

**Statement of
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Department of Veterans Affairs
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Subcommittee on National Security, Emerging Threats, and
International Relations
House Committee on Government Reform
Regarding Research on Gulf War Veterans' Illnesses**

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Mr. Chairman and members of the Subcommittee:

Thank you for providing the Department of Veterans Affairs (VA) this opportunity to discuss the current status of its research program on Gulf War veterans' illnesses. With me today are Mindy Aisen, MD, VA's Deputy Chief Research and Development Officer; and Craig Hyams, MD, VA's Chief Consultant, Occupational and Environmental Health Strategic Healthcare Group.

My testimony today will address four major topics: 1) an update on the status of several major research and treatment studies; 2) promising new initiatives and important ongoing research; 3) VA's assessment of the General Accounting Office (GAO) reports on research related to Gulf War veterans; and 4) an overview of the Veterans Health Administration's collaboration on research and other initiatives with the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC), a congressionally-mandated committee that advises the Secretary of Veterans Affairs.

Background

The United States deployed nearly 700,000 military personnel to the Kuwaiti Theater of Operations (KTO) during Operations Desert Shield and Desert Storm (August 2, 1990, through July 31, 1991). Within months of their return, some Gulf War veterans reported various symptoms and illnesses that they believed were related to their service. Veterans, their families, and VA subsequently became concerned about the possible adverse health effects from various exposures during Operations Desert Shield and Desert Storm.

Of particular concern have been the symptoms and illnesses that, to date, have eluded specific diagnosis. More than 130,000 Gulf War veterans have participated in the two health registries that VA and the Department of Defense (DoD) maintain. Although the majority of the registry participants had readily diagnosable health conditions, we remain very concerned about the veterans whose symptoms could not be diagnosed.

In an effort to better understand the health conditions and health problems experienced by Gulf War veterans, VA, DoD, and the Department of Health and Human Services (HHS) have supported research projects related to Gulf War veterans' illnesses. From FY 1994 through FY 2003 the three Departments have funded 240 projects at a cumulative direct cost of \$247 million. Of these, VA funded 91 projects of these projects — eight in conjunction with DoD — totaling \$53.3 million. The indirect costs for the three Departments for conducting this research (facility, administrative, and operational expenses) are estimated to be \$70 million. In FY 2001 and FY 2002, the Federal Gulf War research portfolio grew by 36 new projects. As of September 2003, 182 of the 240 projects have been completed. All projects and their focus areas are described in detail in annual reports to Congress.

While each Department funds its Gulf War research independently, each closely coordinates its efforts with the others to avoid duplication of effort and to foster the highest standards of competition and scientific merit review for all research on illnesses in Gulf War veterans. The Research Subcommittee of the Deployment Health Work Group, which is a component of the VA/DoD Health Executive Council, currently conducts this coordination. HHS participates in both the Deployment Health Work Group and its Research Subcommittee.

Status Report on VA's Research of Gulf War Veterans' Illnesses

The casualties of war are not limited to the visible wounds of combat, and many veterans have returned from all wars with debilitating health problems. Studies have shown that some Gulf War veterans have reported a variety of chronic and ill-defined symptoms including fatigue, cognitive problems, gastrointestinal, and musculoskeletal problems, at significantly higher rates than the rates reported by non-deployed veterans.

We also know that Army and Air Force veterans who deployed to the KTO have a higher prevalence of the devastating condition amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. VA has sponsored several important research initiatives responding to the needs of these veterans.

Treatment Trials

In 1998, the Office of Research and Development (ORD) began planning for two treatment trials referred to as the "EBT" (exercise-behavioral therapy) and "ABT" (antibiotic treatment) trials. Both addressed similar patient characteristics and were open to all veterans who served in the Gulf War between August 1990 and July 1991. To be eligible for inclusion in the trials, a veteran must have had at least two of three symptoms (fatigue, musculoskeletal pain, and cognitive dysfunction) that began after August 1990 and must have been symptomatic when the study began. In addition, the symptoms must have lasted for more than six months by the time the study began.

