

The background of the slide is a stylized American flag. The top half is a dark blue field with white stars, and the bottom half is a white field with a red diagonal stripe in the bottom right corner. The text is centered and overlaid on this background.

# **Epilepsy and Traumatic Brain Injury**

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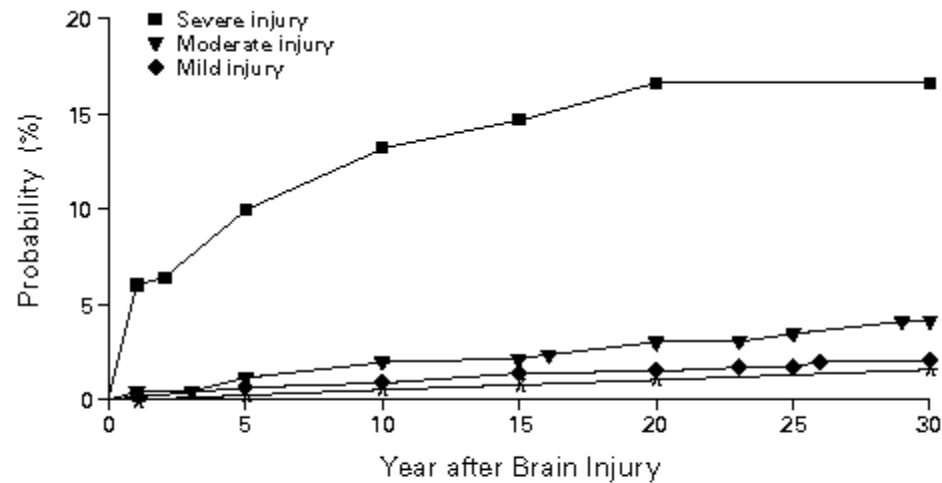
# Definitions

- Post-traumatic epilepsy (PTE) is a disorder characterized by recurrent late seizure episodes, not attributable to another obvious cause, in patients with TBI.

# Definitions

- Post-traumatic seizures (PTS) denote single or recurrent seizures occurring after TBI (2) and are commonly classified into early ( $< 1$  week after TBI) and late ( $>1$  week after TBI).

# Cumulative Probability of Unprovoked Seizures in Patients with Traumatic Brain Injuries



## NO. OF PATIENTS

Mild injury	2758	1751	1191	609
Moderate injury	1455	934	660	351
Severe injury	328	181	136	74
Total	4541	2866	1987	1034

# EPIDEMIOLOGY OF POST-TRAUMATIC SEIZURES

- Traumatic brain injuries are an important cause of epilepsy, accounting for 20% of symptomatic structural epilepsy observed in the general population, and 5% of all epilepsy . TBI is the leading cause of epilepsy in young adults .

# EPIDEMIOLOGY OF POST-TRAUMATIC SEIZURES

- The incidence of seizures among adults after mild TBI is slightly greater than that observed in the general population. PTS will be observed in approximately 35–65% of patients with penetrating TBI (PTBI).

# INCIDENCE OF POST-TRAUMATIC SEIZURES

- The overall incidence of late seizures in hospitalized patients following non-penetrating TBI is approximately 4–7%, varying with the injury and patient characteristics . Late seizures are observed less frequently among children.

# NATURAL HISTORY OF POST-TRAUMATIC SEIZURES AND EPILEPSY

- Approximately one-half to two-thirds of patients who suffer PTS will experience seizure onset within the first 12 months, and 75–80% by the end of the second year following injury



# NATURAL HISTORY OF POST-TRAUMATIC SEIZURES AND EPILEPSY

- After five years, adults with mild TBI do not appear to have a significantly increased risk relative to the general population , However, patients with moderate or severe TBI and PTBI remain at increased risk after this post injury duration
- A subset of the Vietnam Head Injury Study reported very late onset of PTE. (Raymond, 2010).

# NATURAL HISTORY OF POST-TRAUMATIC SEIZURES AND EPILEPSY

- Immediate post-traumatic seizures (IPTS) are generally believed to carry no increased risk of recurrence
- On the other hand, between one-fifth to one-third of patients with LPTS will experience frequent recurrences,

# MANIFESTATIONS OF POST-TRAUMATIC SEIZURES AND EPILEPSY

- Seizures may present with a variety of manifestations, including cognitive, behavioral and affective changes that may not be attributed to underlying seizures.
- Patients with severe TBI may exhibit cognitive, behavioral, and affective sequelae that may mask seizures.

# MANIFESTATIONS OF POST-TRAUMATIC SEIZURES AND EPILEPSY

- Focal-onset seizures are observed in slightly more than half of all patients with PTS, and appear more frequently in adults , focal lesions on CT , penetrating TBI (PTBI), and non-penetrating TBI of greater severity.
- Studies that incorporate video/EEG are more likely to detect subtle clinical signs that may indicate focal-onset PTS .

