Reflections
Science in the cultural context

Introduction
In 1916, eighteen-year-old David Ireland joined the Black Watch as a private in the Highland Cyclist battalion. He was sent to France to dispatch messages between trenches under heavy fire and was wounded twice, first by a German biplane, and later a gunshot to the knee. After World War I (WWI), he returned to his home in Fife, Scotland, and worked briefly as a gardener. But like so many other veterans, memories of his combat experiences haunted him, and in 1924, he was admitted to nearby Stratheden Hospital with “delusory psychosis,” a condition more commonly known to the public as shell shock. He remained a patient at Stratheden until his death in 2001 (1).

Unfortunately, a similar picture is emerging from the combat casualties returning from Iraq and Afghanistan, where head and neck injuries, including brain trauma, now account for one quarter of the evacuated soldiers (2). One-third of all combat soldiers are exposed to blast explosions, half of whom experience brain trauma, and within three years, many have developed altered mental function (3, 4).

Despite hospitalizations nearly a century apart, the veterans from WWI and from Iraq and Afghanistan have more in common than anyone cares to admit. They are casualties of combat-induced stress and brain trauma: two conditions that were long thought to be separate, but are now viewed as parts of the same disorder, with a common cause and, unfortunately, with a complicated, uncertain outcome.

Modern combat conditions have always caused a high number of neurological and psychiatric casualties. Throughout the
twentieth century, explosions killed most soldiers with head injuries before they could be resuscitated or treated. Not surprisingly, WWI shell-shock patients rarely had physical injuries. Now, however, the casualties from high-order (that is, more powerful) explosives commonly used by the insurgency forces in Iraq and Afghanistan are surviving, thanks to advances in body armor and battlefield medicine. But they are suffering complex neurological and psychological impairment caused by a combination of the concussion of those explosives, emotional trauma, and the stress of witnessing the brutality of war: shell shock, of a type that was first proposed nearly a century ago (5, 6).

**History of Combat-Related Head Injuries**

Charles Myers, a British psychiatrist practicing in France, introduced the term “shell shock” to describe the condition of injured soldiers of the British Expeditionary Force he was treating during the retreat from Mons in late 1914 (7, 8). These patients exhibited a combination of apparent neurological and psychological symptoms including: hysteria and anxiety; paralysis; limping and muscle contractions; blindness and deafness; nightmares and insomnia; heart palpitations; depression; dizziness and disorientation; and loss of appetite. Myers hypothesized that long-term bombardment with high explosive shells caused these symptoms (5). By July, 1916, at the Battle of the Somme, 40% of the casualties (16,000 cases) were diagnosed as shell shock (7–9).

However, Myers soon realized that shell shock was a misleading term. Many of the casualties had never served in the front lines, nor been exposed to bombardment (7, 10). Although the methods at that time made it difficult to distinguish between physical and emotional trauma (11), military records from the British Adjutant-General indicated that only 4%–10% of “shell shock” cases arose from concussion injuries (7, 9). Medical circles quickly abandoned shell shock in favor of more descriptive terms such as “functional nervous disorder,” “traumatic war neurosis,” and “neurasthenia” (7, 9). But none of those terms resonated with the British Army or the general public, who found “shell shock” a useful label and continued to use it long after the war (9).

By any name, these casualties presented the military with a monumental medical challenge. In 1919, 38% of hospitalized veterans in the US were classified as mental or nervous cases (9). Experience was similar with the British, French, and German armed forces.

The magnitude and rapid onset of psychiatric problems among otherwise fit soldiers greatly changed the medical community’s attitude toward mental illness (8). Between the two world wars, psychiatrists increasingly reasoned that war-traumatized patients were not inherently insane; everyone

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**Bombardment**

*Four days the earth was rent and torn*
*By bursting steel,*
*The houses fell about us;*
*Three nights we dared not sleep,*
*Sweating, and listening for the imminent crash*
*Which meant our death.*

*The fourth night every man,*
*Nerve-tortured, racked to exhaustion,*
*Slept, muttering and twitching,*
*While the shells crashed overhead.*

*The fifth day there came a hush;*
*We left our holes*
*And looked above the wreckage of the earth*
*To where the white clouds moved in silent lines*
*Across the untroubled blue.*

—Richard Aldington
was vulnerable to mental breakdown when presented with a sufficiently extreme conflict between their sense of duty and the instinct for self-preservation (8). In 1930, the British government responded to this shift in thinking and eliminated the death penalty for desertion and cowardice (8).

At the start of WW II, the new generation of military psychiatrists, lacking experience with shell shock, initially treated combat casualties based on their knowledge of peacetime, civilian neurosis. Combat neurosis, they soon realized, was different. “Even the most normal of soldiers may be brought to neurotic decompensation by war,” wrote army neurologist Frederick Hanson (12).

Two observations in particular guided their thinking about etiology and treatment. First, soldiers were more likely to become psychiatric casualties when they were tired, often presenting with symptoms such as crying, tremor, and emotional lability (12, 13). In April, 1943, the term “exhaustion” was therefore adopted as the official diagnosis for this psychiatric condition (12), which the soldiers and general public called “combat fatigue.” Second, emotional stress was almost directly proportional to the time spent in combat. After viewing the casualties near Monte Cassino and Anzio, army psychiatrist John Appel calculated that by 214 aggregate days of combat duty, all soldiers had broken down psychologically, if they had not been wounded, killed, or lost to physical sickness (14, 15). Opinions varied among military experts as to the actual number of days in combat, but it was clear that duration was a factor in causing combat fatigue (6).

As the war progressed, combat fatigue became an increasingly serious problem. In September, 1943, for example, the US army was barely able to maintain troop strength, with 112,500 enlisted men evacuated or discharged with combat fatigue, and only 118,600 new recruits inducted (9). Overall, 504,000 US ground soldiers (equivalent to fifty army divisions) were psychiatric casualties and permanently lost from service during the war (9).

Despite progress in medical circles to understand and distinguish between inherent mental illness and the neurosis brought on by combat, the military and general public’s attitudes were slower to change. General George Patton’s unsympathetic conduct toward one emotionally traumatized soldier1 reflected the views of many and reinforced the confusion between illness and cowardice (5).

