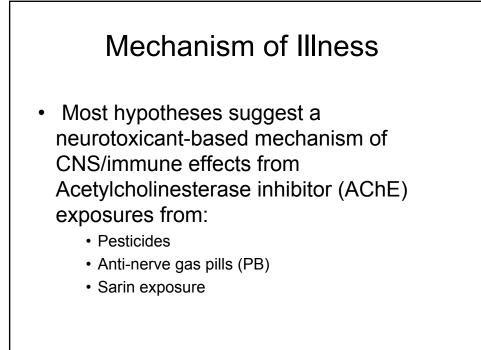
Potential Treatment Trials for Gulf War Illness Discussion

Kimberly Sullivan, Ph.D. Research Advisory Committee on Gulf War Veteran's Illnesses June 29, 2009

Theories of Gulf War Illness

- Disordered pain processing in CNS
- •Mitochondrial dysfunction
- •Neuroinflammatory disorder
- •neuroendocrine dysfunction
- •White matter toxic leukoencephalopathy
- •Hypercoagulable state



Laetz, CA et al. The synergistic toxicity of pesticide mixtures: Implications for risk assessment and the conservation of endangered salmon. Environ. Health persp. 2009;117:348-353.

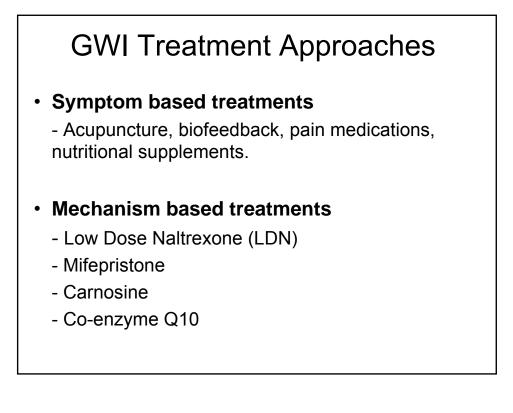
- Found synergistic effects of organophosphate pesticides including malathion, diazinon and chlorpyrifos in wild salmon causing much greater effects than individual exposures or even additive effects.
- These same 3 OP pesticides were some of the most widely used during the Gulf War.

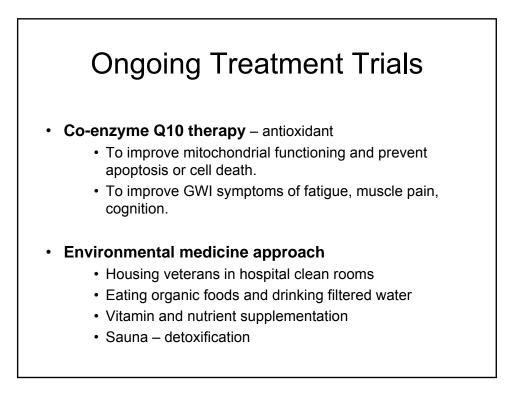
Soltaninejad K & Abdollahi M. Current opinion on the science of organophosphate pesticides and toxic stress: A systematic review. *Med Sci Monit*. 2009;15(3):RA75-90.

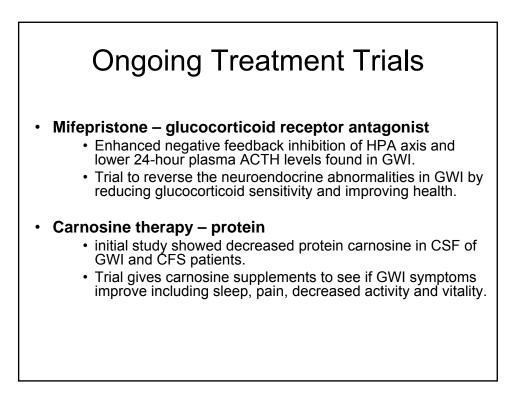
- Review of experimental & clinical studies evaluating OP toxicity
- Oxidative stress = important mechanism of OP poisoning causing depletion of mitochondrial energy and DNA fragmentation leading to apoptosis.
- Suggest that those overexposed to OPs should be given potent antioxidants.

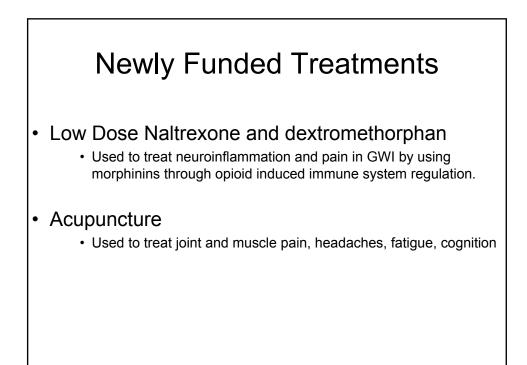
Myhill et al. Chronic fatigue syndrome and mitochondrial dysfunction. *IntJClinExpMed*. 2009;2:1-16.

