

Annual Report
Research Advisory Committee on Gulf War Veterans' Illnesses
December 1, 2006

1. Origin and Membership

The Research Advisory Committee on Gulf War Veterans' Illnesses was first appointed by former Secretary of Veterans Affairs Anthony J. Principi on January 23, 2002, pursuant to Public Law 105-368. Further appointments were made by Secretary of Veterans Affairs R. James Nicholson in October, 2005, and March, 2006. Committee members who served during 2006 are listed in Appendix A. Appointed members of an advisory panel of additional experts are listed in Appendix B.

2. Committee Activities

The Committee held three meetings during 2006: May 15-16 and August 14-15 in Washington, D.C., and November 6-7 in Dallas, Texas. All meetings were open to the public. The first meeting featured presentations by committee members with Gulf War illnesses (GWI) and by committee members and outside investigators on potential mechanisms underlying GWI. The second meeting focused on inflammatory processes in the central nervous system as potential contributing factors in GWI, bringing together leading authorities on the subject. The third meeting featured presentations by researchers from the University of Texas Southwestern Medical Center on GWI research being conducted there. The Department of Veterans Affairs (VA) announced in May that it would establish a research center for GWI at the University of Texas, Southwestern. An agreement formalizing the center was completed in mid-November. Other major topics addressed at 2006 meetings included proteomic and genomic research, and the VA Gulf War Biorepository currently under design.

Research topics discussed in Committee meetings were addressed by multiple investigators in each area. Representatives from VA, the Department of Defense (DoD), and other federal agencies were invited to attend the meetings and participate in discussions with presenting scientists along with Committee members. This structure has

allowed Committee meetings to serve not only as forums for presenting the latest GWI research, but also as a vehicle for advancing that research and disseminating current information to government and government-funded scientists. Meetings also featured regular updates on VA GWI administrative and scientific research activities and on additional published scientific research related to GWI. Time was also reserved each day to allow members of the public to provide comments on the Committee's work and on matters related to GWI.

In January, 2006, the Committee provided to VA's Office of Research and Development (ORD) a document summarizing its recommendations concerning core objectives for VA Gulf War research and specific research priorities relating to the health of Gulf War veterans. These recommendations were provided at the request of ORD to provide guidance concerning research to be funded in 2006 and are attached as Appendix C.

Committee members have been active participants in all aspects of the Committee's work. Meetings have been well-attended throughout the year. In additions, members have devoted substantial time to Committee business outside of meetings.

The Committee has kept VA leadership and ORD informed of its work and its findings on an ongoing basis. This task has been accomplished through attendance and participation of ORD officials at Committee meetings, and regular communications between Committee chairman and scientific director, and the Secretary and ORD.

3. Support Activities

The Committee staff consists of three members including the scientific director, Lea Steele, PhD, an additional research health scientist, and a program specialist. Committee offices are located at VA Eastern Kansas Medical Center in Topeka, Kansas. In addition to ongoing activities relating to monitoring research relating to GWI, preparation of Committee reports, and development of Committee meetings, the staff has primary

responsibility for all Committee administrative activities and management of the Committee's website.

4. Designated Federal Officer

The Designated Federal Officer for the Committee is William Goldberg, PhD, who also serves as manager for the GWI portfolio within the VA Office of Research and Development. Dr. Goldberg's joint role has facilitated regular communications between the Committee and ORD.

5. Accomplishments

VA's establishment of a GWI research center at the University of Texas Southwestern Medical Center (UTSW), with an anticipated funding of \$15 million annually for five years, represents an historic commitment by VA leadership to GWI research. The Committee looks forward to advising and monitoring the work of the center in its ongoing role as advisor to the Secretary. The November Committee meeting in Dallas provided an opportunity to begin this interaction with UTSW researchers. In addition, Dr. Robert Haley, the director of the new center and a former member of the Committee, will continue to attend Committee meetings as the representative of the center and to bring other UTSW researchers with special interest in topics under examination.

In addition, VA ORD continues to conduct internal VA GWI research. An important project begun in 2006 was the VA Gulf War Biorepository, developed in response to recommendations of veterans and the Committee. ORD reported that VA spending for Gulf War research in FY2006 totaled \$13.1 million, including projects funded in previous years. A review of this total, however, indicated that \$4.3 million funded 13 studies of amyotrophic lateral sclerosis (ALS) (only 3 of which have a Gulf War component), \$2.0 million funded studies not relevant to Gulf War service, and \$1.7 million funded studies that relate to stress and psychiatric illnesses. Thus, only \$5.4 million of the expenditures

focused on the chronic multisymptom illnesses that afflict one-quarter of Gulf War veterans.

In a letter to Secretary Nicholson dated September 30, 2005, the Research Advisory Committee expressed concern that the VA Environmental Agents Service had launched several misguided studies by the Institute of Medicine (IOM). As stated in the Committee's 2005 Annual Report: "By restricting the questions asked and/or the research to be considered, these studies invite results that imply Gulf War illnesses are no different from the expected health consequences of any war. These studies continue a pattern of VA and IOM staff misusing the IOM to subvert the will of Congress and mislead the Secretary of Veterans Affairs. For example, the IOM studies will not include toxicology findings from animal research in determining the strength of evidence linking Gulf War exposures to the health of Gulf War veterans, although they are specifically required to do so by law."

