

Presentation 10 – Lea Steele

Update:

**Highlights of Recently Published Research
Relevant to the Health of Gulf War Veterans**

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Research Advisory Committee to Gulf War Veterans' Benefits

**Highlights of Recently Published Research Relevant
to the Health of Gulf War Veterans**

- **Recently Published Reports**
- **Scientific Articles**
- **Gulf War Research Funding Announcement**

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Recently-issued Reports

- **Gulf War and Health Volume 4: Health Effects of Serving in the Gulf War**
- **Gulf War and Health Volume 5: Infectious Diseases**
- *Heroism Exposed:
An Investigation into the Treatment of 1 Combat Engineer Regiment Kuwait Veterans (Canadian MOD ombudsman)*



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Highlights of Recently Published Research

- **Scientific Articles**
 - > **Effects of GW-related exposures**
 - > **Studies of GW veterans**
 - > **Studies of OIF/OEF Veterans**
 - > **Multisymptom Illnesses**



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Effects of Gulf War-Related Exposures

Recently Published Studies

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**Effects of Gulf War-related Exposures
Pyridostigmine, DEET, Permethrin and Stress: A double-blind
Randomized Placebo-Controlled Trial to Assess Safety**
Roy, MJ et al Mayo Clin Proc 2006 Oct 81:1303-10

**Crossover trial, 64 healthy volunteers exposed to
combinations of PB, DEET cream, permethrin-impregnated
uniforms, stress (at recommended doses): 4 sessions total**

- > Combinations had no adverse effects on physical performance, neurocognitive measures
- **Relevant to Gulf War?**
 - > Studied short duration/low level exposures; immediate effects
 - > Gulf War: repeated/sustained exposures/excessive levels; long-term effects

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Effects of Gulf War-related Exposures

Sarin Produces Delayed Cardiac and Autonomic Changes

Morris M et al. Experimental Neurology 2006 [E pub]

- **Mice received 0.05 LD₅₀ of sarin or saline; followed 1 wk, 10 wks; produced no symps, no change in blood AChE activity, no change in heart rate**
 - > Biphasic effect: After 1 wk, sarin-trtd mice had sign increase in baroreflex sensitivity, increase in pulse interval variance; After 10 wks, both were sign decreased
 - > After 10 weeks, sign increase in brainstem levels of tyrosine hydroxylase mRNA (enzyme involved in amine synthesis)
- **Findings suggest centrally-mediated, delayed ANS impairment by low dose sarin**



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Effects of Gulf War-related Exposures

Our Recent Experience with Sarin Poisoning in Japan and Pesticide Users with References to some Selected Chemicals

Yokoyama K Neurotoxicology 2006 [Epub]

- **Reviewed studies of survivors of Japanese sarin attacks, compares results to studies of OP/carbamate-exposed farmers**
 - > Sarin survivors: PTSD in some; also delayed CNS effects evidenced in poorer performance on digit symbol test, increased postural sway with eyes open (impaired CNS/visual coordination)
 - > Pesticide applicators: no decline in digit symbol test, decline in peripheral nerve conduction, increased postural sway with eyes closed
 - > Importance of genetic variation in susceptibility to chemicals



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Effects of Gulf War-related Exposures

Coding Region PON Polymorphisms dictate accentuated neuronal reactions in chronic, sub-threshold pesticide exposure

Browne et al, FASEB Journal Online June 2006

- **Investigated neurophys, neuropsych, biochemical effects of chronic, low-level OP exposure: 60 long-term residents of agricultural community; age, sex-matched controls**

Significant differences in exposed:
 - > Higher PON, arylesterase activity (4x)
 - > EEGs: reduced theta activity in hippocampus, cingulate cortex; increased beta activity in prefrontal cortex
 - > Neuropsych: reduced delayed memory/visual recall
- **EEG effects most pronounced in exposed w/PON1 R allele; also in those with memory deficits**
- **Interaction between genotype and exposure determine enzyme activity levels, CNS consequences**

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Effects of Gulf War-related Exposures

Paraoxonase gene polymorphisms and sporadic ALS

B Slowik et al, Neurology 2006:67

Paraoxonase cluster polymorphisms are associated with sporadic ALS

M Saeed et al, Neurology 2006:67

- **Both studies show significant link between PON genetic variation and risk for sporadic ALS**
 - > Slowik: 185 ALS patients in Krakow vs. 437 controls; sALS sign associated with R allele of Q1921R; C allele of C311S; Having both associated with OR = 3.44
 - > Saeed: 1,891 North American family cohort; SNPs in PON gene cluster (spans PON1, PON2, PON3) associated with sALS
- **Both conclude findings support hypothesis that ALS results from environmental toxicity in susceptible host**

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Research on the Health of Gulf War Veterans, Family Members

Recently Published Studies

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**Studies of Gulf War Veterans/Family Members
Spouses of Persian Gulf War I Veterans: Medical Evaluation of a U.S. Cohort**
Eisen SA et al, Military Medicine 2006: 171:613-618

From Phase III of National GW Veterans Study: Clinical evaluation of 490 nonveteran spouses of GW veterans, 537 spouses of nondeployed GW-era veterans

- > No differences in rates of diagnosed conditions including FM, CFS
- > No difference in SF36 physical scores
- > No differences in healthcare utilization
- > PGW spouses had higher S/R skin rashes, hepatitis; At clinical exam, spouses of nondeployed had more mild skin conditions

● **Remaining Questions:**

- > *Differences in symptom rates? Symptom complexes?*
- > *Differences in spouses of sick vs. healthy veterans?*

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Studies of Gulf War Veterans
Persistence of Symptoms in Veterans of the First Gulf War: 5-Year Follow Up