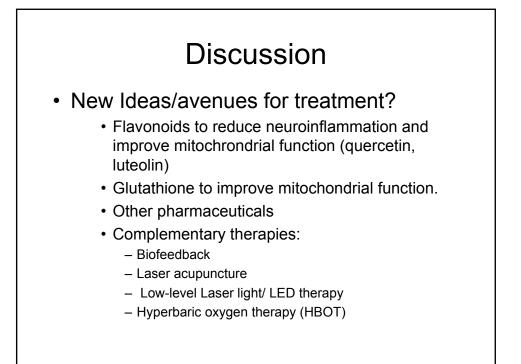
- 71 CFS patients (met CDC criteria) underwent "ATP profile" test for mitochondrial functioning which showed:
 - mitochondrial dysfunction of the neutrophils suggesting specific immune system dysfunction in at least some patients with chronic fatigue syndrome.

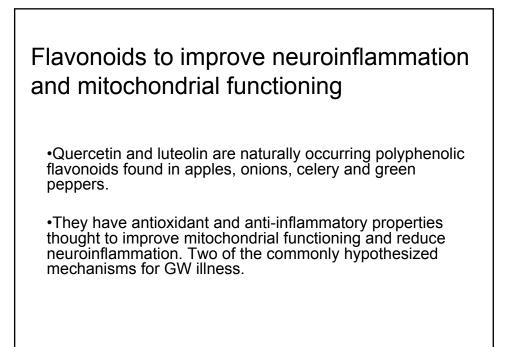












Gong et al. Quercetin up-regulates paraoxonase 1 gene expression with concomitant protection against LDL oxidation. *Biochem. Biophys. Res. Commun.* 2009;article in press.

- ♂ rats fed liquid quercetin [10mg/L] for 4 weeks
 - upregulated PON1 gene expression and activity
 - significantly increased protective capacity of HDL against LDL oxidation
 - PON1 is also associated with clearing neurotoxicants from the body. Could increasing PON1 activity potentially help with GW illness?

Davis et al. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. *Am J Physiol Regul Integr Comp Physiol*. 2009; 296:1071-1077.

- d mice given 12.5-25 mg/kg quercetin daily for 7 days
 enhanced wheel running activity and maximal endurance capacity.
 - exhibited increased mRNA expression in brain & muscle tissue of mitochondrial DNA and its substrates including:
 - PGC-1α thought to be the master regulator of mitochondrial biogenesis.
 - SIRT1- which increases PGC-1 activity.
 - Cytochrome *c* which usually occurs in conjunction with other mitochondrial enzymes of the electron transport chain.
 - Authors suggest that quercetin may enhance exercise tolerance through its activity as an adenosine A1 receptor antagonist in the brain.

Jang et al., Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. PNAS.2008:105;7534-7539.

- Luteolin is a potent anti-inflammatory flavonoid.
- Study showed that luteolin inhibits production of IL-6 in periphery where it plays a role in immunologically mediated fatigue and loss of strength.
- Results suggest that luteolin could be a promising agent for treating neuroinflammation.

Potential white matter volume therapies

- Several studies have shown lower brain white matter volumes in symptomatic GW veterans.
- Many neurotoxicants are lipophilic and can cause demyelination of the white matter tracts.
- The question arises whether GW exposures caused a toxic leukoencephalothy in some GW veterans.
- What therapies might help reduce WM volume loss – pharmaceuticals, stem cells?

Khan et al. Long-term study of brain ¹H-MRS study in MS: Effect of glatiramer acetate therapy on axonal metabolic function and feasibility of long-term ¹H-MRS monitoring in MS. *J Neuroimaging*. 2008; 18(3):314-319.

- Patients with relapsing-remitting MS treated with glatiramer acetate (copaxone) for up to 4 years
 - showed a significant reduction in relapse rate and neurologic disability.
 - increased NAA/Cr ratio suggesting improved neuronal integrity.
 - Could this therapy be beneficial in other demyelinating disorders?

Riordan et al. Non-expanded adipose stromal vascular fraction (SVF) cell therapy for multiple sclerosis. *J Transl Med.* 2009;7:29.

- Adipose tissue may be an alternative stem cell source.
- Mesenchymal stem cells inhibit innate immune activation by suppressing macrophage activation, dendritic cell maturation and blocking inflammatory signalling.
- Stromal vascular fraction infusions from adipose tissue improved 3 MS patients' symptoms & quality of life suggesting its potential utility in MS and other autoimmune conditions.



