

JOEL KUPERSMITH, MD CHIEF RESEARCH AND DEVELOPMENT OFFICER
DEPARTMENT OF VETERANS AFFAIRS

WRITTEN STATEMENT OF
JOEL KUPERSMITH, MD
CHIEF RESEARCH AND DEVELOPMENT OFFICER
DEPARTMENT OF VETERANS AFFAIRS
BEFORE THE
UNITED STATES
SENATE COMMITTEE ON VETERANS' AFFAIRS
SEPTEMBER 25, 2007

Mr. Chairman and members of the Committee, thank you for the invitation to appear before you today to discuss the Department of Veterans Affairs (VA) Persian Gulf War research programs. I appreciate this opportunity to discuss the vital role VA research has in ensuring the health and well-being of our Nation's veterans. With me is Dr. Timothy O'Leary, Director of Biomedical Laboratory and Clinical Science Research and Development. I would like first to give a brief overview of the VA research program.

Overview of the VA Research Program

Dating back more than 80 years, VA research has responded to veterans' needs with landmark contributions to medicine. VA investigators have led the way in developing the cardiac pacemaker, pioneered concepts that led to the development of the CAT scan and improved artificial limbs. VA investigators are distinguished as among the best in their field with three Nobel Laureates and six Lasker Award winners. VA research is a valuable investment with remarkable and lasting returns.

Because more than 70 percent of VA researchers are also clinicians who take care of patients, VA is uniquely positioned to move scientific discovery from investigators' laboratories to patient care. In turn, VA clinician-investigators identify new research questions for the laboratory at the patient's bedside, making the research program one of VA's most effective tools to improve the care of veterans. The fundamental goal is to address the needs of the entire veteran population from the young recruit who returns with injuries from recent conflicts to the aging veteran, and to use research findings proactively to benefit the future veteran.

It is important to note that VA has implemented a substantial and comprehensive research agenda to develop new treatments and tools for clinicians to ease physical and psychological pain, improve access to VA healthcare services and address the full range of health issues of Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF) veterans.

VA research is an intramural program that is also fully integrated with the larger biomedical research community through VA's academic affiliations and collaborations with other organizations. VA scientists partner with colleagues from other Federal agencies, academic medical centers, nonprofit organizations and commercial entities nationwide, further expanding the reach and scope of VA research.

While the focus of VA research is on benefiting current and future veterans, it also impacts veteran families and caregivers, VA healthcare providers, Veterans Service Organizations, other components of the Federal research establishment, academic health centers and practitioners of healthcare across the country. Ultimately, VA research impacts the entire Nation.

Let me now discuss VA's Persian Gulf War research programs.

Background

In response to Iraq's occupation of Kuwait in August 1990, the United States deployed military personnel to Southwest Asian in support of Operations Desert Shield and Desert Storm. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,841 military personnel from all five services to the Kuwaiti Theater of Operations (KTO).

During and after their return from the KTO, a proportion of Gulf War veterans reported a range of chronic symptoms and health problems at rates that exceeded non-deployed era veterans. These symptoms include: persistent headaches, joint pain, extreme fatigue, muscle pain, cognitive problems, gastrointestinal difficulties, sleep disturbances and skin abnormalities.

As of November 2004, more than 30 percent of veterans who served in the 1990-1991 Gulf War had been service-connected for conditions associated with their military service, although fewer than 3,300 had been service-connected for the special "undiagnosed illness" category established for Gulf War veterans. It is recognized that there exists a much larger number of Gulf War veterans with multiple, chronic symptoms who have not sought or received service-connected status.

Overview of the Federal Research Portfolio on GWVI

In an effort to better understand the health conditions and health problems experienced by Gulf War veterans, VA, the Department of Defense (DoD) and the Department of Health and Human Services (HHS) have supported numerous research projects related to Gulf War veterans' illnesses (GWVI). As of September 30, 2006, the three Departments have funded a total of 330 distinct projects pertaining to the health consequences of military service in the Gulf War, as described in Annual Reports to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses, totaling \$314 million. VA has funded 153 of these projects - eight in conjunction with DoD - totaling \$84.8 million. As of the close of FY 2006, 223 projects (68 percent of the 330 projects) were completed and 107 projects (34 percent) were new or ongoing.

