

Presentation 9 – William Goldberg

GULF WAR UPDATE



William J. Goldberg PhD
Portfolio Manager
Gulf War Research
Veterans Health Administration
Department of Veterans Affairs

PORTFOLIO CRITERIA



CRITERIA

(with examples)

■ Studies of chronic multisymptom illnesses (CMI) affecting GW veterans and the general population

- **Case definitions of CMI affecting Gulf War veterans**
 - Evaluation of Stress Response Systems in Gulf War Veterans with CMI (Autonomic system and neurohumoral dysregulation in Gulf War veterans)
 - Autonomic Functions of Gulf War Veterans with Unexplained Illnesses ** (Autonomic dysfunction as an underlying cause of unexplained symptoms in GW veterans)
- **Chronic fatigue syndrome**
 - Tissue Factor and Gulf War-Associated Chronic Coagulopathies ** (Impaired blood flow and circulation as a cause of cognitive difficulties, somatic pain, fatigue)
 - Pituitary Adrenal Function in People with Fatiguing Illness (Neurohumoral dysregulation in Gulf War veterans with fatigue)
 - Mechanisms of Immune Dysfunction in Gulf War Illness ** (Immune dysfunction as a mediator of persistent illness in both CFS and ill GW veterans)
- **Fibromyalgia**
- **Irritable bowel syndrome**
 - Pathophysiology of Irritable Bowel Syndrome in Persian Gulf War Veterans ** (Treatment of GW veterans with gastrointestinal symptoms)
- **Multiple chemical sensitivity**

CRITERIA

(with examples)

■ Symptoms occurring with higher prevalence in GW veterans

- **Fatigue**
 - Patterns of Microarray Gene Expression in Gulf War Illness (Changes in gene expression (biomarkers) in Gulf war veterans with fatigue)
 - Pituitary Adrenal Function in People with Fatiguing Illness (Neurohumoral dysregulation in Gulf War veterans with fatigue)
- **Joint and muscle pain**
 - Functional Imaging of Pain in Veterans with Unexplained Muscle Pain (fMRI of Gulf War veterans with musculoskeletal pain)
 - Pain Among Gulf War Veterans: Secondary Analysis of CSP#458 Data (Prevalence, distribution and characterization of acute and chronic pain in Gulf War veterans)
- **Gastrointestinal complaints (dyspepsia, gastritis, diarrhea, etc.)**
 - Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome (Central nervous system control of gastrointestinal pain)
- **Cognitive dysfunction (memory, attention, etc.)**
 - Glucocorticoid Responsivity in Gulf War Veterans (Positron Emission Tomography (PET) of Gulf War veterans - effects of glucocorticoids on memory)
 - Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics (Neurobiological basis of memory and development of new therapies for memory storage and retrieval dysfunction)

CRITERIA

(with examples)

■ Symptoms occurring with higher prevalence in GW veterans

- **Sleep disturbances**
 - Cholinergic and Monoaminergic Influences on Sleep
(Identification of brain circuits that produce wakefulness versus sleep)
- **CNS disorders (neuroimaging studies, ALS, glioblastoma, etc)**
 - Motor Neuron Function of Gulf War Veterans with Excessive Fatigue **
(Loss or damage of motor nerve cells in GW veterans with muscle and joint pain, muscle spasm, or fatigue)
 - National VA Amyotrophic Lateral Sclerosis Research Consortium
(Phase I study of sodium phenylbutyrate (NaPB) as a therapy for ALS)
 - Biomarkers Discovery in ALS
(Identification of biomarkers for ALS in CSF and serum from Gulf War veterans)
 - Genes, Environment, and Oxidative Stress in Neurodegenerative Disorders
(Gene-environment interactions in an animal model of ALS)
 - Estimates of Cancer Prevalence in Gulf Veterans Using State Registries
(Prevalence of cancer (including brain cancers) in Gulf War veterans)
 - Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas
(Development of new therapies for glioblastoma (brain cancer))
 - Structural Magnetic Resonance Imaging in Gulf War-Era Veterans
 - Effects of Gulf War Illness on Brain Structure, Function and Metabolism:
MRI/MRS at 4 Tesla

CRITERIA

(with examples)

■ Health effects of potentially hazardous substances, to which GW veterans may have been exposed to