The IOM report released in September, 2006, confirmed that these concerns were well founded. Once again, animal studies were not considered in the conclusions, contrary to law and the common sense fact that the vast majority of research on toxic substances must be conducted in animals. Most disturbing, a trivial conclusion of the report that there is no "unique syndrome" (since multisymptom illness also exists in other people), was hyped in the press release and media coverage associated with the report to imply that there is no Gulf War illness.

What is important, of course, is that Gulf War veterans have alarmingly elevated rates of such illness, and, in fact, the report found that Gulf War veterans have high rates of chronic multisymptom illness, as have all other studies. Results from VA's ongoing Longitudinal Health Study of Gulf War Era Veterans show that fully twenty-five percent of Gulf veterans have chronic multisymptom illness over and above the background rate found in their non-deployed counterparts, with fewer than three percent recovering from those conditions since the war.

These figures are a stark reminder of the goal against which VA and other federal Gulf War research should be judged according to the Committee's charter: "to improve the health of ill Gulf War veterans." Regrettably, after five years of operation, neither the Committee nor VA can report progress in achieving this goal. Scientific presentations at 2006 meetings, however, emphasize that the goal is not beyond reach. The research presented at the August meeting was particularly encouraging. It provided state-of-the-art insights concerning the role of central nervous system inflammation in chronic neurological disease and its possible association with Gulf War illnesses, including ways that these processes could be evaluated in ill veterans and potentially treated using medications currently existing or under development.

Of equal importance, VA leadership and Congress have provided adequate funding for VA GWI research as recommended in the Committee's 2004 Report, and VA GWI research has been placed in the hands of scientists committed to the task. Although funding at DoD remains minimal, a similar change has taken place in the management of the small GWI research program there. Thus, when research opportunities are identified, as at the Committee's August meeting, programs are in place to pursue them expeditiously. At long last, research is moving ahead to address the serious health problems of ill Gulf War veterans.

Appendix A
Research Advisory Committee on Gulf War Veterans' Illnesses
2006 Committee Members

Chairman

James H. Binns, former Chairman, Parallel Design, Inc.; former Principal Deputy Assistant Secretary of Defense; Phoenix, Arizona.

Committee Members

Adrian Atizado, Assistant National Legislative Director, Disabled American Veterans; 1990-1991 Gulf War veteran, Washington, D.C.

Carrolee Barlow, MD, PhD, Vice President Biology Research, Brain Cells, Inc., San Diego, California.

Floyd E. Bloom, MD, Professor Emeritus, Molecular and Integrative Neuroscience Department, The Scripps Research Institute, La Jolla, California.

Daniel J. Clauw, MD, Assistant Dean for Clinical and Translation Research and Professor of Medicine, University of Michigan, Ann Arbor, Michigan.

Beatrice A. Golomb, MD, PhD, Associate Professor of Medicine and of Family Preventative Medicine, University of California at San Diego, La Jolla, California.

Joel C. Graves, hospice chaplain and Captain, U.S. Army (Retired); 1990-1991 Gulf War veteran, Lacey, Washington.

Robert W. Haley, MD, Professor of Internal Medicine, Chief of Epidemiology, University of Texas Southwestern Medical Center, Dallas, Texas.*

Anthony Hardie, Executive Assistant, Wisconsin Department of Veterans Affairs; 1990-1991 Gulf War veteran, Madison, Wisconsin.

Marguerite L. Knox, MN, NP, Senior Sales Representative, Teva Neuroscience; 1990-1991 Gulf War veteran, Hopkins, South Carolina.

William J. Meggs, MD, PhD, Professor and Chief, Division of Toxicology, The Brody School of Medicine at East Carolina University, Greenville, North Carolina.

Mary D. Nettleman, MD, MS, Chair, Department of Medicine, Michigan State University, East Lansing, Michigan.

James P. O'Callaghan, PhD, Head of Molecular Neurotoxicology, Toxicology and Molecular Biology Branch, Health Effects Laboratory Division, Centers for Disease Control and Prevention-NIOSH, Morgantown, West Virginia.

Steve Smithson, Deputy Director for Claims Services, The American Legion; 1990-1991 Gulf War veteran, Washington, D.C.

Lea Steele, PhD, Associate Professor, College of Human Ecology, Kansas State University; Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses, Topeka, Kansas.

Hugh H. Tilson, MD, DrPH, Clinical Professor, Public Health Leadership Program, University of North Carolina School of Public Health, Chapel Hill, North Carolina.

Consultant to the Committee

Jack Melling, PhD, Consultant to the United States Government Accountability Office, Vienna, Austria.

* Dr. Haley withdrew from Committee membership in August, 2006

Appendix B

Research Advisory Committee on Gulf War Veterans' Illnesses 2006 Members of the Expert Advisory Panel

Joseph T. Coyle, MD, Eben S. Draper Professor of Psychiatry and Neuroscience, Harvard Medical School, Belmont, Massachusetts.

Eugene M. Johnson, Jr., MD, Professor, Department of Neurology, Washington University, St. Louis, Missouri.

Antonio Sastre, PhD, Principal Science Advisor, Midwest Research Institute, Kansas City, Missouri.

James J. Tuite, III, CEO, ASD Biosystems, Inc., Richmond, Virginia.

Bailus Walker, Jr., MD, MPH, Professor of Environmental and Occupational Medicine, College of Medicine, Howard University, Washington, D.C.

Appendix C

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, 2006, 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 discussion 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 combination of vaccines administered to 1990-91 Gulf War veterans, particularly studies of Gulf War-era veterans from whom reliable vaccine information is available
- Studies of 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