# MECANISMS OF PTS

- The seizures may be due to direct damage of brain tissue which has resulted from shearing forces, infarction, or due to secondary irritation caused by hemorrhage. Seizures may also be triggered by secondary insults including metabolic disturbances and hypoxic episodes.

## **MECHANISMS OF PTS**

- Seizures occurring among patients with TBI may be the result of precipitants unrelated to mechanisms currently linked with post-traumatic epileptogenesis. Seizure precipitants have been defined as any endogenous or exogenous factor that promotes the occurrence of epileptic seizures

# MILITARY TBI

## TBI Numbers By Severity – All Armed Forces



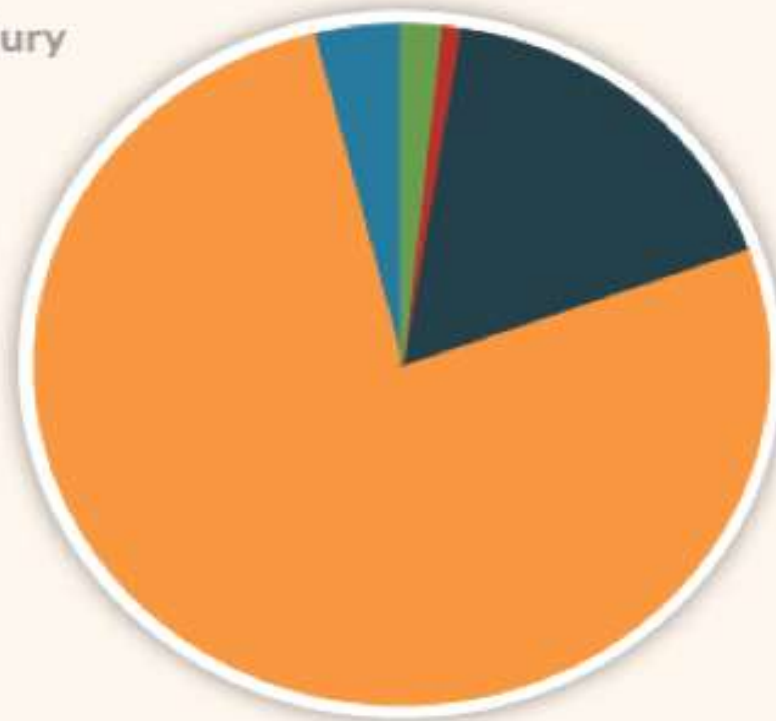
DoD Numbers for Traumatic Brain Injury

### '00-'11 Q1 Totals

Penetrating	3,573
Severe	2,235
Moderate	35,661
Mild	163,181
Not Classifiable	8,092

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**Total - All Severities**      **212,742**



Source: Armed Forces Health Surveillance Center

Numbers for 2000 - 2011 Q1, as of 16 May 2011

<http://www.dvbic.org/TBI-Numbers.aspx> [dod.tbi-2000-2011Q1-as-of-110516.pdf]. Source: Defense Medical Surveillance System (DMSS) and Theater Medical Data Store (TMDS) Prepared by Armed Forces Health Surveillance Center (AFHSC). Accessed 10 Jul 2011.