ORD conducted the \$9.6 million EBT study between 1999 and late 2001, and 1,092 veterans participated at 18 VA and 2 DoD medical centers. Participants were randomly assigned to one of four 12-week treatment courses. All groups continued their usual health care. In addition, three groups received cognitive behavior therapy (CBT), aerobic exercise, or a combination of the two therapies. CBT teaches patients active techniques for reducing the severity of symptoms and is commonly used to enhance traditional treatments for many chronic illnesses, including cancer, coronary artery disease, asthma, and conditions marked by pain and fatigue. Aerobic exercise has been effective in improving the symptoms and functional status of individuals with chronic fatigue syndrome and fibromyalgia.

The results, reported in the March 19, 2003, issue of the *Journal of the American Medical Association*, showed that CBT, with or without exercise, provides modest but significant improvement in physical functioning, mental health functioning, cognitive symptoms, fatigue, and distress. An accompanying editorial in the journal described the study as "a remarkable achievement" and noted it was one of the largest trials of psychological treatment ever published. EBT remains the only evidence-based therapy for Gulf War veterans with undiagnosed symptoms that has been proven to work.

Enrollment for the ABT trial began in May 1999 and eventually included 491 Gulf War veterans at 26 VA and 2 DoD sites. The study's primary hypothesis was that antibiotic treatment, with doxycycline for 12 months, would improve the health status of patients with chronic symptoms who tested positive for *Mycoplasma* infection at baseline. Secondary hypotheses included that the doxycycline treatment would reduce symptoms of fatigue, pain, and memory problems; and that doxycycline treatment would convert patients who were *Mycoplasma* positive to *Mycoplasma* negative. The trial was completed in December 2001, when patient follow-up was finished.

Although the \$10 million trial did not result in a new treatment modality for Gulf War veterans—the results failed to substantiate any of the hypotheses—the study has enabled investigators to focus their time and resources to other lines of inquiry.

VA has also funded two extremely important epidemiological studies, the National Health Survey of Gulf War Veterans and Their Families; and the ALS Prevalence Study, the largest such study ever conducted.

National Health Survey of Gulf War Veterans and Their Families

The National Health Survey of Gulf War Veterans and Their Families began in 1995 and has provided researchers with much valuable information. The data for the first two phases consisted of self-reported responses to surveys that were mailed to 15,000 Gulf War veterans and 15,000 non-deployed veterans. The survey results have been published and provided to the Subcommittee. Results from the initial two phases of this study show that Gulf War veterans are nearly twice as likely to report diverse symptoms, including joint, muscle, respiratory, gastrointestinal, and skin problems. This population also reports higher rates of chronic fatigue (5.6% for Gulf War veterans vs. 1.2% for non-deployed veterans) and symptoms of post-traumatic stress disorder (12.1% for Gulf War veterans vs. 4.3% for non-deployed veterans).

Phase III recruitment began in November 1998 and concluded in April 2001. Unlike the previous two phases, this study relied on complete physical examinations that included a neurological exam. Veterans received several blood tests, neuropsychological testing, nerve conduction velocity tests, and pulmonary function tests. The study also included the family members of deployed and non-deployed Gulf

War era veterans. Veterans and spouses were examined for illnesses that had frequently been reported by Gulf War veterans in previous studies, namely, chronic fatigue syndrome (CFS), fibromyalgia, post-traumatic stress disorder, neurological abnormalities (including cognitive dysfunction and peripheral neuropathy), arthritis, hypertension, asthma, and chronic bronchitis. Children were examined for birth defects, which were diagnosed through pediatric examinations.

Eventually, 1,061 Gulf War veterans and their spouses and children, and 1,128 non-deployed veterans and their spouses and children participated. Family members included 1,584 spouses (758 of deployed veterans and 826 of non-deployed veterans) and 1,139 children (539 of deployed veterans and 600 of non-deployed veterans). Participants were examined at one of 16 VA medical centers across the United States.

The study found that Gulf War deployment is associated with a significantly increased risk of CFS (5.6% for Gulf War veterans vs. 1.2% for non-deployed veterans) ten years after redeployment. In addition, Gulf War deployment is associated with increased prevalence of PTSD, other psychological disorders, and poorer self-reported quality of life. The study findings do not indicate increased prevalence for objectively measured cognitive impairment.

