovery is an array of supplements that function to reduce the presence of oxidative stressors (OS). Only when there is a return to a more neuropermissive environment (NPE) can the processes of reconnection of neurocommunication and modulation of neurotransmitters be accomplished. Until the state of a healthier NPE is met, the individual will continue to struggle and delay a return to their pre-injury status.

Finally, treatment will be primarily based upon the use and interpretation of the Millennium-TBI panel 3426 with the objective being to raise all the hormones to the median (50 percent) of the range and above, if needed. Once treatment is started the patient is assessed by a monthly treatment questionnaire (MTQ) and a small laboratory follow-up test. Based upon the results of an objective blood test and a subjective self-assessment, their treatment protocol can be adjusted up or down. Many times, we add additional supplements to improve mitochondrial functioning along with free radical scavengers, like PQQ.

At the time of writing this segment of the book, we have started using progesterone oral drops (at bed time) to increase the presence in the blood of its metabolite allopregnanolone, which has been found,

along with estradiol and DHEA-s, to provide significant neuroprotection, neuroregeneration, and recovery over the long-term, and lessening of “brain fog” in the short-term.

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