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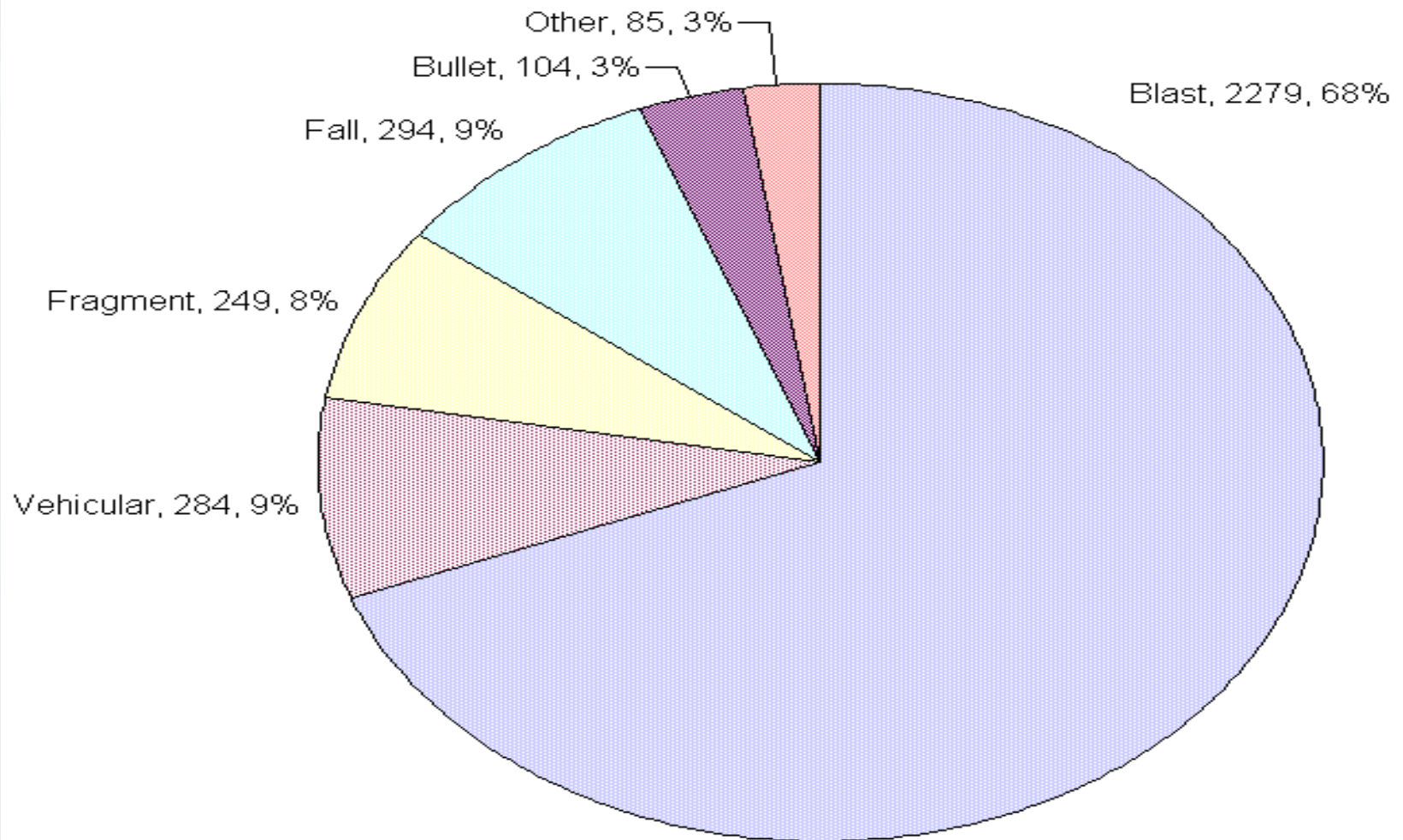
# **Blast is the signature weapon and TBI is the signature injury of the conflicts in Iraq and Afghanistan**

LTG Eric Schoomaker, 42<sup>nd</sup> Surgeon General of the US Army



# TRAUMATIC BRAIN INJURY

## TBI INJURY MECHANISM



# Military TBI

- Some experts have estimated the incidence of TBI among wounded service members to be as high as 22.8%. DVBIC lead VA centers (Minneapolis, Palo Alto, Richmond and Tampa) have treated thousands of OIF/OEF patients with TBI.

# Military TBI

- 256,286 veterans.
- Adjusted OR indicated significant relationships between epilepsy and TBI for all classifications of TBI.
- Mild (1.8; 95% CI 1.6-2.0)
- Moderate (3.1; 95% CI 2.8-3.5)
- Severe (7.0; 95% CI 4.8-10.2)
- Penetrating (21.3, 95% CI 13.6-33.5)

# TBI and Epilepsy

- VA-funded research, conducted in collaboration with the Department of Defense, found that 53 percent of veterans who suffered a penetrating TBI in Vietnam developed epilepsy within 15 years. For these service-connected veterans, the relative risk for developing epilepsy more than 10 to 15 years after their injury was 25 times higher than non-veterans in the same age group. (VHIS)

