Persian Gulf Veterans Coordinating Board – Research Working Group

Annual Report to Congress – 1997

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Research on Gulf War Veterans’ Illnesses

March 1998
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EXECUTIVE SUMMARY

Introduction

On August 31, 1993, in response to Public Law 102-585, President William J. Clinton named the Secretary of Veterans Affairs (VA) to coordinate research funded by the Executive Branch of the Federal Government into the health consequences of service in the Gulf War. VA carries out its research coordinating role through the auspices of the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board (PGVCB). The Secretaries of the Departments of Defense (DoD), Health and Human Services (HHS), and VA chair the PGVCB.

As part of its coordination role, VA is required to submit to the Veterans’ Affairs Committees an annual report on the results and status of research activities. The Annual Report to Congress for 1997 is the fourth report on research and research activities.

In addition to the federally funded research efforts highlighted in this Annual Report, there are noteworthy research projects funded by sources other than the Executive Branch of the Federal Government. Because this research adds to, and builds upon, knowledge gained through federally funded efforts, the Annual Report for 1997 includes research findings of non-federally funded investigators published in peer reviewed scientific journals since the Annual Report for 1996.

The Annual Report for 1997 provides summaries of recently published research findings, an overview of the evolution and current status of the federal research portfolio on Gulf War veterans’ illnesses, a discussion of significant research-related events and milestones since the Annual Report for 1996, and an overview of federal research management. The Appendix to the Report contains detailed supplemental information including brief descriptions of the research protocols; status and results of all ongoing and completed federally funded research projects; annual funding levels of research projects; abstracts from two major national scientific meetings; solicitations for new research; a strategic plan for research on health effects of low-level exposure to chemical warfare nerve agents; and a status report on development and use of experimental serological tests for leishmaniasis infection.

New Research Results

Since the Annual Report for 1996, a number of new research studies have been published which, along with previous research results, are helping to form a body of knowledge that will lead to reliable models of the health problems of Gulf War veterans. In addition, there have been some valuable preliminary findings reported at major scientific meetings. However, until peer-reviewed these findings must be treated with caution.

Before reviewing some of the findings, it is important to note that all research studies have strengths and limitations. Among the limitations, epidemiological studies are frequently subject to a variety of biases. For example, studies that rely on self-reported symptoms and exposures are subject to recall bias, and studies that rely on self-selected cohorts (such as registry participants) are subject to selection bias. Biases can distort the magnitude of differences between cohorts and affect the strength of associations between exposures and outcomes. Other factors potentially affecting epidemiological outcomes include sample size and response rate.

Research using animal models is also subject to limitations in its applicability to a specific situation for humans. Sources of limitations include extrapolation of biological processes from one animal species to another and extrapolation of experimental dosing regimens (route of administration, amount, and duration) in animals to real human exposure situations.

The presence of limitations in a particular study does not necessarily invalidate its findings or conclusions but must be taken into account in evaluating a study’s overall weight and impact. For this reason, the strengths and limitations of each of the new reports of study findings are cited as a guide for the reader.

Brain and Nervous System

A number of papers focusing on neuropsychological performance, psychological health, and symptoms have been published. Although these studies suggest that a number of symptoms reported by Gulf War veterans may be
explained by psychological distress, evidence suggests that distress cannot explain all of the increased symptom reporting. In addition, new research in post-traumatic stress disorder (PTSD) is shedding new light on the nature, prevention, and treatment of the disorder. These findings will assist all veterans of deployments with this disorder, including Gulf War veterans. It will also contribute to the improvement of health outcomes in veterans of future deployments.

**Chemical Warfare**

Recent follow-up studies of victims of the sarin terrorist attacks in Matsumoto and Tokyo, Japan (two years and six to eight months following exposure respectively) are enhancing our understanding of the potential for long-term sequelae of exposure to sarin. A VA scientist collaborated in some of this work. The importance of these studies is the involvement of documented exposures to sarin. Results suggest that exposures causing immediate health responses may lead to persistent chronic effects in a dose-dependent fashion. These effects may vary from clinically undetectable (except through the use of highly sensitive measurement techniques) to clinically significant with overt signs and symptoms. These effects may not be related to the acutely toxic effects of cholinesterase reductions.

These findings are consistent with a DoD funded study in laboratory rats that reported that after anticholinesterase treatment when cholinesterase levels returned to pre-treatment control levels, learning deficits persisted in the animals. However, the rats studied were quite symptomatic when exposed.

The fact that these studies report long-term responses following acute exposures at levels sufficient to produce immediate observable effects somewhat diminishes the relevance to Gulf War veterans. However, the findings reinforce models of anticholinesterase toxicity that extend beyond the immediate effect and may not be directly related to cholinesterase inhibition.

