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: 62.5 μg/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

**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


**DEET absorption enhanced by chems**

- In vitro: Porcine skin flap & silastic diffusion
- (DEET flux sim to human skin, 2μg/cm2/h)
- PB or DFP or sulfur mustard or occlusion increase flux, to max of 5x
- Tough to compare dose to that of PGWV


**GWV: PB assoc with cognitive dysfncn**

- SS: 207 GW deployed & 53 era Veterans. (120 GW referred for neuropsych evals; rest & era were treatment seeking veterans at Boston.)
- Exposures: PB: 44% GW. PTSD: 13.5% overall.
- Tests: multiple neuropsych tests, diff domains
- Results: GWV worse on attention, motor, visuomotor, visual memory, mood, motivation (not exec fun)
- PB exposed: worse on overall exec fun, and card sort
- PTSD exposed: worse on depression, tension, POMS
- No change if exclude those with poor motivation score


**Loss NTE links OP to hyperactivity**

- SS: mice: Ni & disrupt in Nte (gene for NTE)
- Nte−/−: Die embryo d8. (defect nl tube closure)
- Nte+/−: 40% decr brain NTE. No change AChE.
- Nte+/−: Hyperactive (incr. locomotor activity)
- Nte+/−: 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):

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 immunologic 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


Depleted Uranium (DU)

- **Natural Uranium (U):** ubiquitous in soil at 3mg/kg.
- **Depleted Uranium (DU):** 269 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).
- **α radiation dominates.** (α radiation = pos charged ions w/ 2 neutrons, 2 protons.)
- **Penetration range,** "typical" 5MeV α radiation: ~4cm in air; 50μM soft tissue

DU Effects: Review

- Internal exposure: a problem, even w/ short penetration.
- DU dust: generated when DU hits target, inhalation may →protracted exposure to lungs, other organ, esp particles < 10μM.
- Soluble forms: more chemical risk, absorbed from lung to body. Insoluble forms: more radiation risk, stay put.
- Embedded fragments: 2 orders magnitude incr. in bid/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. 8% & 1% (respectively) remain in bone.

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. (~10% did not believe they did.)
- Symptom list: 48 symptoms grouped by organ

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 ≥1 of 24 medical conditions
- Includes FM, IBS, MS, CFS, depression, PTSD, bipolar,
aviety do, thyroid disease, DM, sterility. Hay fever, TB,
 eczema/prosriasis appear less frequent.


Seminal Plasma Hypersensitivity - SPH

- **Sg**: 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.


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 wmen in gen population w sx c/w SPH
  Trend but no relation to PB, pesticides, bess vaccine
  Assoc w evol d w PESTS; involved in decontamination ops, p < .05.

Desensitization: 6 GWV, 2 Gen Population
- Using seminal proteins to which skin test reaction
- 3 of 8 GW complete relief, 1 partial, 1 of 2 gen population success.
- Responders > spec IgE abs to seminal pl protein, nonresponders net.


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 mrnt 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 (2.0-3.8). Mostly Unwin, Gray.
- **Common mental d/o**: 11 studies: RR 1.8, 1.6-2.0. Mostly Kang, Unwin.

Perceived Exertion in GWV

- Ss: 15 GW 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/VO2max, too - diff from civilians
- Effect eliminated if adjust for preexisting fatigue
- Need larger sample; nonGWV ctrl: look at other parameters
- Ss at higher % peak VO2 at gas exchange threshold= point of onset of exercise induced metabolic acidosis (56% v 50.6%)[*]

* $p < 0.05$, 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: 59-74

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.