Researchers also found, among spouses of deployed Gulf War veterans, a higher incidence of PTSD, depression, having at least one psychological disorder, and lower scores on the mental component scale of the SF-36. Researchers found no significant physical health outcomes of clinical concern among spouses of deployed and non-deployed veterans. In addition, the investigators found that Gulf War deployment of a parent is not associated with any significant differences in the frequency of birth defects compared to children of non-deployed veterans.

Amyotrophic lateral sclerosis (ALS) Study

VA's ALS study, conducted in cooperation with DoD, represents the largest prevalence study devoted to that devastating disease. Equally important, the study reflects VA's willingness to respond to its stakeholders. Veterans and advocates consistently inquired whether a connection between ALS and Gulf War service existed.

Although available evidence did not indicate a potential link between the two, VA developed a study that included all 2.5 million Gulf War era veterans.

The study identified and confirmed by medical record review ALS cases occurring over a 10-year period starting from August 1990. Investigators found that among Gulf War veterans, the rate of disease was 6.7 per million. Among other military personnel, it was 3.5 per million.

Since researchers still do not know why Gulf War veterans have a higher rate of ALS, VA has expanded the study to include a national registry for veterans with ALS and a genetic tissue bank (ALS-DNA) for this registry. The goals of the registry are to identify as completely as possible all veterans with ALS, not just Gulf War era veterans, and to provide a mechanism for VA to inform veterans with ALS about clinical drug trials and other studies for which they may be eligible. Enrollment began in April 2003 and has a target of 1,800 patients over a 3-year period. The ALS-DNA bank will involve collection of DNA and plasma from blood samples from consenting ALS registry participants. It is the intent that these materials be made available for future genetic research on ALS. The Veterans ALS Registry has generated great enthusiasm and praise among the national community of ALS researchers.

Promising New Initiatives and Ongoing Research

Although VA and other Federal research have provided valuable insight into Gulf War veterans' illnesses, much remains to be done. New initiatives include an ALS treatment trial, expanded neuroimaging, and a dedicated scientific merit review board for Gulf War and deployment health research proposals.

New Initiatives

VA is currently conducting a review of a proposal for a clinical treatment trial to determine the tolerability and efficacy of sodium phenylbutyrate (NaPB) in research participants with ALS. The study builds on the novel and reproducible findings of a VA investigator. Using ALS mice, the investigator has determined that NaPB, a compound used safely in humans for years, produces a substantial increase in survival in the ALS

mice. The present proposal has been submitted and a review committee will evaluate the submission before a funding decision is made.

A team under the direction of Michael Weiner, MD, at the San Francisco VA Medical Center has begun another project involving neuroimaging. Using a 4-Tesla magnetic resonance imaging – magnetic resonance spectroscopy system that the San Francisco VAMC purchased through grants from DoD and the National Institutes of Health, Dr. Weiner will conduct research to detect any brain changes associated with Gulf War veterans' illnesses and to determine possible relationships with ALS. In addition, this imaging center will act as a coordinating center for future multi-site studies of deployment-related neurodegenerative diseases throughout the VA system.

VA has taken other steps to increase the quantity and quality of Gulf War research proposals. Working closely with the chairman and scientific director of the RAC, VA will divide the current request for proposals (RFP) for Gulf War veterans' illnesses and deployment health into two new RFPs—one for Gulf War research and the other for health consequences of military deployments. The new RFPs will be released this autumn and will provide greater clarity for potential investigators.

In addition, VA issued a special request for applications (RFA) specifically for Gulf War research in April 2004. This RFA will fund meritorious proposals that include, but are not necessarily limited to, immunological changes that may be associated with the unexplained illnesses reported by Gulf War veterans; autonomic changes that may be associated with symptoms reported by Gulf War veterans; and the prevalence of neurological disorders in Gulf War veterans. In 2004, VA has endeavored to work very closely with the RAC to identify internationally acclaimed researchers and encourage them to bring their scientific expertise to bear on the pathophysiology of neurotoxin exposure related illness. I would like to acknowledge the help the RAC has given VA in this area.