**Mortality**

Preliminary results from a follow-up of the VA Mortality Study through 1995 show that disease-specific deaths do not occur at any greater frequency among Gulf War veterans than among their non-deployed counterparts. However, deaths by accidents, in particular motor vehicle accidents, are more frequent in Gulf War veterans. Preliminary results of a study examining the latter findings suggest that behaviors such as speeding and not wearing a seat belt may be contributing factors to the increased motor vehicle deaths among Gulf War veterans.

**Reproductive Health**

Two studies on reproductive health from the Naval Health Research Center in San Diego, CA indicate that there is no difference in the rates of birth defects in the offspring of Gulf War veterans compared to their non-deployed counterparts. A major study of discharge records (over 75,000 records) from military medical facilities found no difference in birth defects overall in the offspring of Gulf War veterans compared to non-deployed veterans. A substudy examining the rate of a rare birth defect known as Goldenhar Syndrome did not detect a statistically significant difference between the rate of Goldenhar Syndrome in the offspring of Gulf War veterans compared to non-deployed veterans. Additional studies are, however, continuing to pursue the question of adverse reproductive outcomes in Gulf War veterans.

**Depleted Uranium (DU)**

Preliminary results from a clinical follow-up study at the Baltimore VA Medical Center (VAMC) of 33 Gulf War veterans with embedded DU fragments show neither evidence of renal damage nor any other long-term consequences to date. This clinical study complements two important animal toxicology studies conducted by the Air Force Radiobiology Research Institute that examine cancer and non-cancer endpoints in laboratory animals with embedded DU.

**Symptoms/General Health**

The undiagnosed illnesses of Gulf War veterans are still associated with a collection of self-reported symptoms and conditions that do not fit into a consistent pattern of disease. Consequently, research into the general problem of symptoms and general health status among Gulf War veterans is very important. A number of studies have reported notable findings this year.

Researchers are beginning to better understand the reliability of self-reported symptoms and exposures by conducting test-retest reliability studies, and exposure validation.
studies. Unfortunately, preliminary results suggest that self-reported symptoms and exposures are inadequate measures of health outcomes and exposure for the purpose of epidemiological research. However, these studies will provide information to better interpret the findings of ongoing epidemiological studies that rely on self-reports. Also, these studies underscore the importance for future deployments of better pre-and post-deployment health assessments, and better quantitative exposure measures.

Based on self-reported symptoms and diagnoses relating to physical and mental health, the first completed study of women Gulf War veterans (done by a DoD funded researcher at the University of Michigan) suggests that women veterans may be experiencing some gender specific health problems at a greater rate than women veterans deployed elsewhere in the world during the Gulf War. Ongoing studies may shed additional light on the significance of these findings. Of particular note from this study, however, are the findings related to PTSD among women veterans. The Gulf War deployed women veterans had higher rates of PTSD compared to women veterans deployed elsewhere. Possibly of greater significance is the finding that both the Gulf War deployed women veterans and the women veterans deployed elsewhere had higher rates of PTSD than what would have been expected based on previous studies of mostly male veteran cohorts. This difference underscores the importance of studying the health problems of women in the military. This finding should be further examined in other ongoing studies of women’s health in Gulf War veterans.

**Funding of Federal Research**

The federal research portfolio for Gulf War veterans’ illnesses is diverse in its scope. Federally funded research covers an array of different exposures and health outcomes using epidemiological, clinical, basic, and developmental approaches, in particular vaccine and drug development.

Since 1994 the Federal Government has sponsored 121 research projects (with new projects about to begin) and has committed $115 million in resources to these projects (see Table ES-1). Over half of these projects involve scientists outside of the government. Through February 1998, 39 of the 121 projects have been completed, 78 projects are ongoing, and 4 have been awarded funds that are pending startup. Table ES-2 shows the number of projects completed and the number of newly funded projects by fiscal year since FY’94.

Figure ES-1 shows the trend over time from 1994 through 1998 of the number of active research projects taking different research approaches.

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<th>Table ES-1. Funding for Research FY’94-FY’98</th>
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<td><strong>Department</strong></td>
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<td>DoD</td>
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<td>HHS</td>
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<td><strong>Total</strong></td>
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<th>Table ES-2 Number of New and Completed Projects by Year</th>
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<tr>
<td><strong>Fiscal Year</strong></td>
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<td>1994</td>
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*Projected for all of FY’98  **Does not include projects starting after 3/1/98 nor projects under final negotiation
As the number of active research projects has increased from 32 in 1994 to as many as 90 in 1998, the patterns of investment have changed. The proportion of research projects funded in epidemiology research has appropriately declined while the number of research projects on chemical weapons, both in relative and absolute terms, has markedly increased.

