RAC 2009 Annual Report Discussion

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RAC: Charter and Statutory Mission

- Review research findings and research plans regarding health consequences of GW service.
- Evaluate research against the standard of whether it makes a difference to the health of GW veterans.

RAC 2009 Annual Report

- The RAC published an extensive 452-page report in November 2008 called Gulf War Illness, Scientific findings and Recommendations.
- This brief follow-up report is written with the goal of documenting and discussing new pathophysiological research studies relevant to Gulf War illness (GWI) published since the 2008 report was released.
- It is not meant to be all-inclusive but rather to highlight and focus on promising new mechanisms and treatment options that were discussed during the RAC meetings in February, June and November 2009.
- Recommendations regarding future research and clinical trials are also included.

Annual Report Layout

Five Sections:

- Part I. – Recent Gulf War Studies
- Part II – Promising New Research Mechanisms
- Part III – Treatment Research Developments
- Part IV – UTSW Gulf War Illness Research Program
- Part V – Recommendations for new VA Gulf War Illness Program

Part I. Recent GW Related Studies

- Four studies were summarized from Dr. Kang and the VA Environmental Epidemiology Service regarding:
  - Current rates of multi-symptom illness
  - Current mortality rates
  - Current Cancer rates
  - Neuropsychological functioning

Part 1. Summary

- Findings:
  - There was a 25% increase in chronic multisymptom illness.
  - There was a roughly 3-fold increase in chronic-fatigue like symptoms.
  - There was significantly increased symptom reporting when compared with non-deployed veterans.
  - There were significant neuropsychological differences between groups.

Part I. Summary (2)

- Findings:
  - Cancer rates were not significantly increased when comparing GW vs. non-deployed
  - However, when comparing particular exposure groups, Khamisiyah exposed veterans showed 3 times the mortality rate and those exposed to oil well fires showed 2 times the mortality rate from brain cancer than non-exposed veterans.

Part I. Summary (3)

- Neuropsychological findings also showed significant differences between Khamisiyah exposed and non-exposed veterans.
- Khamisiyah exposed veterans showed slowing on psychomotor tasks. These results are consistent with previous reports of psychomotor slowing in persons with organophosphate exposures (Terry et al., 2007) and veterans with Khamisiyah exposure (Proctor et al., 2007).
- These behavioral results appear to correspond to mechanistic animal models reporting altered axonal transport mechanisms from OP induced thinning of axonal microtubules. Because microtubules provide fast transport of organelles down the axon, damage to microtubules has been hypothesized to result in slowing of cognitive processing speeds (Grigoryan et al., 2008; Jiang et al., 2010).

Part II. Promising New Mechanisms related to GWI

- New information regarding mechanistic biomarkers of illness and exposure.
  - Do pesticides cause lasting effects without acute poisoning?
  - Can chronic low-level organophosphate exposures cause lasting health effects outside of the acetylcholinergic neurotransmitter system?
  - Do multiple exposures cause synergistic effects?
  - What is the role of brain white matter and glia in Gulf War illness?
  - What is the role of neuroinflammation in GWI?
  - What types of immune system alterations have been found in GW veterans?

Part II. New Mechanisms (2)

- The 2008 RAC report concluded that the weight of evidence reviewed showed that GWI was related to combinations of exposures to similarly acting substances found in pesticides, PB pills and possibly also low-level sarin exposure from Khamisiyah detonations.

Part II. New Mechanisms (3)

- Organophosphate pesticides and sarin are acetylcholinesterase inhibitors.
- However, new research suggests they may also work through other mechanisms to exert long-term effects by disrupting microtubule functioning in axons and altering axonal transport mechanisms (Jiang et al., 2010; Grigoryan et al., 2009) and through mitochondrial damage and oxidative stress (Laetz, 2009; Kaur et al, 2007; Binukumar et al., 2010).
- Dr. Oksana Lockridge presented her work to the Committee regarding OP binding to tubulin resulting in significantly smaller axonal microtubules in animals treated for 14 days with low-level chlorpyrifos suggesting long-term biological effects from these low-level exposures (Jiang et al., 2010).