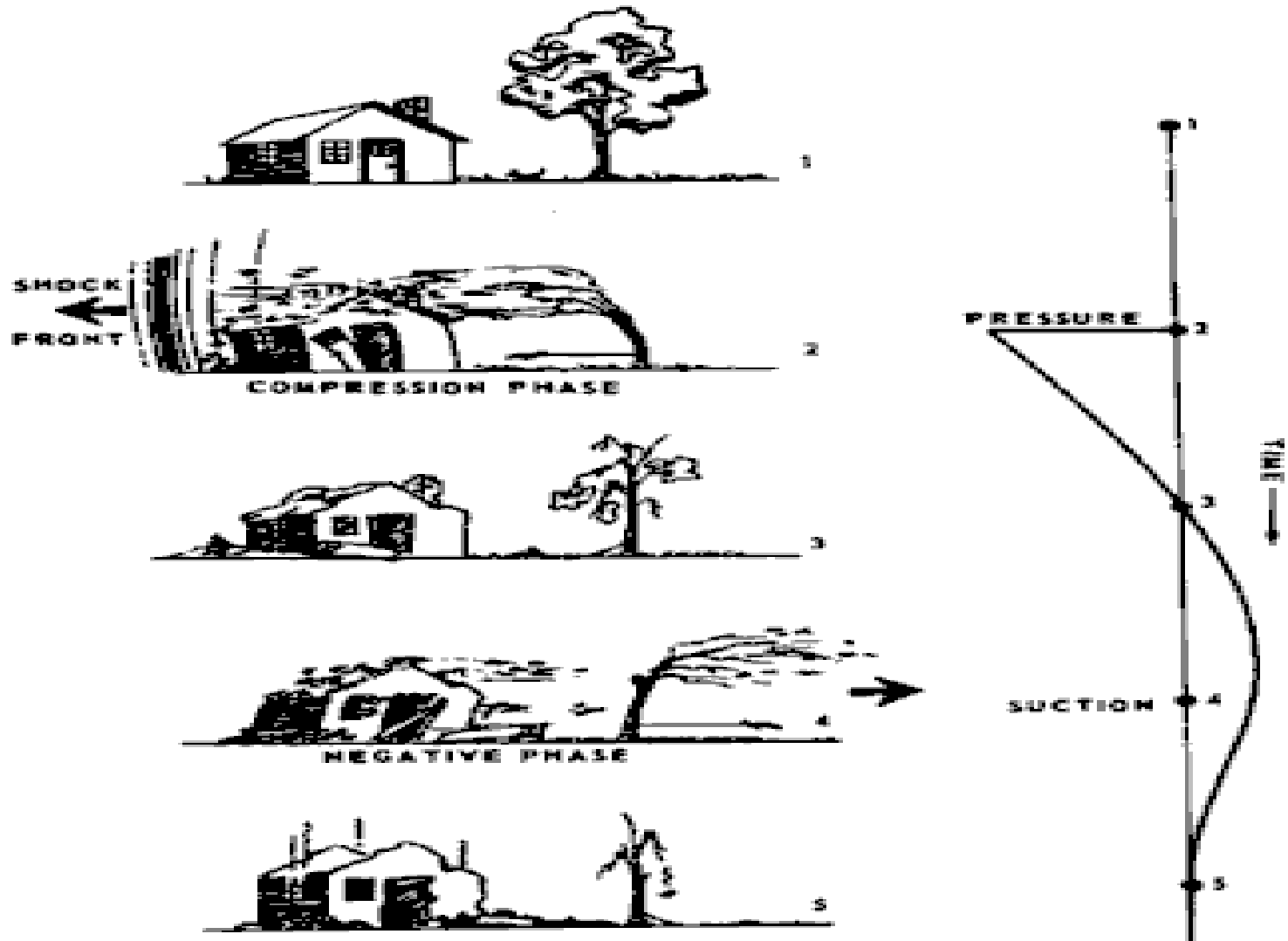
# TBI and Epilepsy

- **Indeed, 15 percent did not manifest epilepsy until five or more years after their combat injury. As neurologists, we believe that the rate of epilepsy from blast TBI will also be high," Booss said.**

# Epilepsy Centers of Excellence

- **House Veterans' Affairs Committee Approves Legislation to Establish Epilepsy Centers of Excellence**
- FOR IMMEDIATE RELEASE  
June 11, 2008
- Washington, D.C. – Today, the House Veterans' Affairs Committee led by Chairman Bob Filner (D-CA), approved a bill that would comprehensively address epilepsy treatment and care at the Department of Veterans' Affairs (VA).
- **H.R. 2818** provides for the establishment of Epilepsy Centers of Excellence. The bill requires each center to research the long-term effects of epilepsy, develop evidence-based treatment for epilepsy, and coordinate care for veterans that suffer from epilepsy, among other things. The bill was introduced by Representative Ed Perlmutter (D-CO).
- "Studies show that 50 percent of U.S. Vietnam War veterans with penetrating brain injuries developed epilepsy within one to fifteen years post-trauma," said Chairman Filner. "Traumatic brain injury is the signature wound of the current wars and we should be prepared to care for Iraq and Afghanistan veterans that have been exposed to blast trauma and are at risk of developing this neurological disorder."

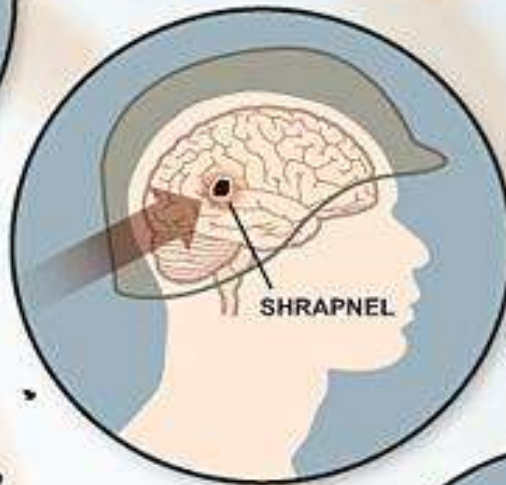
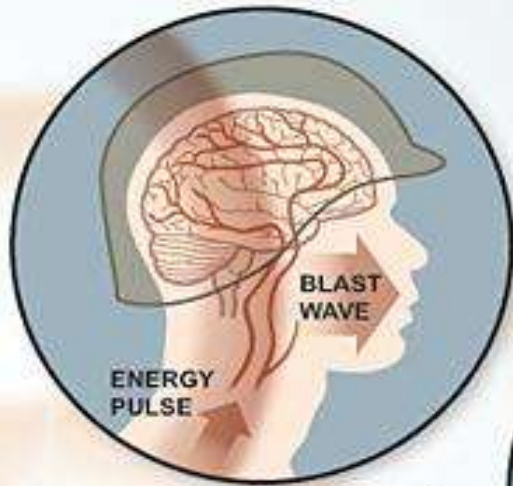
# BLAST INJURY