In Vietnam, shorter combat patrols alternating with periods of rest reduced the cases of “exhaustion” (6), and duration was replaced by a more important precipitating factor. Instead of the cohesive combat units that provided moral support in previous wars, soldiers in Vietnam were deployed and relieved individually (9). Consequently, combat stress resulted from the intensity, remoteness, and loneliness of combat (6).

Many veterans of the Vietnam War returned home without apparent combat injuries, but nevertheless suffered emotionally (5). An army chaplain, Maj. David Hoh, coined “Vietnam Syndrome” in 1970 to describe this depression, which appeared to be aggravated by returning Vietnam veterans’ difficult adjustment to their communities and a lack of public support for their efforts (5, 16). Nearly one-third of the 3.15 million soldiers who fought in Vietnam developed psychiatric disorders (5, 9).

1 While visiting patients at a military hospital in Sicily in August, 1943, General Patton came upon a 24-year-old soldier who was weeping but with no visible injuries. When the soldier attributed his condition to his nerves and sensitivity to the shelling, Patton burst into a rage, called the soldier a coward and ordered him back to the front. In front of the hospital staff, Patton slapped the soldier with the back of his hand. Although Patton later apologized, the incident was widely reported in the press.
In parallel, Israeli physicians were noting similar symptoms of mental and physical fatigue. The syndrome observed in soldiers who fought in the 1973 Yom Kippur War and the 1982 Lebanon Invasion was called Combat Stress Reactions (CSR) and accounted for nearly 30% of the total casualties in these conflicts (5).

In 1980, the American Psychiatric Association developed diagnostic criteria for Post Traumatic Stress Disorder (PTSD) (5). As defined in the Diagnostic and Statistical Manual – Fourth Edition (DSM-IV), PTSD characteristics include exposure to a traumatic event, persistent re-experience of the trauma in real or imagined events, persistent avoidance of stimuli associated with the trauma, and persistent symptoms of increased arousal that were not present before the trauma (17, 18).

Unlike the confusing and contradictory descriptions in previous wars, the standardized PTSD criteria have permitted more accurate classification of Iraq-Afghanistan casualties from the outset. From 2002 through March, 2007, 39,243 soldiers were diagnosed with PTSD, and in 2006, PTSD represented 56% of all psychiatric cases seen in returning soldiers (19). A large portion of these veterans developed PTSD as a result of exposure to blast explosions, with or without diagnosed traumatic brain injuries.

Whereas the typical WWI shell-shock victim did not suffer physical injuries, in recent conflicts, chronic PTSD strongly correlates with combat exposure (3, 4, 18). Higher rates (two- to three-fold) of PTSD have been observed among injured Vietnam veterans compared to non-injured veterans (18). Similarly, in Iraq and Afghanistan, PTSD is more likely among combat veterans who are injured, especially those with brain injuries (3, 18).

Physicians have known for more than 150 years that physical trauma to the head can result in both neurological and psychological changes in the patient. In 1848, Phineas Gage, a railway construction foreman, became the first well-documented victim of traumatic brain injury. An accidental explosion propelled a three-foot tamping rod through the top of Gage’s skull, passing through his brain, and exiting at the temple. Gage survived, but his injury caused alarming personality and behavioral changes that persisted until his death in 1861 (20).

Traumatic Brain Injury (TBI) is the general term now used to describe brain damage that results from a sudden head trauma. The brain damage can be either focal or diffuse, and the injuries are classified as either closed or penetrating. Closed head injury is damage to the brain without breaking the skull. Penetrating head injury is damage such as Gage’s in which an object pierces the skull and brain tissue. Approximately 1.4 million people in the US suffer TBIs from various causes each year, largely from motor vehicle and sports accidents (20).

Not surprisingly, battlefield casualties have always included TBIs. Firearms and other projectiles cause penetrating head injuries. Sudden and violent blows to the head (concussion) often result in closed head injuries. Until the end of the twentieth century, medical understanding of TBIs was based on an assumption of physical damage to the brain, resulting in neurological dysfunction. Therefore, a clear distinction was made by military physicians between TBI casualties, whose physical injuries were usually apparent, and stress casualties (now called PTSD), who typically exhibited no, or only mild, physical injury.

The casualties from Iraq and Afghanistan cannot be so discretely classified for four reasons. First, many PTSD symptoms overlap with symptoms of mild TBI, such as headache, dizziness, irritability, decreased concentration, delayed problem solving reaction time, memory impairment, fatigue, visual disturbances, sleep disruption, sensitivity to light and noise, judgment problems, impulsiveness, emotional outbursts, anxiety, and depression (2, 18, 21–24). Second, PTSD symptoms can develop gradually after traumatic brain injury (18). A Department of Veterans Affairs (VA) rehabilitation center noted that affected patients, although initially judged fit for duty or independent living at home, dramatically worsened...
Initially confined in the explosive’s container, this gas creates enormous pressure within a few microseconds, spiking to a maximal peak overpressure (i.e., the peak of the pressure curve) \((11, 32, 34)\). High-order explosives such as C4 can create pressures of over four million psi \((34)\). The high pressure gas then expands from its point of origin to compress the surrounding air in an accelerating wave of superheated air molecules and generates a pressure pulse (called a “blast wave”) in all directions \((11, 33, 34)\).

The high pressure blast wave, which lasts only a fraction of a second, travels at an initial velocity of 1,600 feet per second \((32, 34, 35)\). Anyone standing in the vicinity of the blast wave will experience stress and shear forces 1,000 times greater than atmospheric pressure \((11, 35)\). At the same time, projectile fragments from the IED can travel at initial velocities up to 3,000 mph \((34)\). After the initial blast wave, there is an exponential decay in pressure as the large volume of displaced air floods back into this relative vacuum, again under high pressure \((11, 33, 35)\). This “secondary wind” dissipates as the pressure returns to steady state \((32)\). Blast winds from both the positive and negative pressure phases can propel objects and people considerable distances \((34)\).