Also reflecting our commitment to studying and identifying treatments for the health consequences of service in the KTO and other military deployments, the Veterans Health Administration has requested that Secretary Principi approve a new scientific merit review board within the Office of Research and Development (ORD). The new board will review and evaluate all proposals dealing with Gulf War veterans'

illnesses and deployment health. Through review by a scientific merit review board dedicated to Gulf War research proposals, these proposals will not have to compete for funding with more than a thousand other proposals that VA's other four scientific merit review boards consider each year. I am confident that this step will enable VA to improve the relevance, scientific merit, and quality of such proposals.

Ongoing Research

VA has also contributed to on-going efforts to understand the health consequences of service in the KTO. VA is funding the Gulf War Health Effects studies that the Institute of Medicine (IOM) has been conducting. Two volumes have already been published. Volume 1, released in 2000, examined the potential effects of depleted uranium, pyridostigmine bromide, sarin, and vaccines. In 2003, IOM released Volume 2, a literature review of insecticides and solvents. Although neither volume found any evidence of an association with Gulf War veterans' illnesses (several solvents were linked to a few specific cancers), VA still funds research germane to these areas to ensure that nothing has been overlooked.

Work on Volume 3—Selected Environmental Agents, Pollutants and Synthetic Chemical Compounds—is underway, and the volume should be published in August 2004. In addition, VA commissioned IOM to conduct an update on the Gulf War Health Effects of sarin.

VA continues to fund an invaluable clinical health surveillance of Gulf War veterans who received large exposures to depleted uranium (DU) oxides as a result of friendly fire incidents. Approximately one-third of the 70 surveillance participants, have retained DU fragments that cannot be removed due to medical considerations and have had significantly higher exposures than other service members who served in the KTO. Testing of all participants to date has found no differences in the frequency of musculoskeletal, cardiovascular, psychiatric, nervous system, or other disorders. Although the kidney is the putative critical organ for uranium toxicity under acute and chronic exposure conditions, no evidence of renal dysfunction has been found. Of note, none of the participants' offspring have birth defects, a rate far better than the national

norm. Despite these favorable outcomes, VA will continue to fund this surveillance to monitor for any potential DU-related long-term health problems.

The surveillance program offers DU screening for any KTO and Operation Iraqi Freedom veterans with concerns about potential exposures. Several hundred screens have been performed without any veteran being found with elevated levels of DU.

In addition, VA epidemiologists have been conducting a cancer prevalence pilot study to determine the feasibility of using state cancer registries. Previous studies have focused on cancer mortality, and the results have been reassuring. Gulf War veterans have not experienced elevated rates of cancer deaths. However, not all cancers are fatal although they may cause grievous long-term effects. Since many states maintain registries for fatal and non-fatal cancers, VA has examined those of six states (including California, Florida, Maryland, New Jersey, Texas, and Virginia) and the District of Columbia to determine whether such registries can be used to ascertain whether any differences in cancer rates exist between deployed and non-deployed Gulf War era veterans. The pilot study indicates that state registries can address this question. VA is now considering how best to expand and fund this project.

GAO Report on Research Related to Gulf War Veterans

In its draft report, “Federal Gulf War Illnesses Research Strategy Needs Reassessment (GAO-04-767)”, GAO states that VA “has not analyzed the latest Gulf War research findings to identify whether there are gaps in current research or to identify promising areas of future research.” “In addition,” GAO states, “VA has not reassessed the extent to which the collective findings of completed Gulf War Illnesses research projects have addressed key research findings.” GAO’s proposed recommendations include that VA take the following actions:

- conduct a reassessment of the Gulf War illnesses research strategy to determine whether the 21 key research questions have been answered, whether they remain relevant, and whether there are promising areas for future research;
- ensure that a liaison who is knowledgeable about Gulf War illnesses research is appointed to routinely share information with the Research Advisory Committee

(RAC), and ensure that VA's research offices collaborate with the RAC on the development activities for the Gulf War illnesses research program.

In general, we agree with these two recommendations, and, in fact, had already begun to address the issues prior to learning what recommendations GAO would propose.

