

Appendix B

January 17, 2006, memorandum from Committee to VA ORD

Research Priorities: VA FY2006 Gulf War Illness Request for Proposals Submitted to VA Office of Research and Development January 17, 2006

Research Advisory Committee on Gulf War Veterans' Illnesses

The Research Advisory Committee on Gulf War Veterans' Illnesses (RAC) is providing the following information in response to a December 13, 2005, request from VA's Office of Research and Development for specific guidance concerning research areas of importance to be identified in VA's 2006 Request for Proposals (RFP) for Gulf War Research.

The following principles and priorities are general in nature, and represent a preliminary summary of Committee recommendations from previous years along with more recent discussions at public meetings. Complete and detailed research findings and recommendations will be finalized and provided to the Secretary later this year in the Committee's 2006 report.

Gulf War Research: Core Research Objectives and Principles

In general, the highest priority Gulf War research studies will address the following objectives:

- Advance efforts to identify beneficial treatments for Gulf War veterans' illnesses either directly by evaluating specific treatments or indirectly by identifying pathophysiological processes potentially amenable to treatments
- Identify measurable differences between symptomatic and healthy Gulf War veterans, particularly specific markers that distinguish individual GWI cases from controls
- Evaluate epidemiologic, clinical, and laboratory parameters in Gulf War veterans stratified into subgroups defined according to exposures, locations, units, or other characteristics potentially associated with the outcome of interest, as opposed to evaluation of all deployed veterans as a single group
- Integrate findings from experimental studies that characterize effects of Gulf War-related exposures with human studies of Gulf War veterans

Studies of Gulf War illnesses should use well-constructed and clearly-described case definitions for Gulf War-associated multisymptom conditions and illness subsets

Proposals whose principal focus is on psychological stress or psychiatric conditions as the primary cause of Gulf War illnesses should not be considered under this RFP.

Priority Gulf War Illness Research Topics

The highest priority Gulf War research studies should address the core objectives previously outlined (i.e., advance knowledge related to treatments, identify objective measures of pathology, evaluate important subsets of Gulf War veterans, and integrate findings in Gulf War veterans with those in experimental studies). Because previous research studies have consistently identified Gulf War-related neurotoxic exposures to be most strongly associated with excess illness in Gulf War veterans, specific research topics of highest priority include:

- Studies that characterize molecular, cellular, systemic, and behavioral effects of individual and combined exposures to neurotoxic substances to which Gulf war veterans were exposed during deployment (e.g., pyridostigmine bromide, low-dose chemical agents, pesticides, insect repellants)
- Comprehensive evaluation of autonomic nervous system function in Gulf War veterans with multisymptom conditions and in illness and/or exposure subgroups
- Epidemiologic studies of rates of diagnosed neurological diseases (e.g., multiple sclerosis, Parkinson's Disease, amyotrophic lateral sclerosis, brain cancer)—as well as CNS abnormalities that are difficult to precisely diagnose—in Gulf War veterans and appropriate comparison groups
- Evaluation of alterations in proinflammatory and inflammatory processes in Gulf War veterans affected by multisymptom conditions; experimental studies that characterize persistent effects of Gulf war-related exposures on proinflammatory and inflammatory processes and their biological mediators in the central nervous system and other target organs
- Studies that investigate biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, for example, associations between Gulf War illnesses and genetic polymorphisms and activity levels of enzymes (e.g. paraoxonase, butyrylcholinesterase, acetylcholinesterase) responsible for uptake and metabolism of Gulf War-related neurotoxic exposures
- Studies that utilize new technologies (e.g., proteomic, genomic, and metabolomic methods) capable of characterizing molecular differences between ill Gulf War veterans and healthy comparison groups
- Studies that utilize technologies capable of identifying markers (e.g. retention of toxins, secondary metabolites) that persist after exposure to Gulf War-related compounds individually and in combination
- Use of state-of-the art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish ill Gulf War veterans (including illness/exposure subgroups) from healthy veterans

Gulf War Research: Other Topics of Importance

- Epidemiologic research utilizing a sample size sufficient to evaluate health outcomes of interest (e.g., rates of symptoms and multisymptom conditions, cancer, reproductive effects) among Gulf War veterans known to have been exposed to depleted uranium in comparison to veterans not exposed to depleted uranium during deployment
- Studies of chronic symptoms and health characteristics of military personnel known to have received individual and combinations of vaccines administered to 1990-91 Gulf War veterans, particularly studies of Gulf War-era veterans for whom reliable vaccine information is available
- Studies of veterans with Gulf War illnesses that evaluate clinical, laboratory, and treatment findings associated with multisymptom conditions in the general population (e.g. fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, irritable bowel syndrome), including comparisons between Gulf War illnesses and these conditions
- Experimental studies that characterize molecular, cellular, systemic, and behavioral effects of compounds to which Gulf war veterans were exposed (e.g., individual and multiple vaccine combinations, depleted uranium, oil fire smoke, jet fuel) individually, and in combination with other exposures of potential concern
- Comprehensive evaluation of immune parameters among Gulf War veterans with multisymptom conditions, including parameters that may differ among illness and/or exposure subgroups
- Use of diverse methods, including serological testing, polymerase chain reaction testing, and lymphocyte challenge tests, to determine whether Gulf War veterans with multisymptom conditions are affected by undetected infectious conditions (e.g. leishmaniasis, mycoplasma fermentans)
- Use of innovative study designs to evaluate risk of specific types of birth defects or other conditions previously suggested to be elevated among children of Gulf war veterans
- Additional utilization of available epidemiologic and clinical data to more clearly characterize associations between illnesses affecting Gulf War veterans and reported or modeled exposures, using analytic methods capable of distinguishing effects of multiple concurrent exposures and combinations of exposures
- Studies of chronic symptoms and other health characteristics of populations known to have been exposed to chemical weapons