Most pathophysiologic damage from blast explosions results from the extreme pressure differentials developed at body surfaces \((34)\). The force of the blast’s leading edge rapidly creates a high-frequency “stress wave” that propagates from the body surface into the underlying tissues \((34)\), generating velocities of nearly 185 mph that cause great damage to tissues and organs \((32, 34)\). In addition to the blast front, the amount of damage from the pressure wave depends on the peak overpressure, duration of overpressure, medium in...
which the explosion occurs (i.e., open air, confined space, or water), and the distance from the explosion (21).

Body armor now saves the lives of many who would otherwise be killed by blast injuries (22). In Vietnam and earlier wars, the mortality from brain injuries was greater than 75% (2), and the overall ratio of wounded soldiers to fatalities was 2.6 to 1 (2, 35). Improved body armor and battlefield trauma care account for the high survival of victims of blast injuries in Iraq and Afghanistan, where the wounded-to-fatality ratio is 16 to 1 (29, 35).

Unlike previous wars, soldiers are now very unlikely to die if they are still alive when the battlefield medic arrives (35), but they are surviving with new and complex patterns of injuries (29). More than two-thirds of all casualties in Iraq and Afghanistan are caused by explosions (22, 36, 37), and approximately 60% of those have brain injuries (2, 22, 36). The number of serious brain injuries is approximately five times the number of amputees (22).

Ironically, Kevlar body armor and helmets are one reason for the high proportion of brain injuries and PTSD among soldiers in Iraq and Afghanistan (2). Kevlar helmets have reduced the frequency of penetrating head injuries, but provide little protection from blast overpressure (24, 38) and do not prevent the closed-brain injuries produced by blasts (2, 24).

**Primary Blast Injury**

Because the blast survivors from Iraq and Afghanistan frequently have complex physical injuries and emotional trauma, they represent a new medical challenge to military physicians (39). To meet this need, the Veterans Health Administration has coined the term “polytrauma” to describe injuries to the brain (and other body parts or systems) resulting in physical, cognitive, psychological, or psychosocial impairments, and functional disability (23).

The Centers for Disease Control and Prevention (CDC) has established a four-part classification system for these polytrauma blast injuries. Primary blast injury results from the impact of the blast wave overpressure on body surfaces and is unique to high-order explosives such as IEDs. Secondary blast injury results from flying debris and bomb fragments, which are propelled by the blast wind. Tertiary blast injury results when individuals are thrown by the blast wind into stationary objects. Quaternary blast injury includes all other explosion-related injuries and complications, such as burns, crush injuries, and respiratory problems (11, 32, 33, 40).

Air-filled organs, including the middle ear and lung, and organs surrounded by fluid-filled cavities such as the brain are highly vulnerable to primary blast injury (32, 33, 41). The rapid compression/decompression of blast overpressure forces the air and/or blood in hollow organs against various compartments and cell walls, causing them to rupture (32).

Because combat armor shields most other body surfaces, the ear is the organ most vulnerable to damage by blast overpressure (32, 33, 37, 38, 42). All major structures of the ear (tympanic membrane, middle and inner ear) may be affected by blast overpressure, but rupture of the tympanic membrane is the sentinel finding from blast explosions and occurs at relatively low pressure changes (11, 33, 34, 38).

A hearing loss of 0-30 decibels (dB) in the low frequency range and 40-80 dB in the high frequency range can result from tympanic membrane rupture or obliteration (32, 33). Middle ear injury (fractures of the ossicles and/or displacement of the stapes) results in a conductive hearing loss of 0-25 dB (33). Injury to the inner ear causes symptoms of tinnitus and 0-100 dB hearing loss and is of utmost concern because the hearing loss may be irreversible (33).

The damage specifically caused by blast injuries to the ear appears to be long lasting. In a six-year retrospective study, blast-injured Iraq-Afghanistan veterans had a two-fold increase in hearing loss and tinnitus compared with those who suffered brain injuries from non-blast causes (43). The mean hearing threshold was reduced by approximately 10 dB over the entire auditory range from 250 to 8000 Hz (43).

Hearing loss has always been one of the largest classes of disability awarded to US veterans, representing 30% of those who serve in combat (33). With regard to blast injuries and IEDs in particular, however, ear damage is an important indicator of brain injury, even when no other signs of head trauma are apparent. In a study of 682 blast injury casualties from Iraq, investigators found a significant correlation between tympanic membrane perforation and loss of consciousness including amnesia (38).
Unlike secondary and tertiary blast injuries, which are easy to diagnose because of the obvious physical injuries, primary blast injuries are occult and often missed. They occur without a direct blow to the head [40], and diagnosis may be overlooked by physicians who are distracted and caring for other body injuries such as burns, fractures, and hemorrhages [22, 23]. Diagnosis of primary blast injuries is also difficult, because the symptoms may be delayed [34, 35] and because clinical assessment must rely on objective evaluations of altered consciousness, cognition, and behavior [24]. The Glasgow Coma Scale, which is the standard for assessing TBI severity, is not sufficiently sensitive to rank blast injuries [44, Alisa Gean, personal communication].

Assessing the number and frequency of concussion injuries among combat soldiers is also difficult, because many affected soldiers do not report for medical treatment [18]. A blast that causes unconsciousness, however, could result in brain injury, even if the soldier regains consciousness quickly and shows no immediate signs of impairment [38, 45]. Also, mild but recurrent concussions can cumulatively affect brain functions [3, 18]. Neurologists estimate that up to 30% of soldiers who have been on active duty for four months or longer in Iraq or Afghanistan are at risk of disabling neurological damage [5, 29, 35].

These observations have led to recommendations that military physicians should closely examine eardrums in blast survivors. Tympanic membrane perforation, especially in the presence of blood, could indicate not only hearing loss but also latent neurologic injury [34, 38, 43].

**Mechanisms of Blast Injury**

Brain injury from blast explosions is classified as an indirect dynamic brain injury [46] and operates through different mechanisms than brain injuries from non-blast sources [47]. The special vulnerability of the brain to blast injury primarily arises from two factors: the presence of bony protuberances on the inferior cranial vault, and the delicate composition of the cerebral cortex, brainstem, and axonal fibers [24].

