

Presentation 7 – Beatrice Golomb

**New Research Update  
6-03**

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**Topics**

- AChEi
- DU
- Vaccines
- Characterizing Illness
- Birth Defects (separately)

**AChEi, Chemicals**

**Sarin delayed effects**

- Adult male rats treated x3wks w/ either or both
- **Sarin (S) sc:** 62.5µg/kg, 0.5xLD(50) 3x/wk
- **PB po:** 80 mg/L in drinking water
- **Measure:** Passive avoidance, open field activity, acoustic startle, nociceptive threshold
- **2 wk:** Sarin -> musc downreg in caudate/putamen & mesencephalon. Incr startle; Decr OFA
- **4 wk:** no effect
- **16 wk:** S incr, PB+S decr habituation in OFA. PB+S incr pain threshold. No change ChAT, AChE
- **No effects of PB alone on \*these\* outcomes**
- Scremin, O.U., et al., Delayed neurologic and behavioral effects of subtoxic doses of cholinesterase inhibitors. J Pharmacol Exp Ther, 2003; 304(3): p. 1111-9.

### **PB suppressed IL-8 cytokine release**

- In vitro: Porcine skin flap model
- In vitro: Human epidermal keratinocytes
- Permethrin, DEET, both: + PB or DFP in medium (50 & 30 ng/ml)
- IL-8, TFalpha, PGE2 at 1,2,4,8,12,24h
- IL-8 suppressed by PB at many times
- Effect on TNFalpha depends on vehicle
- **Monteiro-Riviere, N.A., et al.** Pyridostigmine bromide modulates topical irritant-induced cytokine release from human epidermal keratinocytes and isolated perfused porcine skin. *Toxicology*, 2003. 183(1-3): p. 15-28.

### **DEET absorption enhanced by chems**

- In vitro: Porcine skin flap & silastic diffusion
- (DEET flux sim to human skin, 2µg/cm<sup>2</sup>/h)
- PB or DFP or sulfur mustard or occlusion increase flux, to max of 5x
- Tough to compare dose to that of PGWV
- \* **Riviere, J.E., et al.**, *Percutaneous absorption of topical N,N-diethyl-m-toluamide (DEET): effects of exposure variables and coadministered toxicants.* *J Toxicol Environ Health A*, 2003. 66(2): p. 133-51.

### **GWV: PB assoc with cognitive dysfcn**

- SS: 207 GWV deployed & 53 era Veterans. (120 GWV referred for neuropsych evals; rest & era were treatment seeking veterans at Boston.)
- Exposures: PB: 44% GWV. PTSD: 13.5% overall.
- Tests: multiple neuropsych tests, dif domains
- Results: GWV worse on attention, motor, visuomotor, visual memory, mood, motivation (not exec fcn)
- PB exposed: worse on overall exec fcn, and card sort
- PTSD exposed: worse on depression, tension, POMS
- No change if exclude those with poor motivation score
- \* **Sullivan K et al.** Cognitive Functioning in Treatment-Seeking Gulf War Veterans: Pyridostigmine Bromide Use and PTSD. *J Psychopath & Behav Assessment*, 25: 95-103.

### **Loss NTE links OP to hyperactivity**

- SS: mice: NI & disruptx in Nte (gene for NTE)
- Nte<sup>-/-</sup>: Die embryo d8. (?defect NI tube closure)
- Nte<sup>+/-</sup>: 40% decr brain NTE. No change AChE.
- Nte<sup>+/-</sup>: Hyperactive (incr. locomotor activity)
- Nte<sup>+/-</sup>: More sensitive to OP exposure: EOPF
- -- Increased death from delayed OP toxicity (EOPF@ 6,10mg/kg)
- -- Lowers locomotion in +/-, Raises in +/+ (EOPF 1mg/kg)
- (85% inh NTE mouse brain at 5mg/kg in vivo):
- \* **Winrow, C.J., et al.**, Loss of neuroathy target esterase in mice links organophosphate exposure to hyperactivity. *Nat Genet*, 2003. 33(4): p. 477-85.