- **Pyridostigmine bromide**
- **DEET**
- **Permethrin**
 - Proteomic Analysis of Cellular Response to Biological Warfare Agents **
(response of human cells to PB, DEET, permethrin, and/or anthrax vaccine)
 - Direct Delivery of Neurotoxins to the Brain by an Intranasal Route **
(Effects of pyridostigmine bromide, DEET, and permethrin)
 - Neurochemical and Neurobehavioral impact of Pyridostigmine Bromide
Treatment and Stress
(Interaction of physiologic stress and PB exposure on acetylcholinesterase)
- **Oil well fire smoke**
- **Petroleum products (e.g., jet fuels) and combustion products**
- **Multiple vaccinations**

CRITERIA (with examples)

- **Other topics from the 21 research questions**
 - **Prevalence of altered immune function or host defense**
 - > **Mechanisms of Immune Dysfunction in Gulf War Illness ****
(Immune dysfunction as a mediator of persistent illness in both CFS and ill GW veterans)
 - > **T Cell Responses to Multiple Immunizations and Stress**
(Effects of multiple immunizations on immune function)
 - **Exposure to, and prevalence of, leishmania tropica**
 - > **The Diagnosis and Pathogenesis of Occult Leishmaniasis ****
 - > **Vaccination Against Visceral Leishmaniasis with a multi-epitope vaccine**
 - **Physiological responses to biological stress**
 - > **Effect of Hyperthermic Exposure on Susceptibility to Experimental Lung Injury ****
(Effects of stressful conditions on the ability to respond to subsequent stress, infection or injury)
 - **Likelihood/prevalence of experiencing non-specific symptoms and symptom complexes**
 - > **Profile of GW Veterans who Applied for Undiagnosed Illness Compensation ****

PROGRESS ON FY 2004 RECOMMENDATIONS



STATUS REPORT

- **Finding 2: Treatments that improve the health of veterans with Gulf War illnesses are urgently needed**
- **Committee recommends that the Department of Veterans Affairs (VA) immediately establish a comprehensive program specifically tasked with evaluating treatment-related information and research, and developing data and pilot studies as necessary to identify promising candidate treatments for clinical trials for Gulf War veterans' illnesses**
 - Pathophysiology of Irritable Bowel Syndrome in Persian Gulf War Veterans (Treatment of GW veterans with gastrointestinal symptoms)
 - National VA Amyotrophic Lateral Sclerosis Research Consortium (Phase I study of sodium phenylbutyrate as a therapy for ALS)
 - Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS (Therapies to reduce the severity of symptoms in an animal model of ALS)
 - Gulf War Treatment Research Centers (up to 3 to begin funding in FY 2006)

STATUS REPORT

- **Finding 3: A growing body of research indicates that an important component of Gulf War veterans' illnesses is neurological in character**
- **Expand research efforts that utilize magnetic resonance spectroscopy as well as other state-of-the-art neuroimaging technology suited to study brain cell injury and dysfunction ...to better characterize differences between ill Gulf War veterans and comparison groups.**
 - Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla
 - Structural Magnetic Resonance Imaging in Gulf War-Era Veterans
 - Glucocorticoid Responsivity in Gulf War Veterans (Positron Emission Tomography (PET) of Gulf War veterans)
- **Develop a comprehensive research strategy designed to evaluate and expand on the growing body of evidence regarding autonomic dysfunction in ill Gulf War veterans**
 - Autonomic Functions of Gulf War Veterans with Unexplained Illnesses (Autonomic dysfunction as an underlying cause of GWVI)
 - Evaluation of Stress Response Systems in Gulf War Veterans with CMI (Autonomic system and neurohumoral dysregulation in Gulf War veterans)

STATUS REPORT

- **Finding 4: Evidence supports a probable link between exposure to neurotoxins and the development of Gulf War veterans' illnesses**
- **Finding 5: A variety of exposures potentially encountered by military personnel in the Persian Gulf theater have been suggested as possible causes or contributors to Gulf War veterans' illnesses. A broad range of Gulf War-related exposures must be thoroughly evaluated as possible contributors to the development of veterans' illnesses.**
- **The Committee recommends ... expand research efforts to systematically investigate the chronic effects of exposure to neurotoxins encountered during the Gulf War, including possible chronic effects of combinations of Gulf War-related exposures..**
 - Proteomic Analysis of Cellular Response to Biological Warfare Agents (Effects of pyridostigmine bromide, DEET, and permethrin)
 - Direct Delivery of Neurotoxins to the Brain by an Intranasal Route (Effects of pyridostigmine bromide, DEET, and permethrin)
 - Neurochemical and Neurobehavioral impact of Pyridostigmine Bromide Treatment and Stress (Effects of pyridostigmine bromide)
 - T Cell Responses to Multiple Immunizations and Stress (Effects of multiple immunizations on immune function)