The kinetic energy of blast overpressure is transferred to brain tissue, which may undergo direct injury such as cerebral contusion with or without skull fracture, and coup-contrecoup injuries (Box 1). Regardless of the direction of the blast, the frontal and the temporal lobes are the most vulnerable structural areas of the brain [11, 18].

The blast’s mechanical force damages blood vessels, resulting in subdural hematoma, cerebral hemorrhage, or edema [33]. Magnetic resonance images from moderate to severe TBI patients show punctate (i.e., pinpoint) hemorrhages and sometimes evidence of swelling [2, 33, 48]. The harmful consequences of cerebral edema include elevated intracranial pressure, low cerebral blood flow, reduced cerebrospinal fluid, and deformation and shifting of brain tissue [49].

Blast overpressure also causes indirect cerebral infarction from air emboli [33, 48]. Air emboli form in blood vessels from overpressurization of the lungs and travel to the brain. The resulting cerebral arterial air emboli cause cerebral infarcts and hypoxemia [2, 34].

The pathophysiological sequelae of blast-induced injuries are mediated by an interaction of acute and delayed molecular, neurochemical, and metabolic events that are both complex and multifaceted [35, 46, 48–50]. These events are noticeable from minutes to days after brain trauma [51]. The mechanical forces cause shearing, tearing, and stretching, which damage axons, glia, and neurons and induce diffuse axonal injury [48, 49]. Shearing also causes massive ion fluxes across neuronal membranes, widespread loss of membrane potential, affenter hyperexcitability, and the rapid release of a “storm” of neurotransmitters from damaged cells [49], including acetylcholine, serotonin, norepinephrine, and glutamate [18]. Excitatory neurotransmitters such as glutamate are released within minutes of brain trauma and remain elevated for several days [51]. The released glutamate binds to N-methyl-D-aspartate (NMDA) receptors, facilitating the release of a large calcium influx, as well as stimulation of non-NMDA receptors [51]. The ion channel–mediated influx of calcium triggers biochemical events that generate high concentrations of toxic and pro-inflammatory molecules such as nitric oxide, prostaglandins, oxygen free-radicals, and inflammatory cytokines [49]. The inflammatory response breaks down the blood-brain barrier, resulting in edema and increased intracranial pressure, which may cause localized

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**Box 1. Coup-Contrecoup Injuries**

Focal bruises on (and, if sufficiently severe, within) the brain result when the brain collides with the inner surface of the skull, similar to the beads in a baby’s rattle, and are referred to as coup-contrecoup injuries. Coup lesions occur at the site of impact, and contrecoup lesions occur when the brain strikes the skull on the opposite side. Although originally defined relative to impact with an external object, coup-contrecoup injuries from blast explosions result from rapid acceleration and deceleration caused by a blast wave and in the absence of a tangible object.
hypoxia, ischemia, and neuronal cell death via necrosis and apoptosis (49).

Cerebral edema is a secondary injury factor following brain trauma and can be either local or diffuse (49). Vasogenic edema occurs rapidly, increasing blood-brain barrier permeability and causing an imbalance in the movement of fluid between the vasculature and the brain interstitial fluid (49, 51). There is a net gain in interstitial fluid and subsequent cerebral fluid retention (49). Vasogenic edema is seen primarily in the cerebral white matter (49).

Cytotoxic edema develops slowly as osmotic pressure increases in the intracellular space, accounting for most of the brain swelling after brain trauma (51). Cytotoxic edema is characterized by intracellular swelling in neurons, glia, and endothelial cells without breakdown of the blood-brain barrier. Glutamate-mediated excitotoxicity facilitates cytotoxic edema by causing accumulation of intracellular calcium and sodium, causing an osmotic gradient to draw water in, increasing the intracellular fluid volume. Cytotoxic edema occurs mainly in the gray matter and is often associated with ischemia and energy depletion (49).

The brain’s energy consumption is high, and brain tissue is extremely vulnerable to oxidative damage, because of its high oxidative metabolic rate, production of reactive oxygen metabolites, low antioxidant capacity, low repair mechanism activity, the limited ability of neurons to replicate, and the high membrane-to-cytoplasm ratio (49). Under normal conditions, glutathione and superoxide dismutase tightly control oxidative metabolism and the formation of oxygen free radicals (51), but these defense mechanisms are overwhelmed by the reactive oxygen metabolites generated by blast injuries (32).

As a result of blast overpressure injury, the biochemical changes in free radical-mediated oxidative stress include antioxidant depletion, increased lipid peroxidation, and deficient energy metabolism (50). Even without direct damage to the head, these free radical–mediated changes cause considerable damage to proteins, lipids, and DNA, and, subsequently, cell death (51). Biochemical changes such as lipid peroxidation correlate with the magnitude of blast peak overpressure (32). In a rat model of whole-body blast exposure, significant deficits in performance on an active avoidance task correlated with oxidative stress and altered antioxidant enzymes [e.g., superoxide anion generation, increased malondialdehyde, and increased superoxide dismutase] (48).

Magnesium regulates many cellular processes essential for normal cellular bioenergetics, including oxidative phosphorylation, and is a mandatory cofactor for all energy-producing and energy-consuming reactions involving carbohydrate, lipid, nucleic acid, and protein metabolism (51). Magnesium also mediates ion channel activity, inhibiting glutamate release and calcium influx (51). After brain trauma, intracellular magnesium decreases (52).

In patients, many of the neurochemical, endocrine, and structural changes of TBI appear to be similar to those responsible for the pathophysiology noted in PTSD (18). For example, many neurotransmitter and neurochemical pathways [i.e., serotonin, norepinephrine, glutamate, and γ-aminobutyric acid (GABA)] are dysregulated in PTSD. The neurotransmitter storm associated with TBI involves many of these same neurochemical pathways (18). Likewise, PTSD and TBI are both associated with decreased function of the pituitary gland. In PTSD patients, negative feedback to the pituitary arises from the increased sensitivity and number of glucocorticoid receptors. TBI patients have impaired pituitary function, including decreased release of hormones—most commonly somatotrophs and gonadotrophs (18).