## VACCINE

### Vaccine: Macrophagic Myofasciitis

- Design: Review
- Findings: AI-adjuvanted vaccines may produce macrophagic myofasciitis (MMf)
- MMf SX: fatigue and myopathy. 50% meet CFS criteria.
- 1/3 develop an MS-like syndrome
- MMf Genetic Susceptibility: HLA-DRB1\*01 (->PMR, RA)
- Vaccine site: persistence of AI adjuvant. Immunologically active lesion.
- AI associated because: EM, microanalytic studies, expts, epi
- WHO: advise study to link focal findings to immunolog active lesions
- “Strikingly similar” to Gulf War sx
- NOTE: Most people with AI-containing vaccines don't get this...
- BG Suggestion: Test HLA type in GWV with MS; ± test for MMf
- \* Gherardi, R.K., [Lessons from macrophagic myofasciitis: towards definition of a vaccine adjuvant-related syndrome] Rev Neurol (Paris), 2003. 159(2): p. 162-4.

## Depleted Uranium (DU)

### DU Effects: Review

- Natural Uranium (U): ubiquitous in soil at 3mg/kg.
- Depleted Uranium (DU): 259 tons munitions used, GW
- DU: same chemotoxicity as U: same # protons
- DU: ~40% of the radiotoxicity of U, dif speciation (less % low-half-life isotopes).
- $\alpha$  radiation dominates. ( $\alpha$  radiation = pos charged ions w/ 2 neutrons, 2 protons.)
- Penetration range, “typical” 5MeV  $\alpha$  radiation: ~4cm in air; 50 $\mu$ M soft tissue

\* Bleise, A., P.R. Danesi, and W. Burkart, *Properties, use and health effects of depleted uranium (DU): a general overview*. J Environ Radioact, 2003. 64(2-3): p. 93-112.

### DU Effects: Review

- External exposure: thought safe:  $\beta, \gamma$  radiation.
- Internal exposure: a problem, even w/ short penetration.
- - DU dust: generated when DU hits target, inhalation may  $\rightarrow$  protracted exposure to lungs, other organ, esp particles  $< 10\mu\text{M}$ .
- - Soluble forms: more chemical risk, absorbed from lung to body. Insoluble forms: more radiation risk, stay put.
- - Embedded fragments: 2 orders magnitude incr. in bld/urine several years after exposure.
- - DU resuspension: after deposition on ground, if fine enough
- - DU in water/food: 2-5% ingested DU is absorbed; 90% leaves body within 1wk. Rest distributed - 10% to kidneys, most elim in a few wks. 15% to bone: at 5 & 25 yrs - sev% & 1% (respectively) remains in bone

### DU Effects: Review

- Body load in GWV (urine, feces, hair, nail record): not  $>$  range for natural U.
- Exception: crews of military vehicles hit by DU
- For these: urine U .01-30.7  $\mu\text{g/g}$  creatinine (vs 0.1-0.05 nonexposed)
- "Observable health effects not expected" (with exception as noted).
- CA risk estimates m be based on theoretical considerations. Depends on actual speciation (238U,  $\sim 2\%$  235U)
- BG comments: Doesn't consider possible heavy metal immunological effects (cytokine, etc.)
- \* Bleise, A., P.R. Danesi, and W. Eurlart, *Properties, use and health effects of depleted uranium (DU): a general overview*. J Environ Radioact, 2003. 64(2-3): p.93-112.

### Illness Characterization

### Symptom patterns in Registry GWV

- Design: mail survey completed by 1161 Registry GWV
- 84.5% of respondents believed they had med problems attributable to GW service;
- 5.3% did not answer. ( $\sim 10\%$  did not believe they did.)
- Symptom list: 48 symptoms grouped by organ
- \* Hallman, W.K., et al., *Symptom patterns among Gulf War registry veterans*. Am J Public Health, 2003. 93(4): p. 624-30.

### Symptom patterns in Registry GWV

- **Exploratory factor analysis:** 4 symptom factors.
  1. Mood/memory/fatigue
  2. Musculoskeletal
  3. Gastrointestinal
  4. Throat/breathing
- **K-means cluster analysis:** 2 groups
  1. Healthier, 60%: ave 18 sx: 33% mod, 11% severe
  2. Sicker, 40%: ave 37 sx, 40%mod, 35% severe
- Cluster 2 more likely to have  $\geq 1$  of 24 medical conditions
  - Includes FM, IBS, MS, CFS, depression, PTSD, bipolar, anxiety d/o, thyroid disease, DM, sterility. Hay fever, TB, eczema/prosriasis appear less frequent.
- \* **Hallman, W.K., et al.,** *Symptom patterns among Gulf War registry veterans.* Am J Public Health, 2003, 93(4): p. 624-30.