Two weeks prior to the team's debrief, VA began its assessment of the existing Federal Gulf War veterans' illnesses research strategy to ensure its continued validity and to identify promising areas for future research. Each of the 21 research questions will be thoroughly evaluated to determine which ones have been answered, which ones require additional study, and what new questions should be added. To date, reviews of four questions have been done. Once its initial assessment is completed, VA will present it to the RAC and to the Research Subcommittee of the Deployment Health Working Group for their comment.

VA has also taken numerous steps to ensure that an effective relationship exists with the RAC. The Deputy Chief Research and Development Officer and I regularly communicate with the RAC chairman, Mr. Binns. Since February 2004, we have had a designated liaison to the RAC scientific officer. However, since our liaison also has other duties, we hope to recruit a full-time health science PhD in the near future to serve as liaison to the RAC and as portfolio manager for Gulf War and deployment health studies.

In addition, VA coordinated its most recent Gulf War RFA with the committee and will do the same with the planned Gulf War veterans' illnesses RFP for autumn 2004. The RAC provided valuable recommendations, and while our coordination efforts may not have been seamless, we believe that they have improved significantly over the past two years.

GAO Report on U.S. Troops Exposure to Chemical Warfare Agents

I would also like to briefly address a second recent draft GAO report (GAO-04-159), which evaluates DoD's conclusions about U.S. troops exposure to chemical warfare (CW) agents following demolition of Iraqi facilities at Khamisiyah in March 1991.

These conclusions were based on GAO's analysis of the DoD and Central Intelligence Agency plume modeling. It was GAO's finding that the models were not fully developed for analyzing long-range dispersion of CW agents and that the model's assumptions on source term data were inaccurate. Accordingly, GAO recommended that VA and DoD not use the plume-modeling data for future epidemiological studies. VA has concurred with this recommendation and will not use the plume modeling for future research studies on Gulf War veterans' illnesses.

Collaboration with the Research Advisory Committee on Gulf War Veterans' Illnesses

VA is very pleased with recent efforts with the RAC to lay the groundwork for improved collaboration.

By way of recent example, at the urging of the RAC, VA contacted a foreign investigator who had developed a novel bioassay for measuring acetyl cholinesterase (AChE) activity to determine the feasibility of conducting a study with VA researchers. The resulting project analyzed previously collected blood samples from deployed and non-deployed Gulf War era veterans to test three hypotheses: (1) blood AChE levels are associated with mood and anxiety disorders; (2) deployed Gulf War veterans have lower blood AChE levels than non-deployed veterans; and (3) veterans with symptoms of Gulf War veterans' illnesses have lower AChE levels than veterans without. As often occurs in scientific investigations, the study did not substantiate any of the hypotheses. However, the study enhanced VA and RAC relations.

In addition to the steps already outlined earlier in my testimony, VA and the RAC have agreed to several other steps to improve the quality of VA's Gulf War research portfolio. The RAC will recommend scientific experts to serve as research review panel members of the soon to be established scientific merit review board. In addition, VA will consult with the RAC regarding the relevancy of proposals that have been identified as being fundable. As I indicated earlier, VA and the RAC will also work together to identify researchers who can partner with VA investigators. Already this effort has shown promise. Due to the efforts of the RAC chairman, VA is now in contact with Dr. Paul Greengard, a Nobel laureate, to conduct research on the effects of subacute

exposures to sarin, a nerve agent to which perhaps 100,000 Gulf War veterans were exposed.

Conclusion

Mr. Chairman, let me conclude by emphasizing the following points:

- VA has an extensive Gulf War research history, ongoing epidemiological studies, expanding research initiatives, and a robust Gulf War Research portfolio.
- VA has taken positive steps to address the proposed recommendations in the two GAO reports on research related to Gulf War veterans.
- VA has taken positive steps to improve collaboration with the RAC.
- As VA's and other Federal research programs continue to provide more results, we will substantially increase our understanding of Gulf War veterans' illnesses. This will enhance our ability to diagnose and treat them.
- All newly gained knowledge will enhance prevention and intervention in illnesses of service members in future deployments.
- This knowledge will also increase our ability for research to improve the health and welfare of those who served our country in the Gulf War.

Mr. Chairman, this concludes my testimony, and I am ready to answer any questions that you and the other subcommittee members might have.