Cortical inputs and direct damage to the hippocampus and amygdala are the brain areas most vulnerable to TBI and the most involved with dysfunction in PTSD patients (18). Immunohistochemical changes after brain trauma include damage to the neuronal cytoskeleton in layers II-IV of the temporal cortex, cingulate gyrus, and CA1 region of the hippocampus (46). The loss of these cortical axonal inputs to the hippocampus and amygdala alters hippocampal plasticity and the pattern of dendritic structural reorganization.
and axonal sprouting. Areas of dysfunction in PTSD appear to be the anterior cingulate gyrus and medial frontal gyrus within the frontal lobes, accompanied by atrophy of the hippocampus (18). In Vietnam veterans with PTSD, imaging studies show hippocampal atrophy and reduced density of neurons (18).

These observations support the notion that there are common biological and biochemical mechanisms that underlie the symptoms of PTSD and mild brain trauma (3) and may account for the biological risk of a patient with TBI developing PTSD or a PTSD-like syndrome (18).

**Treatment**

WWI physicians concluded from their observations that most shell shock casualties were suffering from acute psychiatric illness. They drew on the principles of treatment already established by Russian physicians during the Russo-Japanese War (7) and the contemporary experience of French physicians: immediate, individualized psychotherapy near the front lines, accompanied by sleep, hot meals, and other temporary relief from battle (6, 9). These measures greatly reduced the number of shell shock casualties that required evacuation and long term care; most casualties recovered quickly and returned to duty (7, 9).

Of those with severe shell shock requiring evacuation from the front and hospitalization, 80% never returned to military duty because of their disabilities (10). During WWI, British physicians treated the evacuated shell shock soldiers using two very different approaches. Disciplinary treatment addressed symptoms directly, using forceful methods such as electric shock, shouted commands, isolation, and restricted diet. Success relied on the patient’s faith in the doctor, who persisted with these “treatments” until the patient was cured (8, 9). Psychotherapists, on the other hand, believed that these casualties suffered from a neurosis caused by repressed memories and painful emotions associated with the traumatic events they had witnessed (8, 9). They used psychotherapeutic techniques including hypnosis to help the patient uncover the trauma, come to terms with his feelings, and reintegrate his memories into his personality (8, 9). One psychotherapist, Arthur Hurst at Seale Hayne Military Hospital in Devon, UK, enjoyed an apparently high success rate (53, 54), reportedly curing many patients after a single treatment session (9, 54).

At the outbreak of WWII, military physicians introduced drug therapy for combat neurosis. William Sargant and others who followed his lead advocated barbiturates, which provided immediate relief from severe anxiety and hysteria (55). Although amobarbital, pentobarbital, and thiopental induced a catharsis of repressed battlefield experiences, most patients relapsed to their former hostility once the drugs wore off (9). Psychiatrists soon realized that sedatives were not a reliable means of reaching their patients’ deeply repressed thoughts and used barbiturates as a last resort (9).

Although other pharmacological treatments were tried, medical thinking during WWII gradually settled on the same approaches that had been effective in WWI. Analytically trained psychiatrists successfully treated most cases of combat fatigue near the front (12). After rest, hot meals, and a bath, the majority of fatigued soldiers returned to combat within three days (9, 12, 56).

By the time of the Korean War, military psychiatrists had reduced treatment to a simple formula called PIE: Combat stress casualties should be treated near the front lines (Proximity), as soon as possible (Immediacy), and in an atmosphere that encouraged them to return to their units (Expectancy) (9).

Similarly, the treatment philosophy during the Vietnam War and the war in Lebanon centered on temporary rest and recuperation away from battlefield stresses, accompanied by supportive counseling. During the Lebanon War, 90% of those treated in this manner for combat stress reactions returned to their units within a few days (5).

Strides were made through the 1980s and 1990s in understanding how and why PTSD develops, as well as growing confidence in the ability to measure, manage, and treat the disorder. The insightful and pioneering work of WWI physicians such as Charles Myers and Arthur Hurst (53, 54) established psychotherapeutic guidelines for treating shell shock that are very similar to the current thinking about how to treat.
PTSD: initiate treatment promptly; induce re-experience and acknowledgement of the traumatic events; individualize the analysis to that which is meaningful to each patient; use cognitive restructuring; use a collaborative approach between patient and therapist; and be mindful that breakdowns depend on the patient’s previous experiences (8).

In addition to psychotherapy, many pharmacological approaches are now used to treat PTSD including antidepressants, psychomotor anticonvulsants, and anxiolytics (17). Animal studies provide growing evidence that both pharmacotherapy and effective psychotherapies may stimulate hippocampal neurogenesis and the regrowth of dendritic connections in PTSD patients (18).

Treatment of TBI has proven to be more challenging. Based on the Glasgow Coma Scale score, initial treatment is symptomatic: control hemorrhage and relieve increased intracranial pressure (20, 57). No standards for drug treatment of the biochemical abnormalities have been established. More than twenty drugs and therapeutic interventions have been described and used in more than fifty clinical trials in the last thirty years, almost all of which have failed to show improvement in TBI outcome (49).

In 2005, the Defense and Veterans Brain Injury Center (DVBIC) commissioned the Brain Trauma Foundation to establish guidelines for the field management of combat-related head trauma (57). Using the best available evidence-based experience (mostly from civilian studies), these guidelines provide a decision-tree approach to assess, stabilize, and monitor casualties until they can be evacuated to an aid station and surgical facility (57). Blast injuries may respond differently to treatment than brain injuries from sports and motor vehicle accidents, however, and DVBIC recommended no guidelines for the recovery and long-term care of blast injury patients.

Pharmacological intervention is particularly challenging, because TBI is a heterogeneous injury and leads to a complex secondary injury cascade (51). A polypharmacy approach to treat each of the individual biochemical abnormalities introduces multiple side effects and the potential for multiple drug interactions (51). Instead, attention is now focused on broad-spectrum therapeutic candidates, that have multifactorial mechanisms of action and that hopefully normalize the multitude of biochemical and physiological changes (51, 58) (Table 1). Unfortunately, the clinical performance of broad-spectrum agents, such as magnesium salts and progesterone, so far has not been encouraging, despite impressive efficacy in animal models (51).