The federal research portfolio on GWVI can be generally divided into five research focus areas:

- Brain and Nervous System Function (e.g., studies on neurological or psychological deficits and/or alterations);
- Environmental Toxicology (e.g., studies focused on specific environmental exposures such as pesticides, oil well fires, jet fuel, vaccines and medical prophylactic agents);
- Immune Function and Infectious Diseases (e.g., studies on alterations in immune function, host defenses or detection and treatment of infectious diseases);
- Reproductive Health (e.g., studies on sexual or reproductive dysfunction); and
- Symptoms and General Health (e.g., studies on pulmonary disease, cancer, chronic multisymptom illnesses and mortality).

While each Department funds its GWVI 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 GWVI. The Research Subcommittee of the interagency Deployment Health Working Group currently conducts this coordination and compilation of the Annual Reports to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses.

Status of the VA Research Portfolio on GWVI

In FY 2006, VA supported 67 GWVI research projects for a total of \$12.9 million. Nineteen of these were new projects examining brain and nervous system function, environmental toxicology, immune function and infectious diseases and symptoms and general health. VA is projecting a direct expenditure of \$6.8 million for new and ongoing research projects in FY 2007. The expenditures in FY 2006 and FY 2007 are in addition to the allocation of \$15 million per year to support a contractual agreement with the University of Texas Southwestern Medical Center for research related to illnesses affecting Gulf War veterans.

The VA Gulf War research program has been at the forefront of the field from the outset. In 1995, VA initiated The National Health Survey of Gulf War Veterans and Their Families. The first two phases of this study used surveys of self-reported symptoms mailed to 15,000 Gulf War veterans and 15,000 non-deployed veterans to demonstrate that Gulf War veterans were nearly twice as likely to report diverse symptoms, including joint, muscle, respiratory, gastrointestinal and skin problems. This population also reported higher rates of chronic fatigue (5.6 percent for Gulf War veterans vs. 1.2 percent for non-deployed veterans) and symptoms of post-traumatic stress disorder (PTSD) (12.1 percent for Gulf War veterans vs. 4.3 percent for non-deployed veterans). The final phase of the study, which completed recruitment in 2001, relied on complete physical examinations (including a neurological exam) of 1,061 Gulf War veterans and 1,128 non-deployed veterans and found that Gulf War deployment was associated with a significantly increased risk of chronic fatigue syndrome (5.6 percent for Gulf War veterans vs. 1.2 percent for non-deployed veterans) ten years after redeployment. In addition, Gulf War deployment was associated with increased prevalence of PTSD, other psychological disorders and poorer self-reported quality of life. The study findings did not indicate increased prevalence for objectively measured cognitive impairment. Researchers found no significant physical health outcomes of clinical concern among spouses of deployed or non-deployed veterans. In addition, the investigators found that Gulf War deployment of a parent was not associated with any significant differences in the frequency of birth defects compared to children of non-deployed veterans.

In 1998, VA 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, the symptoms must have persisted for more than six months and they must have been symptomatic when the study began.

VA 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. All groups continued their usual healthcare. In addition, three groups received cognitive behavior therapy (CBT), aerobic exercise or a combination of the two therapies. 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.

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 failure to substantiate any of the hypotheses has enabled investigators to focus their time and resources to other lines of inquiry.

VA also supported a recent study led by Dr. Seth Eisen, now Director of VA's Health Services Research and Development Service, to assess and compare the prevalence of fibromyalgia, chronic fatigue syndrome, skin conditions, dyspepsia, physical health-related quality of life, hypertension, obstructive lung disease, arthralgias and peripheral neuropathy in a group of deployed and non-deployed Gulf War veterans. The study concluded that ten years after the Gulf War, the physical health of deployed and non-deployed veterans is generally similar, with four of the conditions studied found to be more prevalent among deployed than non-deployed veterans: fibromyalgia, chronic fatigue syndrome, skin conditions and dyspepsia. There were no significant differences between deployed and non-deployed veterans related to the other studied conditions.