### Seminal Plasma Hypersensitivity - SPH

- **Ss:** 211 Gulf war males, questionnaire. (No females responded) Desensitization in sev females.
- **Design:** Survey -> medical testing. Desensitization done in some meeting criteria for seminal plasma hypersensitivity (SPH).
- **Survey:** 89% reported burning after contact with their own semen, or sex partner with burning after contact with their semen.
- 48% 1st noted on 1st sexual contact after war. < 50% couples had relief of sx with condom, vs 100% gen population.
- \* **Bernstein JA, et al.,** *Is burning semen syndrom a variant form of seminal plasma hypersensitivity.* Obstetrics and Gynecology 2003 101:93-102.

### Seminal Plasma Hypersensitivity

- Desensitization**
- 67 female partners initially satisfied criteria of condom prevention or didn't answer, 43 from internet and 24 referred by VA GW physicians. 40% had full relief w condom (vs 75% in gen population w sx of SPH)
  - Cohort control of 36 women in gen population with sx c/w SPH
    - Trend but no relation to PB, pesticides; less so vaccine*
    - Assoc w eval & rx PTSD; involved in decontamination ops, p < .05.*
- Desensitization: 5 GWV, 2 Gen Population**
- Using seminal proteins to which skin test reaction
  - 3 of 5 GW complete relief, 1 partial. 1 of 2 gen population success.
  - Responders -> spec IgE abs to seminal pl protein, nonresponders not.
  - \* **Bernstein JA, et al.,** *Is burning semen syndrom a variant form of seminal plasma hyper sensitivity.* Obstetrics and Gynecology 2003 101:93-102.

### Psychiatric d/o in PGWV: Review

- Design:** Systematic review
- Articles:** 2296 abstracts and 409 articles reviewed.  
Duplicate abstrax.
- Abstract:** Hypothesis, quality (resp rate, poss selex bias, outcome msrmt bias, data on confounders, adjustment)
- Analysis:** Summary OR/RR with random effects model with inverse variance due to heterogeneity ("METAN" command with stata), using studies with dichotomous outcomes
- Result**
- PTSD:** 11 studies. RR 2.9 (2-4.2). Mostly Unwin, Gray.
  - Common mental d/o:** 11 studies: RR 1.8, 1.6-2.0. Mostly Kang, Unwin.
  - \* **Stimson, N.J,** 2003, Psychiatric disorder in veterans of the Persian Gulf War of 1991. Brit J

### Perceived Exertion in GWV

- Ss: 15 GWV with CFS; 19 healthy GWV
- Intervention: Exercise to exhaustion on cycle ergometer
- Measure: Rating of Perceived Exertion (RPE); also as % of exercise capacity. (In CFS females: not elevated as a fraction of capacity.)
- Result: Higher RPE at each power output,  $p < 0.001$ ;
- Result: Higher RPE/ $VO_2$ max, too - diff from civilians
- Effect eliminated if adjust for preexisting fatigue

Need larger sample; nonGWV ctrl: look at other parameters

Ss at higher % peak  $VO_2$  at gas exchange threshold= point of onset of exercise induced metabolic acidosis (56% v 50.6%\*)

\* $p < .05$ , CFS vs healthy Cook D.B. 2003. Perceived Exertion in Fatiguing Illness: Gulf War veterans with chronic fatigue syndrome. *Medicine & Science in Sports and Exercise*: 39-74

### Olfactory Functioning

- Ss: 82 GWV, 33 era activated.
- GW had more “concerns” about health, cognition, depression.
- Pennsylvania Smell Identification Test of hyposmia and anosmia (scratch & sniff): No difference
- Emotional distress correlated with self-report health/cognition
- Didn’t test for adverse response to smell.

\* Vasterling, J.J., et al., Olfactory functioning in Gulf War-era veterans: relationships to war-zone duty, self-reported hazards exposures, and psychological distress. *J Int Neuropsychol Soc*, 2003. 9(3): p. 407-18.