Turning away from conventional pharmacotherapies, researchers are now exploring innovative approaches such as nanotechnology. Various nanomaterials are being designed to provide scaffolding for axonal regrowth, support dendrite elongation and cell adhesion, and improve drug delivery across the blood brain barrier (58).

Treating the polytrauma resulting from blast-related injuries is particularly challenging. Although clinical guidelines for the long-term treatment of concomitant TBI and PTSD are not yet available (18), the psychotherapeutic interventions with the strongest scientific support are trauma-focused cognitive behavioral therapy, Eye Movement Desensitization Reprocessing (EMDR)², and non-trauma-focused stress management (18). Antidepressant drugs such as the selective serotonin receptor inhibitors (SSRIs) are of value in the early stages of treatment, especially in cases of emotional instability. Other treatments

Table 1. Novel or Experimental Interventions Targeting Traumatic Brian Injury (TBI)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mechanism/Rationale</th>
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<tbody>
<tr>
<td>Cell cycle inhibitors (e.g., flavopiridol) [58, 64]</td>
<td>Reduces neuronal cell death, reduces astroglial scar formation, decreases lesion volume, improves experimental motor and cognitive performance</td>
</tr>
<tr>
<td>Magnesium salts [49, 52, 58]</td>
<td>Blocks calcium entry, potentiates adenosine action, attenuates brain edema, cerebral vasospasms, glutamate excitotoxicity, calcium-mediated events, lipid peroxidation, mitochondrial permeability transition, and apoptosis</td>
</tr>
<tr>
<td>Cyclosporin A [49, 52]</td>
<td>Inhibits opening of the mitochondrial permeability transition pore, attenuates post-traumatic cytoskeletal changes and axonal injury, decreases lesion volume, improves brain oxygen consumption, blocks free radical production, and inhibits traumatic axonal injury</td>
</tr>
<tr>
<td>Substance P (neurokinin 1) receptor inhibitor [52, 58]</td>
<td>Reduces neurogenic inflammation, blood-brain barrier permeability, edema, lesion volume</td>
</tr>
<tr>
<td>Progesterone [32, 49, 52, 58]</td>
<td>Modulates neuronal excitability, reduces membrane lipid peroxidation, and inhibits caspase-3 activation</td>
</tr>
<tr>
<td>Cannabinoids [49, 58]</td>
<td>Reduces glutamate excitotoxicity, free radical production, and inflammatory response</td>
</tr>
<tr>
<td>Cyclic dipeptides [58]</td>
<td>Attenuates apoptotic and necrotic cell death, reduces intracellular calcium, stabilizes mitochondrial membrane potential, and decreases cytochrome c release</td>
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² For more information about the EMDR technique, see the EMDR Institute, Inc. (www.emdr.com)
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(Table 2) are prescribed symptomatically.

The VA coordinates treatment and rehabilitation of polytrauma patients through a network of five Polytrauma Rehabilitation Centers (in Minneapolis, MN, Tampa, FL, Palo Alto, CA, Richmond, VA, and San Antonio, TX), twenty-one Polytrauma Network Sites, 130 Polytrauma Support Clinic Teams and numerous Polytrauma Points of Contact (47). Their treatment approach uses an interdisciplinary team to provide a combined program of counseling, psychotherapy, and medical treatments that are individualized and comprehensive (23). Military personnel returning from combat receive a thorough neuropsychological evaluation to guide rehabilitation, including medical and psychosocial interventions for their long term care (39).

Long Term Outcome

If history is a reliable indicator, the prognosis for polytrauma patients is not encouraging. The body heals and recovers, but combat-related brain injuries produce symptoms that are often severe, delayed in onset, and persistent.

As early as WWI, physicians noted a delayed onset of PTSD symptoms (8). In Britain, numerous veterans who had managed to avoid a nervous breakdown during the war exhibited severe symptoms in 1921 or 1922 (9). By 1939, primary psychiatric disability was recorded for 120,000 British ex-servicemen, comprising 15% of all pensioned disabilities. The US government spent almost a billion dollars on the psychiatric problems of veterans between WWI and WWII. The cost in 1940 alone amounted to forty-two million dollars (9).

In 1970, Chaim Shatan organized the first discussion groups in response to the growing numbers of returning Vietnam veterans who exhibited the chronic condition labeled “Post-Vietnam Syndrome” at the time (16, 59). In one study of Vietnam veterans, the incidence of PTSD symptoms in an individual rapidly increased over the first few years after exposure to combat trauma and then plateaued to become chronic and unremitting (18). Despite increased awareness, diagnosis, treatment, and long-term follow-up, the lifetime prevalence of PTSD in male Vietnam War veterans is 30%, compared to a 5% incidence rate in the general population (9, 18).

Gulf War veterans reported continued PTSD symptoms two years post-combat (18). Most recently, onset of PTSD and depression was noted in 79% of Iraq-Afghanistan soldiers seven months after suffering severe, combat-related injuries, despite no clinical evidence of either disorder one month after injury (26). A ten-year chart review of TBI patients treated at the Veterans Brain Injury Center in Palo Alto showed that more than 75% of patients continued to exhibit multiple psychological and emotional problems two years after discharge (27).

In another long-term study, combat veterans with acute combat stress reactions were six-times more likely than veterans not exhibiting acute stress to experience PTSD at one, two, four, and twenty years post-combat (18). Observations such as this raise the question whether the PIE method of treatment attenuates long-term disability.