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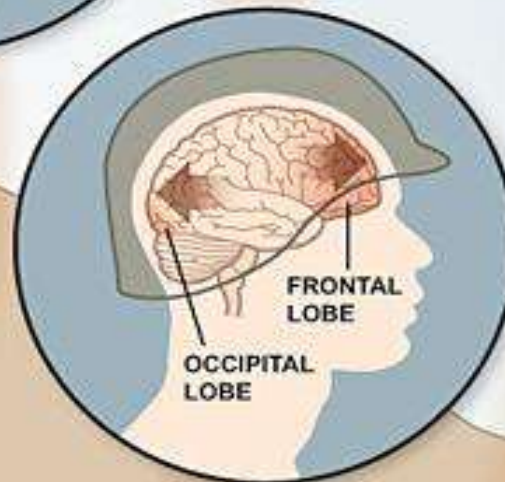
## PRIMARY BLAST INJURY

An explosion generates a blast wave traveling faster than sound and creating a surge of high pressure followed by a vacuum. Studies show that the blast wave shoots through armor and soldiers' skulls and brains, even if it doesn't draw blood. While the exact mechanisms by which it damages the brain's cells and circuits are still being studied, the blast wave's pressure has been shown to compress the torso, impacting blood vessels, which send damaging energy pulses into the brain. The pressure can also be transferred partially through the skull, interacting with the brain.



## SECONDARY BLAST INJURY

Shrapnel and debris propelled by the blast can strike a soldier's head, causing either a closed-head injury through blunt force or a penetrating head injury that damages brain tissue.



## TERTIARY BLAST INJURY

The kinetic energy generated and released by an explosion can accelerate a soldier's body through the air and into the ground or nearby solid object. Once the body stops, the brain continues to move in the direction of the force, hitting the interior of the skull and then bouncing back into the opposite side, causing a coup-contrecoup injury.





# Blast Injuries

- Neurologic injuries may present as "dead on the scene" events.
- Subarachnoid and subdural hemorrhages are most often found in fatalities, and severe head injury is the chief cause of mortality in blast victims.
- Head injuries accounted for 29% of injuries in the Madrid bombings and 80 of the victims of the Oklahoma City bombing.