Ozakinci et al, Environ Health Perspect Oct 2006

Resurveyed 390 Gulf War veterans in GW Registry 5 years after initial 1995 survey

- > Overall, no significant change in symptom number or severity
- > Some symptom reduction in subset who had been most symptomatic in the first survey; but still substantially worse than those who had had fewer symptoms
- **Conclude that post-Gulf War symptomatic illness has not abated over time (or progressed)**
- **Requires improved understanding and better care for ill veterans**

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Studies of Gulf War Veterans
Effects of Sarin and Cyclosarin Exposure During the 1991 Gulf War on Neurobehavioral Functioning in US Army Veterans

Proctor SP et al, Neurotoxicology 2006 [Epub]

Neurocognitive testing results collected 1994-1996 in 140 Army veterans; compared results in 3 groups: high, moderate, low/no exposure (based on Khamisiyah plume modeling)

- > Significant dose response effects on tests of psychomotor function, visuospatial ability:
low/no exposure group > moderate exposure > high exposure
- > Exposure level not associated with CMI (Fukuda)
- > High exposure not related to changes in mood states; low/no exposure group had highest rate of depression

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Studies of Gulf War Veterans
The ACTH Response to Dexamethasone in Persian Gulf War Veterans

Golier JA et al, Ann NY Acad Sci 2006:1071:448-453

PTSD is associated with increased ACTH, CRF, and cortisol suppression response to dexamethasone (DEX)

This study compared ACTH levels after low dose DEX in 14 GW veterans with PTSD, 11 GW without PTSD, 12 nondeployed healthy veterans (all with history of trauma)

- > GW veterans with or without PTSD had lower post-DEX ACTH levels than nondeployed veterans
- > In GW veterans, post-DEX ACTH levels inversely correlated with musculoskeletal symps,* mood/cogn symps, total symps

Conclude: altered HPA function related to some aspect of Gulf War exposure, associated with GW symptoms



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Studies of Gulf War Veterans
Enhanced cortisol suppression to dexamethasone associated with Gulf War deployment

Golier JA et al, Psychoneuroendocrinology 2006 [Epub]

Compared plasma cortisol and lymphocyte glucocorticoid receptor (GR) levels after low dose DEX in 16 GW veterans with PTSD, 12 GW with dep+PTSD, 14 with no psych dx, and 12 nondeployed healthy veterans (all with hx of trauma)

- > GW veterans had greater cortisol suppression after DEX than nondeployed; PTSD or depression not associated with differences in cortisol suppression
- > In GW veterans, post-DEX cortisol suppression sign associated with musculoskeletal symps, not mood/cogn symps
- > Those reporting PB use had sign greater cortisol suppression than those who did not; no other exposures associated



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Studies of OIF/OEF Veterans

Recently Published Studies



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Studies of OIF/OEF Veterans The Health of UK Military Personnel Who Deployed to the 2003 Iraq War: a Cohort Study

Hotopf et al The Lancet 2006 [Epub]

Is there an Iraq war syndrome? Comparison of the Health of UK Service Personnel after the Gulf and Iraq Wars

Horn et al. The Lancet online May 16,2006

UK study of OIF veterans (n=4722) vs. nondeployed (n=5550) (OIF deployed vs. nondeployed unclear; ~70% had also deployed to previous conflicts)

- OIF deployment assoc with LOWER rate of PTSD
 - > Reanalyses: participation in combat associated with PTSD
 - > Small increase in % reporting multiple symptoms
- No increase in symptom reporting, s/r poor health as seen in PGW



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**Studies of OIF/OEF Veterans
Neuropsychological Outcomes of Army Personnel Following
Deployment to the Iraq War**

Vasterling J, et al JAMA Aug 2006, 296:519-529

**Prospective study collected neurocognitive data pre and post
deployment for 654 Army personnel; and 307 nondeployed
personnel at 2 time points**

- Deployment associated with mild but sign. neurocognitive declines in tasks of sustained attention, verbal learning, visual-spatial memory; greater feelings of confusion and tension; improved reaction time
- Deployment not associated with higher frequency of veterans' subjective estimates of cognitive impairment



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Recently Published Research:

Multisymptom Illnesses

**Current Research Priorities in Chronic Fatigue Syndrome/
Myalgic Encephalomyelitis Disease Mechanisms, a
Diagnostic Test, and Specific Treatments**

Kerr JR et al, J Clin Pathology Published Online Aug 25, 2006

- **Collaborative study group at St. George's University since 2001**
 - > Develop understanding of molecular pathogenesis of CFS
 - > Develop diagnostic test
 - > Develop specific and curative treatments



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Recently Published Research:

CFS Collaborative Research (Kerr et al)

- **CFS Pathogenesis:**
 - > Genomic studies: genetic signature?
 - > Theme of genes id'd to date: immunity and defense
- **Diagnostic test:**
 - > "Surface enhanced, laser desorption and ionization-time of flight mass spectrometry" identifies unique proteins in cases vs. controls
- **Clinical treatment trials planned**
 - > IFN beta (regulates humoral immunity, stimulates NK activity, improves fatigue in MS patients)
 - > TNF alpha inhibitors (e.g. Etanercept, sign CFS benefit in small pilot study)



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Army CDMRP Gulf War Research Program Funding Announcement

- **\$ 5 Million total funding**
- **Emphasis on innovative research**
- **Funding Priority Areas**
 - > Identification/evaluation of treatments for GWI
 - > Identification of objective markers of pathology
- **Deadlines**
 - > Preproposals: Dec 1, 2006
 - > Full proposals: Feb 2, 2007



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