STATUS REPORT

- **Finding 6: Epidemiologic studies have provided preliminary indications that ... Gulf veterans may also suffer from elevated rates of diagnosed medical conditions**
- **The Committee recommends that rates of medical conditions and disease-specific mortality among Gulf War veterans be regularly assessed and reported, and that studies be undertaken to actively identify veterans with conditions of particular concern. Specifically, VA should:**
- **Identify ALS cases among Gulf War veterans, and evaluate the potential role of toxic exposures encountered in theater or after the war in the development or progression of this disease**
 - National Registry of Veterans with ALS
- **Undertake epidemiologic studies to determine the prevalence of other serious neurological conditions, including multiple sclerosis (MS), Parkinson's disease, and brain cancers, among Gulf War veterans in relation to appropriate comparison groups.**
 - Estimates of Cancer Prevalence in Gulf Veterans Using State Registries
 - Post War Mortality from Neurologic Diseases in Gulf Veterans, 1991-2004 (Prevalence of brain cancer (including glioblastoma) in Gulf War veterans)

STATUS REPORT

- **Finding 10: Overall progress in addressing Gulf War veterans' illnesses has been delayed by the lack of a well-coordinated federal research effort ... The Committee therefore recommends that VA**
- ... adopt a ... research program that ... addresses key research questions regarding the nature, causes, and treatments for Gulf War veterans' illnesses, utilizing research solicitations that address specific priority Gulf War illnesses research topics
- ... VA should allocate not less than 15 million dollars in each of the next four years in support of a comprehensive and well-managed research portfolio.
- ... The program should be directed by a doctoral-level scientist with appropriate expertise in research directly relevant to Gulf War veterans' illnesses.
- Adopt a mechanism for reviewing and funding ... proposals that takes into account the relevance of proposed projects to identified Gulf War illnesses research priorities Ment review panels should include scientists familiar with ... research on Gulf War veterans' illnesses
- ... regularly review progress on the objectives ... to determine which have been adequately addressed, which should be revised, and which require additional follow-through with new and/or more specific funding announcements

ANNUAL REPORT TO CONGRESS



GULF WAR DATABASE

Combined data from VA, DoD, and HHS



GW Research Priorities

- **Symptoms and General Health Status**
 - Q 1: Prevalence of symptoms/illnesses
 - Q 9: More likely to experience non-specific symptoms and symptom complexes?
 - Q 14: More pulmonary symptoms or diagnoses
 - Q 15: Smaller baseline lung function or greater degree of non-specific airway reactivity
 - Q 20: Greater risk of developing cancers of any type
 - Q 21: Higher mortality rate

GW Research Priorities

■ Exposures (Non-Infectious)

- Q 3: Exposure concentrations to various petroleum products and combustion products
- Q 4: Exposure to occupational/environmental hazards
- Q 5: Exposure to organophosphorus nerve agent and/or sulfur mustard from bombing at Muhammadiyah or weapons bunker at Khamisiyah
- Q 6: Exposure to chemical agent, other than at Khamisiyah
- Q 7: Prevalence of pyridostigmine bromide use
- Q 8: Prevalence of various psychophysiological stressors

GW Research Priorities

■ Brain & Nervous System Function

- Q 16: Prevalence of organic neuropsychological and neurological deficits
- Q 17: Can short term, low level exposures to pyridostigmine bromide, DEET, or permethrin, alone or in combination, cause short-term and/or long-term neurological effects
- Q 18: Prevalence of psychological symptoms and/or diagnoses

■ Immune Function and Infectious Diseases

- Q 2: Exposure to leishmania tropica
- Q 10: Prevalence of altered immune function or host defense
- Q 19: Prevalence of leishmaniasis and other infectious diseases

GW Research Priorities

- **Reproductive Health**
 - Q 11: Prevalence of birth defects in offspring
 - Q 12: Lower reproductive success
 - Q 13: Prevalence of sexual dysfunction

GW Database Coding

- **Project Type**
 - Clinical
 - Development
 - Epidemiology
 - Mechanistic
- **Focus**

GW Database Coding

- **Focus (new 2-tiered scheme)**
 - Project Focus
 - Diagnosis
 - Exposure
 - Interactions
 - Prevention
 - Symptoms
 - Treatment
 - Research Focus
 - Brain and Nervous System Function
 - Chemical Weapons
 - Exposures (Non-Infectious)
 - Pyridostigmine Bromide
 - Immune Function and Infectious Diseases
 - Reproductive Health
 - Symptoms and General Health