Most hypotheses suggest a neurotoxicant-based mechanism of neuro-immune effects from Acetylcholinesterase inhibitor (AChE) exposures from:

- Pesticides
- Anti-nerve gas pills (PB)
- Sarin exposure

From an innate immune perspective, these exposures could be considered exogenous danger signals and any resultant cellular damage (cell death and cellular debris) would be considered endogenous danger signals or "alarmins".
Theories of Gulf War Illness

- Neuroinflammatory disorder

- Disordered pain processing in CNS – chronic glial overactivation

- White matter toxic leukoencephalopathy

- Mitochondrial dysfunction – ROS induction

- Hypercoagulable state

- Others – neuroendocrine alterations, exercise-induced immune changes

Neuroinflammation

- Theory suggests GWI is related to proinflammatory cytokines and microglia in CNS. This can occur through TLR activation or other mechanisms:
  - Toll-like receptors are surface proteins on glia that cause glial cells to release proinflammatory cytokines.
  - Glial activation loops of TLR4 occurs from endogenous danger signals (alarmins) or exogenous stimuli (environmental toxins, stress, injury) resulting in release of proinflammatory cytokines (IL1, IL6, TNF).
  - Cytokines are chemical messengers generated as part of the body’s nonspecific innate immune response to diverse threats including infection, tissue injury and toxicant exposures.
  - For example, enhanced glial activation and CNS cytokine production have been shown in animal models following exposure to low-level sarin.
What activates Glia?

- TLR4 on glia is activated by bacteria but also by endogenous danger signals or "alarmins" such as damaged or dying cells or by leakage of blood products into the CNS.
- Proinflammatory cytokines themselves also activate glia and can cause chronic glial activation loops.

Pain Processing

- A specific instance of neuroinflammation theory relates to pathological pain where the cause of the pain may be gone but the pain still remains.
- Theory suggests that microglia (immune cells of CNS) become primed and chronic glial activation loops are formed that release proinflammatory cytokines (IL-1, IL-6, TNF) that can create chronic pain states (Watkins et al., 2007).
- It suggests that glial activation loops occur through TLR4 activation on microglia. TLRs are surface proteins on glia that cause glial cells to release proinflammatory cytokines (Watkins & Maier, 2003).
- As Linda Watkins explains, TLR4 can be thought of as the "not me, not right, not OK" receptor that recognizes not only pathogens that should not be in the extracellular spaces but also the endogenous danger signals including bits of you that are not supposed to be there.
Once activated, glial cells release proinflammatory cytokines including IL-1 and when in pain pathways this results in pathological pain.

- Immune cells in & around peripheral nerves and Glia in spinal cord & brain are important in these brain-immune cross-talk pathways.
- Glial “priming” by immune changes & CNS damage may be setting the stage for Gulf War Illness.
- Suggests that cross-talk pathways between immune system and brain may be altered by initial glial “activation” and then “priming” to cause stronger and longer responses when activated by alarmins or exogenous stimuli.
- TLR4 activation and release of proinflammatory cytokines can induce sickness response behaviors including joint and muscle pain, fatigue, & cognitive complaints, much like GWI.
White Matter volume loss in GWI

- White matter is highly susceptible to the effects of neurotoxicants.
- Several studies of GW veterans with exposure to low-dose sarin (Heaton et al., 2008), pesticides (Sullivan et al., 2010) or reporting increased health symptoms (Powell, 2009) have shown lower brain white matter volumes.
- Did GW exposures caused a toxic leukoencephalopathy in some GW veterans causing myelin breakdown products and other cellular debris to be in the extracellular spaces?
- Cellular debris or other “alarmins” can activate microglia and release proinflammatory cytokines through activation of TLR4 (Rivest, 2010).

Mitochondrial Dysfunction

- Symptoms of mitochondrial dysfunction include fatigue, headache, muscle weakness, and cognitive problems much like GWI.
- Research has shown that AChE inhibitors can exert damage on brain tissue through mitochondrial damage by inducing cellular levels of reactive oxygen species (ROS).
- In the periphery, innate immune system activation can result in generation of ROS through activation of monocytes, neutrophils and macrophages.
- ROS damage mitochondrial DNA, leading to mito dysfunction and/or cell death potentially as a result of TLR9 induced innate immune activation (more from Dr. Hauser).
Chronic Platelet Activation and Hypercoagulable State

- Individuals with GWI have abnormal intravascular tissue factor (TF) procoagulant activity (PCA). The observed changes in intravascular TF PCA and Factor VII are consistent with a chronic hypercoagulable state (Bach et al., 2009).

- This theory suggests the etiology of GWI is chronic inflammation produced by autostimulatory crosstalk between the immune and coagulation systems.

- Studies showed blood coagulant Factor VII was significantly altered in organophosphate exposed rats and a clinically exposed case-report.

- Platelets are often first responders to inflammation or injury sites and are activated in neurological disease including MS. TLR2, TLR4, TLR9 are found on platelets as well (more from Dr. Beaulieu).

Other relevant GWI findings:

Altered neuroendocrine functioning

Exercise induced immune system changes

- Hypothalamic-pituitary adrenal (HPA) axis alterations were associated with chronic health symptoms and were distinct from those associated with PTSD in GW veterans (Golier et al., 2007).

- Suggests GW veterans share a neuroendocrine characteristic similar to those in other multi-symptom illnesses but the overall neuroendocrine profile is unique. Theory suggests that GW veterans may have abnormal pituitary functioning (Golier et al., 2009).

- Immune studies show exercise-induced immune network remodeling changes in proinflammatory cytokines and inflammatory markers suggesting an autoimmune component to GW illness (Whistler et al., 2009; Broderick et al., 2010).
Different parts of the Puzzle?

- Could altered cross-talk pathways in the neuro-immune-coagulation systems from TLR-induced chronic inflammation be the link that binds all of these somewhat overlapping findings and theories of GWI?

- Could this represent a TLR activated autoimmune state?

- TLR dysregulation has been implicated in chronic autoimmune states including skin, lung, joint and gastrointestinal disease, systems also affected in GWI.