# Blast Injury

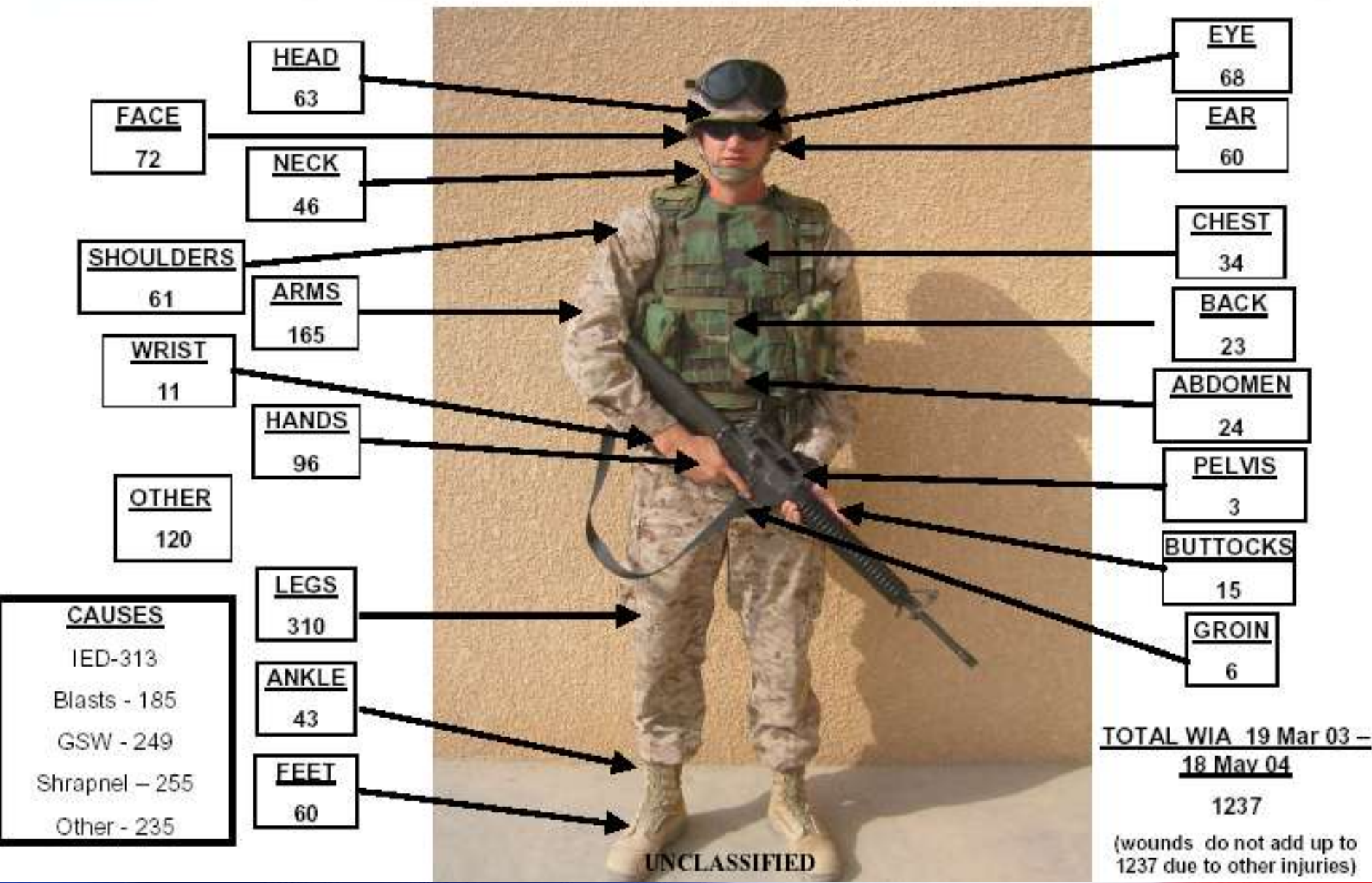
- Primary blast injuries to the brain include concussion as well as barotrauma caused by acute gas embolism.
- Loss of consciousness and coup and contrecoup injuries formerly were considered secondary or tertiary injuries, but with the increased use of body armor in the military, damage to the central nervous system after an explosion has been increasingly attributed to the direct effects of the blast.



UNCLASSIFIED

# WIA WOUNDED AREAS

19 March 2003 – 18 May 2004



# VBIED's and IED's















# Blast Injury

- Multifactorial injury mechanism:
- Primary: Direct exposure to overpressurization wave – velocity  $\geq 300\text{m/sec}$  (speed of sound in air)
- Impact from blast energized debris – penetrating and nonpenetrating
- Displacement of the person by the blast and impact
- Burns/Inhalation of gases
- Combination with MVA in war theater