Beginning in 1998 new research will begin to focus on clinical trials for treatment of Gulf War veterans. VA and DoD have invested approximately $10 million in what may be the single largest treatment trial of Chronic Fatigue Syndrome and Fibromyalgia in the United States. In addition to treatment, future research investments will increasingly serve both the needs of Gulf War veterans and those of participants in future deployments.

Figure ES-2 shows the cumulative investment in research across various areas of research focus. The nature of each research funded research project in the portfolio described by up to three focus areas, as appropriate. Figure ES-2 shows the investments according to the primary focus area of each project, and according to all focus areas assigned to each project. The investment of funds has been greatest in the focus areas of the Brain and Nervous System and in Symptoms and General Health. The third largest investment is in the focus area of Diagnosis that is research directed toward characterizing Gulf War veterans’ illnesses, and on specific diagnostic tests such as the research on a serological assay for leishmaniasis.

The distribution of research projects across various research focus areas has changed over time since 1994 as a reflection of the evolution of issues centered on Gulf War veterans’ illnesses. There has been a relatively greater increase over the years of research on chemical interactions, chemical warfare agents and pyridostigmine bromide. These increases are an outgrowth of increased concern over the health risks posed to veterans by exposures to multiple toxic agents at low-levels. It is significant to note that of all potential etiologic agents, the largest investment in research on chemical weapons.

New Research Projects, Initiatives, and Milestones
In addition to new research results, a number of new research projects and initiatives have been started, and some significant milestones
have been reached. Many of the new research projects and initiatives are the direct result of recommendations from a variety of sources including the Presidential Advisory Committee on Gulf War Veterans’ Illnesses (PAC, 1996b), the Institute of Medicine Panel on the Health Consequences of Service in the Persian Gulf War (IOM, 1996), and the RWG (PGVCB, 1995, 1996b)

- DoD funded 12 new research projects on the health effects of low-level exposures to chemical war nerve agent, interactions of multiple chemical stressors, and other new research;

- CDC funded two major cooperative agreements with Boston University and the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School to study in depth the characteristics of Gulf War veterans illnesses and to attempt to develop a case definition;

- The Iowa Study of Gulf War Veterans will be extended to include physical examinations on a subset of participants in the original project;

- The Medical Follow-Up Agency of the Institute of Medicine will conduct an epidemiological investigation of the health of troops potentially exposed to sarin as a result of the demolition of a weapons depot in Khamisiyah, Iraq in March, 1991;

- VA and DoD will begin collaboration on the development and implementation of a multi-site treatment trial for Gulf War veterans with Chronic Fatigue Syndrome and Fibromyalgia;

- VA issued a Program Announcement (an open-ended request for proposals) soliciting proposals for additional treatment trials for Gulf War veterans’ illnesses;

- Following scientific peer-review and programmatic review, VA and DoD will be funding new research projects on the neurobiology of stress;
• DoD is providing funding for follow-up studies of research reported in the *Journal of the American Medical Association* in January 1997 that suggest the presence of neurological problems in Gulf War veterans possibly associated with exposure to neurotoxins;

• Research will attempt to validate a test for mycoplasma infection and, once validated, be used to investigate suggested links among service in the Gulf, mycoplasma infection, and symptoms;

• The Research Working Group developed a *Strategy for: Research on the Health Effects of Exposure to Low-Levels of Chemical Warfare Nerve Agents*;

• VA researchers developed Phase III of the VA National Survey of Gulf War Veterans, which is the last phase of this major population-based survey;

• A plume model was developed and peer-reviewed for estimation of troop exposure to sarin from the Khamisiyah, Iraq demolition;

• The Research Working Group conducted an evaluation of the status of research on serological testing for leishmaniasis; and

• DoD issued a Broad Agency Announcement for $8 million in additional research on the pathogenesis of Gulf War veterans’ illnesses, and on methods to prevent such occurrences in future deployments. Proposals were due February 4, 1998.

• DoD established a dedicated program element for GWVI research beginning in FY ‘99, with FY ‘98 being the transition year. This should improve DoD oversight and expedite Congressional review since program accomplishments, plans and resource information will be centrally documented.

• DoD chartered a Working Integrated Process Team (WIPT) on Deployment Toxicology. The WIPT will review current deployment toxicology initiatives and develop recommendations regarding appropriate DoD-level sponsorship and oversight of related policy issues, doctrinal matters, and requirements generation. Such initiatives are essential for protecting the forces during future deployments.

• DoD incorporated review of DoD-sponsored research on Gulf War veterans’ illnesses in the annual Technology Areas Review and Assessment process. This review is utilized by DoD to obtain advice and recommendations on its science and technology programs and utilizes the expertise of independent technical experts.