Because of the delayed onset (and sometimes subtle injuries), many blast-injured veterans may go undiagnosed. For this reason, discharged veterans are now advised to return for on-site, comprehensive, follow up evaluations at one and two years post-injury (27). The very nature of blast injuries complicates the diagnosis, treatment, and recovery of these patients in several ways. First, soldiers with closed head injuries show no external signs of injury, appear normal, and therefore may fail to realize that something is wrong (5, 22). Indeed, family members and colleagues are often the first to note changes in emotions and functional behaviors that are not recognized by the patients themselves (60). Second, some combat casualties fail to report their symptoms and fail to seek treatment, even though they suspect a medical problem. Proud and career-oriented service personnel avoid entries of mental problems in their service records. Consequently, many closed-brain injuries are not reflected in casualty figures (24). To address

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Examples</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI antidepressants</td>
<td>Sertraline, paroxetine, fluoxetine, citalopram, fluvoxamine</td>
<td>Considered first-line therapy for both PTSD and depression (2, 18, 26)</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>Bupropion, nefazodone, trazodone, venlafaxine, phenelzine</td>
<td>Considered second-line therapy for PTSD and depression (18)</td>
</tr>
<tr>
<td>Sympatholics</td>
<td>Prazocin</td>
<td>Block autonomic hyperarousal, treat nightmares (18)</td>
</tr>
<tr>
<td>Other psychotropic drugs</td>
<td>Carbamazepine, duloxetine</td>
<td>For irritability, flash anger, and violent outbursts (18)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Valproate</td>
<td>Migraines and behavioral symptoms (2)</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Quetiapine</td>
<td>For insomnia (18)</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Methylphenidate, dextroamphetamine</td>
<td>For attention problems or information processing (2)</td>
</tr>
</tbody>
</table>

(Table 2) Co-treatment of TBI and Post-Traumatic Stress Disorder
the impaired awareness as well as the reluctance to report symptoms, the VA Central Office issued a directive in April, 2007, implementing mandatory procedures for screening and evaluating possible brain injuries in all Iraq-Afghanistan veterans (39, 47, 61). Third, PTSD and TBI can impair memory and concentration. Patients are prone to forgetfulness and may confuse drug dosages, especially if they are on multiple medications (18). Cognitive and emotional deficits decrease the capacity and initiative of patients to seek appropriate care on their own (27). Unfortunately, those with severe mental impairment and who need follow up the most are the ones who do not return for treatment. Finally, cognitive impairment and behavioral disturbance from PTSD and TBI are often more demoralizing and stigmatizing than an obvious physical disability (18). The social and occupational consequences include medical separation from military service, loss of job or unemployment, relationship strife and divorce or breakup, and charges for traffic violations, assault, drug abuse, etc. (18).

**New Treatment Initiatives**

A number of proactive steps have been taken to meet the needs of blast victims and to protect against future blast injuries. Counter-measures are being developed to enhance troop protection and survival from blast injuries (5, 31). Numerous approaches are being used to detect and disarm IEDs before they are detonated, although with limited success so far (31). New blast mitigating materials are being used in vehicles and helmets to dampen the overpressure energy of explosions, just as Kevlar stops bullets and shrapnel (5).

A new triage instrument is currently being field tested to assist in early diagnosis of blast-induced brain damage. BrainScope, a minicomputer resembling an oversized iPod, collects EEG samples, computes quantitative EEG scores, and displays color-coded graphs of abnormal brain activity (62). Although BrainScope’s efficacy remains to be proven, rapid detection in cases where the blast-induced symptoms are not obvious may lead to more effective treatment of underlying brain injuries.

In an effort to encourage progress in diagnosis and treatment, the VA Office of Research & Development is funding fifty-two PTSD research studies (19). Similarly, the government’s clinical trials website (clinicaltrials.gov) currently lists nearly sixty ongoing clinical trials to study TBI diagnosis, treatment, and rehabilitation (58). In addition, an NIH committee has been established to develop a new classification system that accounts for the heterogeneity of brain injuries and will enhance the sensitivity of the Glasgow Coma Scale (44).

Perhaps most importantly, a number of military, government, and private organizations have established programs and support groups specifically to meet the needs of polytrauma survivors.

**Table 3. Guidelines for Combat-induced TBI and PTSD**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Iraq War Clinician Guide, 2nd Ed</td>
<td>Developed by the National Center for PTSD and the Department of Defense for clinicians and addresses the unique needs of veterans of the Iraq war.</td>
</tr>
<tr>
<td>Available at: <a href="http://www.ncptsd.va.gov/ncmain/ncdocs/manuals/nc_manual_iwcguide.html">www.ncptsd.va.gov/ncmain/ncdocs/manuals/nc_manual_iwcguide.html</a></td>
<td></td>
</tr>
<tr>
<td>Guidelines for the field management of combat related head trauma</td>
<td>Developed by the Brain Trauma Foundation for battlefield medics and addresses standards of care for field treatment of head trauma</td>
</tr>
<tr>
<td>Available at: <a href="http://www.braintrauma.org/site/PageServer?pagename=Guidelines">www.braintrauma.org/site/PageServer?pagename=Guidelines</a></td>
<td></td>
</tr>
<tr>
<td>Veterans Health Initiative</td>
<td>Independent study courses developed by the Department of Veterans Affairs for healthcare providers and addresses the health care needs of veterans with TBI and PTSD</td>
</tr>
<tr>
<td>- Traumatic Brain Injury</td>
<td></td>
</tr>
<tr>
<td>- Post-Traumatic Stress Disorder: Implications for Primary Care</td>
<td></td>
</tr>
<tr>
<td>Available at: www1.va.gov/vhi</td>
<td></td>
</tr>
<tr>
<td>Management of post-traumatic stress</td>
<td>Developed by the Department of Veterans Affairs and Department of Defense Clinical Practice Group for primary care providers and addresses the prevention, diagnosis, treatment, and management of PTSD veterans</td>
</tr>
<tr>
<td>Available at: <a href="http://www.oqp.med.va.gov/cpg/PTSD/PTSD_Base.htm">www.oqp.med.va.gov/cpg/PTSD/PTSD_Base.htm</a></td>
<td></td>
</tr>
<tr>
<td>Blast Injury</td>
<td>Developed by Defense and Veterans Brain Injury Center and addresses frequently asked questions about blast injuries</td>
</tr>
<tr>
<td>Available at: <a href="http://www.dvbic.org/cms.php?p=Blast_injury">www.dvbic.org/cms.php?p=Blast_injury</a></td>
<td></td>
</tr>
<tr>
<td>Explosions and blast injuries: A primer for clinicians</td>
<td>Developed by the Centers for Disease Control and Prevention for clinicians and addresses the pathophysiology, assessment and treatment of injuries associated with explosions</td>
</tr>
<tr>
<td>Available at: <a href="http://www.bt.cdc.gov/masscasualties/explosions.asp">www.bt.cdc.gov/masscasualties/explosions.asp</a></td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury: Hope through research</td>
<td>Developed by the National Institute of Neurological Disorders and Stroke and addresses the pathophysiology, assessment, rehabilitation and research on TBIs</td>
</tr>
<tr>
<td>Available at: <a href="http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm">www.ninds.nih.gov/disorders/tbi/detail_tbi.htm</a></td>
<td></td>
</tr>
<tr>
<td>Marine Corps Combat/Operational Stress Control (COSC) Program</td>
<td>Developed by Marine Corps Community Services for Marine Corps personnel and addresses training, resources and support to control combat stress</td>
</tr>
<tr>
<td>Available at: <a href="http://www.usmc-mccs.org/cosc/index.cfm?sid=ml&amp;smid=1">www.usmc-mccs.org/cosc/index.cfm?sid=ml&amp;smid=1</a></td>
<td></td>
</tr>
</tbody>
</table>
patients and their families. Prior to deployment, military medics receive special training in how to recognize and treat traumatic brain injuries (35, 63). Soldiers, especially those in a leadership role, also receive training in how to monitor, aid, and cope with combat stress and brain injuries. In addition, several manuals for treating combat TBI and PTSD have been produced specifically for military clinicians (Table 3).