VA's commitment to funding clinical trials to identify new therapies for ill Gulf War veterans continues to this day. Three pilot clinical trials are currently underway to examine two new therapies for sleep disturbances and gastrointestinal problems, and to test the feasibility of performing CBT via telephone with Gulf War veterans; CBT was found to provide modest but significant improvement in physical functioning, mental health functioning, cognitive symptoms, fatigue and distress in the earlier exercise-behavioral therapy trial done on an in-patient basis.

Another major focus of the current Gulf War research portfolio is to identify objective markers (i.e., biomarkers or tests) that can distinguish ill Gulf War veterans from their healthy counterparts. Such biomarkers serve two vital purposes. First, they may provide critical clues to understand mechanisms responsible for how and why these veterans are ill. Second, they may provide objective measures for testing the effectiveness of new therapies. VA currently funds 12 such projects, ranging from genetic markers, to advanced neuroimaging procedures, to altered protein profiles in blood or cerebrospinal fluid.

Accordingly, VA supports a broad research portfolio composed of studies dedicated to understanding chronic multi-symptom illnesses, long-term health effects of potentially hazardous

substances to which Gulf War veterans may have been exposed to during deployment and conditions or symptoms that may be occurring with higher prevalence in Gulf War veterans.

Recently, the Institute of Medicine reviewed the available published literature and concluded that Gulf War and other combat veterans may be at increased risk for amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) as a result of their service. Of the studies included in this review, the largest prevalence study devoted to that devastating disease was one funded by VA in cooperation with DoD. The study, which included all 2.5 million Gulf War era veterans, 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 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. VA continues to fund other ALS research, including clinical trials and animal model of the disease, to study potential disease mechanisms and test new therapies.

Because of persistent concerns about the risk of multiple sclerosis (MS) and brain cancer in Gulf War veterans, in 2008 VA will begin a large study to identify the date of onset and clinical subtype of all Gulf War MS service-connected cases between 1990 and 2006. This study will also attempt to quantify the risk for developing MS in Gulf War veterans deployed to the combat theater versus those not deployed, as well as the risk for developing MS in Gulf War veterans potentially exposed to smoke from oil well fires or sarin. Another project is examining the overall and cause-specific mortality risk of ALS, MS or brain cancer in a group of more than 620,000 Gulf War veterans and assessing the in-theater exposure characteristics associated with those deaths. VA supports several additional projects examining MS, as well as basic science and rehabilitation research centers with a focus on MS. Further, VA has established a Gulf War brain bank to collect and store postmortem specimens for future investigations.

Collaboration with the Research Advisory Committee on GWVI

It is important to note that VA research continues to have a positive working relationship with the Research Advisory Committee on GWVI (RAC), a congressionally-mandated committee that advises the Secretary of Veterans Affairs. In response to advice provided by the RAC, VA research has performed an annual portfolio review to ensure the appropriateness of all projects contained in the portfolio. The RAC's advice has also been sought when designing new Requests for Applications to solicit additional research proposals from VA investigators; the RAC was also consulted for recommendations of appropriate reviewers of these proposals.

The efforts by the RAC have improved the VA GWVI research portfolio and continue to bring us closer to finding new treatments for ill Gulf War veterans. The dedicated service by RAC members in support of veterans who served in the Gulf War is greatly appreciated.

Early on, VA recognized the need to assure training of our healthcare providers to allow them to best respond to the specific healthcare needs of Gulf War veterans. With that in mind, and in collaboration with DoD, VA clinicians developed two Clinical Practice Guidelines that give VA

healthcare providers access to the best medical evidence for diagnoses and treatment. VA clinicians also developed a study guide to provide information about the problems and concerns of Gulf War veterans and information about VA programs to help these veterans. Cumulatively, from October 1990 through October 2004, VA clinicians provided high quality inpatient and outpatient care to 335,558 Gulf War veterans, or nearly half of the service members deployed to that conflict.

Conclusion

In conclusion, VA remains committed to funding scientifically meritorious research projects that improve our understanding of GWVI and enhance our ability to diagnose and treat ill Gulf War veterans. Moreover, the knowledge we gain from these efforts may improve our ability to prevent and treat illnesses affecting participants of current and future deployments.

Mr. Chairman, that concludes my statement. I am pleased to respond to any questions you or the Committee members may have.

Thank you.