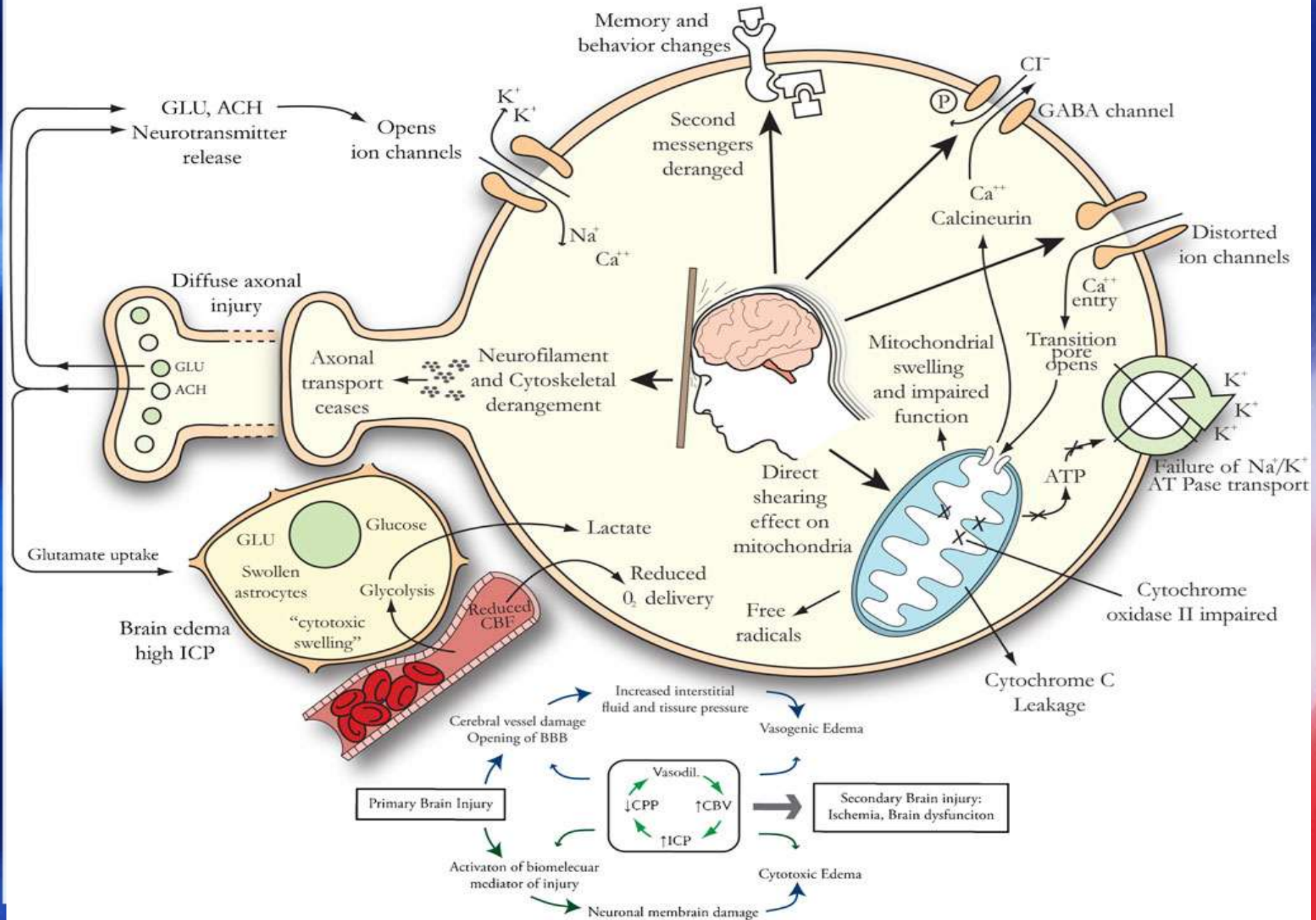
## **Blast Injury**

- Military physicians have observed that exposure to high-amplitude blasts results in brain edema, intracranial hemorrhage, vasospasm and SAH. (Ling et al. 2009)
- Pseudoaneurysms of cerebral vessels have also been observed (Armonda et al. 2006).

## **Blast Exposure Causes Redistribution of Phosphorylated Neurofilament Subunits in Neurons of the Adult Rat Brain**

The abnormalities seen in the present study are similar to that observed in the central nervous system of patients with neurodegenerative disorders, including Parkinson's and Alzheimers's diseases as well as amyotrophic lateral sclerosis.

# Neuromembrane Events in TBI



# TBI and PTSD

- There is an overlap of symptoms between TBI and Acute Stress Reaction (ASR) or Posttraumatic Stress Disorder (PTSD). This issue is most pertinent in the mTBI population as there are higher rates of ASR and PTSD seen in patients with mTBI than with more severe injuries. Sustaining any kind of physical injury in theater is known to increase a service member's risk for PTSD. There are several symptoms which are found in both PTSD and mTBI, such as deficits in attention and memory, irritability and sleep disturbance.

# Neurobehavioral symptoms associated with TBI

- **Impulse control:**
  - Disinhibition
  - Impulsivity
- **Emotion and affect:**
  - Anxiety, depression, emotional lability
  - Bizarre/psychotic behavior or ideation
  - Irritability
  - Poor self-image
- **Cognition and memory:**
  - Poor concentration, memory problems
  - Lack of awareness of deficits
- **Behavior:**
  - Apathy, amotivation dependency, passivity, childlike/childish behavior
  - Loss of sensitivity and concern
  - Aggression
- **Somatic symptoms:**
  - Sleep disturbances
  - Fatigue, slowness
  - Dizziness, headache
  - Light/Noise sensitivity

# Risk Factors for Late Post-traumatic Seizures

## Patient Characteristics

Age: children lower risk LPTS

Alcohol use: increased risk

Family history: ? Increased seizures

APOE ε1ε1: increased risk of LPTE



# Risk Factors for Late Post-traumatic Seizures

## Injury Characteristics:

Bone/metal fragments

Intracranial hemorrhage

Depressed skull fracture

Injury severity

Focal contusions/injury

Focal hypoperfusion

Focal neurological deficits

Dural penetration



# PNES

- Psychogenic non-epileptic seizures, (PNES) often called pseudo-seizures or psychogenic seizures, are terms used for episodic behavioral events which superficially resemble epileptic attacks but which are not associated with paroxysmal activity within the brain .

## **PNES**

- Non-epileptic seizures may be psychogenic, but must be differentiated from other non-epileptic events such as syncopal episodes and cardiac events. PNES are not uncommon in neurologic settings, and may coexist with epileptic seizures in patients with epilepsy.

## **PNES**

- The differentiation between nonepileptic and epileptic seizures cannot be made on the basis of clinical characteristics alone. Electroencephalographic monitoring (particularly with video) is often helpful in establishing a diagnosis.