Since 1992, DVBIC has served active duty military, their dependents, and veterans with traumatic brain injury through state-of-the-art medical care, innovative clinical research initiatives, and educational programs (41). DVBIC coordinates nine healthcare centers (two civilian, three military, and five VA sites) that provide evidence-based treatment, education, and research on TBI. The five VA Polytrauma Rehabilitation Centers in the DVBIC network have a mandated core staffing of 2.8 full-time medical and consulting specialists for each patient (36).

In 1998, the Department of Veteran Affairs launched the VA Quality Enhancement Research Initiative (QUERI) to ensure that quality clinical research and evidence-based medicine is systematically incorporated into routine practice at VA hospitals (29). Because there is a lack of well-established evidence from which to create clinical practice standards and measure treatment outcomes for blast injuries, funding was authorized in October, 2005, for a specific QUERI program focused on Polytrauma and Blast-Related Injuries (29, 47).

In April, 2007, polytrauma resources were supplemented via a new Veteran Affairs Directive (2007-013), which established the policy for screening all Iraq-Afghanistan veterans for possible brain injuries and PTSD (61). Veterans identified through this screening process are offered further evaluation and treatment, based on the clinical findings, including long-term follow up and rehabilitation (39).

Conclusions

In the past one hundred years, the human brain has not changed. Nor has the brain’s response changed when subjected to trauma (whether from penetrating wounds or blast overpressure) or to the stressful conditions of combat. Charles Myers’ initial hypothesis that shell shock arose from brain injury from explosive blasts was more accurate than even he knew. However, it has taken almost a century to establish that blast overpressure results in neurological and psychological symptoms that are persistent, sometimes delayed, and often extreme—even in cases of mild or occult brain damage.

Only in the past few years have clinicians realized that TBI and post-traumatic stress from blast explosions are interrelated, because some things have changed, significantly. Thanks to improved body armor and efficient emergency medical care, the warfare in Iraq and Afghanistan has created casualties plagued more by disabilities than by deaths (5). The greatly improved survival rate, coupled with discoveries from experimental studies, provide increasing clinical evidence that blast injuries alter brain function in complex and long-lasting ways.

Iraq and Afghanistan represent warfare of many firsts (6). It is the first time that patients can be consistently and reliably diagnosed using the PTSD standards. It is the first time that measures have been employed to prevent development of psychiatric symptoms, through pre-deployment training programs and in-country monitoring of vulnerable soldiers before they become casualties. It is the first time that effective psychotropic drugs (primarily antidepressants) have been used. It is the first time that the general public has accepted combat stress as a medical category—not a moral failing.

Mental Cases

Who are these? Why sit they here in twilight? Wherefore rock they, purgatorial shadows, Drooping tongues from jaws that slob their relish, Baring teeth that leer like skulls’ tongues wicked? Stroke on stroke of pain, – but what slow panic, Gouged these chasms round their fretted sockets? Ever from their hair and through their hand palms Misery swells. Surely we have perished Sleeping, and walk hell; but who these hellish?

These are men whose minds the Dead have ravished. Memory fingers in their hair of murders, Multitudinous murders they once witnessed. Wading sloughs of flesh these helpless wander, Treading blood from lungs that had loved laughter. Always they must see these things and hear them, Batter of guns and shatter of flying muscles, Carnage incomparable and human squander Rucked too thick for these men’s extrication.

Therefore still their eyeballs shrink tormented Back into their brains, because on their sense Sunlight seems a bloodsmear; night comes blood-black; Dawn breaks open like a wound that bleeds afresh · – Thus their heads wear this hilarious, hideous, Awful falseness of set-smiling corpses.

· – Thus their hands are plucking at each other; Picking at the rope-knouts of their scourging; Snatching after us who smote them, brother, Pawing us who dealt them war and madness.

—Wilfred Owen
Perhaps because of the extensive and long-term disabilities of Vietnam era veterans, or perhaps because of an all-volunteer military that makes concessions to recruit and retain soldiers, the former bias against psychiatric failings has largely been replaced by public understanding, sympathy, and support. Finally, unlike the attitude toward Agent Orange casualties in Vietnam and the Gulf War Syndrome in the first Gulf War, this is the first time the US military has been willing to face combat stress head-on. Proactive steps have been taken to screen, treat, and provide follow up care for both active duty personnel and veterans with polytrauma injuries.

Nevertheless, based on the fate of veterans from previous wars, the prognosis for the thousands of veterans returning from Iraq and Afghanistan with blast injuries is not encouraging. They are likely to face many years of uphill challenges, compensating for lost neurological function and conquering psychological imbalances that may never be fully restored.

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