Part II. New Mechanisms (4)

- In addition, Dr. Freya Kamel reported results from her large cohort from the Agricultural Health Study (n=57,000) who showed long-term effects from chronic exposures without individuals with clinical poisoning.
- Dr. Clement Furlong reported that the consequences of genetic variability in modulating mixed exposure effects depends on PON1 genotypes. This is particularly important given that GW veterans were exposed to up to 12 different pesticides of concern during their deployment. Some individuals could be at particular risk when exposed to multiple similarly acting pesticides at the same time.
- A recent report in a fish model reported that exposure to three OP pesticides (that were all used in the GW) resulted in synergistic toxic effects in these salmon that was greater than the expected additive effects alone (2+2=6).

Part III. Treatment Research Developments

- Treatments can be conceptualized as symptom-based or mechanism-based therapies.
  - Mechanism-based therapies are largely targeted to reduce neuroinflammation and improve mitochondrial functioning and if proven successful, could translate into viable treatments relatively quickly.
  - However, symptom-based therapies are being assessed to relieve common symptoms of GWI including chronic pain, fatigue and sleep disturbance and cognitive complaints.

GWI Treatment Approaches

- Symptom based treatments
  - Acupuncture, laser acupuncture, CPAP, biofeedback, pain medications, nutritional supplements.
- Mechanism based treatments
  - Low Dose Naltrexone (LDN)
  - Mifepristone
  - Carnosine
  - Co-enzyme Q10
  - Minocycline

Part IV. UTSW program

- In Sept. 2009, VA determined that it would not renew the contract with UTSW program. The Committee devoted much of the February 2009 and some of the Nov. 2009 meetings to hearing presentations regarding the preliminary findings from UTSW neuroimaging and preclinical animal research studies.

Part IV. UTSW Program (2)

- Neuroimaging study results
  - Dr. Haley and colleagues reported significant differences on structural MRI scanning as well as functional brain imaging between groups. Neurochemical brain differences were also replicated from prior results using MRS techniques.
  - Although sample sizes were small (n=26) further results with larger sample sizes will further elucidate these preliminary findings.

Part IV. UTSW Program (3)

- Preclinical animal model studies
  - Dr. Haley presented these results at the Nov. 2009 meeting and summarized results comparing the neurological effects of chemicals present in the Gulf War including chlorpyrifos and PB.
  - Preliminary results were reported in relation to memory circuits, autonomic nervous system functioning, dopamine turnover, and development of ALS and brain cancer in animal models.

Part V. Recommendations

RAC Recommendations Regarding new VA Gulf War illness research Program.

- **Comprehensive plan.** Begin with a comprehensive research plan that addresses priority research topics identified in RAC reports. The plan should include information on the objectives and hypotheses of the program and of each study, the design of each study, and how individual studies and components relate to one another.
- **Expert Panel.** Utilize a formal expert panel of scientists from inside and outside VA knowledgeable in GWI and related fields to develop the plan, including some RAC members.
- Place responsibility for **reviewing proposals** and approving what studies to fund in the hands of the same or similar scientists taking into account the relevance to the plan as well as the scientific merit of the proposals.
- **Manage** the program as a coherent whole, under the direction of people committed to solving the problem with expertise directly relevant to GWI.

Part V. Recommendations (2)

- Establish s**ophisticated models for GWI case definitions**
- Re-establish prior **longitudinal cohorts** of Gulf War veterans which could provide sensitivity and power to detect increased rates of neurological illnesses such as primary brain cancer and amyotrophic lateral sclerosis (ALS) and could be utilized to recruit participants for cooperative studies or research programs and for inclusion in the brain-tissue bank.
- Include areas of Gulf War Illness **mechanisms** and potential for **treatment avenues** such as axonal transport mechanisms, glial mechanisms of neuroinflammation and chronic pain, exercise-induced immune parameters, neuroendocrine alterations and hypercoagulation effects.

Further Topics for 2010 meetings

- Glial mechanisms in pain processing and neuroinflammation have been identified as topics for discussion at the 2010 RAC meetings.
- Continued presentations and discussion regarding neuroimaging in GW veterans and animal models are planned.
- Further discussion regarding altered microtubule functioning and axonal transport defects in chronic disease states.
- Newly identified potential mechanism-based treatments will be discussed particularly in regard to modulating glial mechanisms of chronic pain and neuroinflammation as well as modulation of reactive oxygen species (ROS) and improvement of mitochondrial functions.
- Other less specific symptom-based approaches will also be discussed including CPAP for sleep disturbances and traditional and laser acupuncture for pain management and enhanced overall well-being.

Discussion

- Comments?
- Concerns?
- Suggestions?