# PNES

- In a study comparing veterans and civilians admitted to the EMU, PNES was identified in 25% of veterans and 26% of civilians. Fifty-eight percent of veterans with PNES were thought to have seizures related to traumatic brain injury. In the veteran group, PNES was the single most common discharge diagnosis and more common than the discharge diagnosis of epilepsy.

# PNES

- Post-traumatic stress disorder (PTSD) has also been shown to be a significant risk factor for developing PNES.

# EEG

- The EEG provides valuable information in focus localization, seizure persistence, and severity prognostication once PTS have been observed . In addition, the EEG may identify the presence of non-convulsive seizures among patients with impaired consciousness, particularly early after severe TBI . The utility of the EEG in predicting PTS recurrence following a seizure-free period has not been established.



# EEG

- EEG has been shown to be useful for the localization of a seizure focus in patients in patients who develop PTE, but it has not proved to be helpful in predicating the development of epilepsy after TBI.

- Lowenstein, 2009

## EEG

- A change from focal slow wave activity to focal spike discharges, particularly during the first month post injury, or persistence of focal spike or sharp wave discharges may be suggestive of increased seizure risk. However, such discharges may be observed on the EEG of patients without PTS .

## EEG

- A normal EEG may precede PTS onset, though this finding is more frequently associated with a favorable prognosis . EEG findings should be evaluated in context with other clinical risk factors when assessing the likelihood of PTS onset.

# EEG

- The utility of the interictal EEG as an objective predictor of subsequent PTS appears limited. It is frequently abnormal in patients with TBI, both with and without PTS, reflecting the severity of brain damage sustained.

# EEG

- Although interictal epileptiform activity is apparent in approximately 50% of single awake recordings in adults with epilepsy, this proportion rises to approximately 80–85% if sleep is included.
- Two recordings obtained while the patient is awake will demonstrate epileptiform activity in 85% of individuals with epilepsy, and this rises to 92% of persons within four recordings (Binnie, 1999).

## EEG

- When initial standard evaluations fail to resolve the clinical diagnosis, long-term EEG monitoring techniques, including ambulatory EEG monitoring and/or inpatient Video/EEG telemetry are effective and clinically valuable .

# EEG

- Hudak et al. described the utility of prolonged Video/EEG monitoring in the clinical management of paroxysmal behaviors in TBI survivors .
- Monitoring was conducted for an average of 4.6 days and was successful in establishing a diagnosis in 82% of the cases referred.
- 62% the evaluated patients had focal seizures, 6% had generalized seizures and 33% had psychogenic NES.

# MANAGEMENT OF PTE AND PTS

- **Diagnosis and classification:** An initial step in the management of suspected seizures is establishing whether or not a seizure exists.
- **AEDs:** Overall, about 33 percent of patients with a first unprovoked seizure can be expected to have a second within the subsequent three to five years. This risk varies considerably, however, depending on clinical characteristics of the patient . Increased risk is observed among patients with remote lesional (symptomatic) epilepsy.



# AEDs

- Over 50% percent of patients with a first remote symptomatic seizure (lesional) will experience a second seizure in the next three to five years.
- Of the patients with a second seizure, almost 87% will experience a third seizure at five years.
- Seizures occurring immediately following an acute precipitant or injury to the brain carries a lower risk of recurrence than a late seizure.

# AEDs

- The decision to start treatment in a patient with a first seizure must balance that patient's risk of relapse, the benefits of avoiding the consequences of a second seizure and the risk of AED toxicity.
- The decision of which specific agent to use will reflect the type of post-traumatic seizure, the route and frequency of drug administration, as well as the anticipated and realized adverse effects and comorbidities.

# Surgical Treatment of Post-traumatic Seizures

- Surgical excision of the seizure focus provides an important treatment option for carefully selected patients with refractory PTE. Favorable responses, including seizure freedom have been described among selected patients with PTE treated with resective surgery.
- Patients with unilateral post-traumatic frontal lesions who undergo complete resection of perilesional encephalomalacia /gliosis and adjacent electrophysiologically abnormal tissue respond particularly well to surgery.

# Vagus Nerve Stimulation (VNS)

- VNS is considered to be an appropriate therapy for patients with medically refractory epileptic seizures who are not optimal candidates for resective epilepsy surgery.
- A potential advantage to the use of VNS in the context of LPTS is the relative absence of cognitive adverse effects. However the role of this technology in the treatment of epilepsy in the context of TBI remains to be delineated.

# Areas for further research in TBI

## Seizures and Epilepsy

- Neuroimaging including diffusion tensor imaging
- Genetic factors that may influence PTE (APOE etc.)
- TBI and PTE in OIF/OEF Veterans database
- ECOE database for outcome parameters.
- Long-term cognitive outcome and PTE.
- PNES in veteran population prevalence and treatment .
- Develop modalities to prevent epileptogenesis.



# Questions ?

