

**DEPARTMENT OF VETERANS AFFAIRS
VETERANS HEALTH ADMINISTRATION
WASHINGTON DC 20420**

**OFFICE OF RESEARCH AND DEVELOPMENT
PROGRAM ANNOUNCEMENT**

DEPLOYMENT HEALTH RESEARCH

1. Purpose. The Veterans Health Administration (VHA) is expanding its systematic approach to linking research and practice in the epidemiology, diagnosis, treatment, and prevention of deployment-related illnesses. Designated research funds are available to support research focused on potential long-term health effects of exposures and risk factors among veterans of hazardous deployments, such as the Gulf War, Project SHAD, Bosnia/Kosovo, or Afghanistan. This is an initiative of the Office of Research and Development (ORD), Department of Veterans Affairs (VA). ORD recognizes five major research categories related to deployment health as priorities:

- Long-term health impacts of hazardous deployments
- Health impacts of specific military occupational and environmental exposures
- Improvements in evaluation and diagnosis of deployment-related illnesses
- Improvements in treatment of deployment-related illnesses
- Health risk communication for veterans and health care providers

All research services will accept appropriate proposals under this solicitation (Medical Research Service, Health Services Research and Development Service, Rehabilitation Research and Development Service, and the Cooperative Studies Program).

2. Eligibility. Investigators who hold a paid VA appointment of at least 5/8 time are eligible to apply.

3. Background. Deployments often present unique and difficult challenges for active-duty service members and veterans. Service members may experience physical or psychological illnesses and injuries from a variety of factors, such as combat, environmental and climatic extremes, endemic infectious diseases, non-battle injury (such as motor vehicle accidents), and toxic environmental exposures. The Department of Defense (DoD) defines deployment as any duty in the armed forces that involves an operation, location, command, or duty that is different from the military member's normal duty assignment. Military members meet deployment criteria anytime they enter an environment for operational deployment or are stationed in a hostile territory. Deployments can be to a well-supported foreign military base in a developed country, a field setting in an urban or rural part of a developing country, or on a ship visiting foreign ports.

Deployment missions vary widely and can include joint and coalition force exercises (war games), construction projects, humanitarian assistance, refugee relief, peacekeeping, low-intensity conflict, and war. During the past decade, U.S. troops have been deployed to overseas military operations other than war much more frequently than ever before. Frequently, reserve and National Guard troops have been activated for as long as two years to participate in these overseas deployments. During the same period, members of the National Guard have been increasingly deployed within the U.S. to conduct operations such as fighting forest fires, providing disaster relief, supporting border patrol and drug interdiction operations, and assisting with counter-terrorism actions, such as providing security at airports.

Because of this increased frequency of deployments, coupled with a significant downsizing of the active-duty force over the past decade, service members have faced potentially hazardous environments with increasing regularity. This makes it more imperative that ORD expand its research program on military occupational and environmental exposures, in order to fill gaps in knowledge and practice. The results of this research program should provide useful guidance in improving the medical care of veterans who have returned from hazardous deployments, and in improving force health protection efforts in current and future deployments. Force health protection is the umbrella term that DoD now uses that includes a variety of preventive medicine efforts.

4. Scope of ORD Research Interests. Since the Gulf War, many scientific and governmental committees have identified research needs related to improvements in the health of active-duty members and veterans. Some organizations that have made research recommendations related to deployment health and force health protection include:

- Presidential Advisory Committee on Gulf War Veterans' Illnesses (1996)
- Special Investigation Unit of the Senate Veterans' Affairs Committee (1998)
- National Science and Technology Council of the Executive Office of the President (1998)
- Joint Chiefs of Staff, Medical Readiness Division (1999)
- Institute of Medicine Committee on Strategies to Protect the Health of Deployed U.S. Forces (2000)
- VA Research Advisory Committee on Gulf War Veterans' Illnesses (2002)
- President's Task Force to Improve Health Care Delivery for Our Nation's Veterans (2002)

Further information on the reports published by these organizations is provided in Appendix A. The hazards of each deployment are different, but there are some common factors:

- extremes of climate (ranging from very hot and humid to very cold);
- high altitude (defined as over 6,000 feet by DoD);
- risks of serious injury during combat and other life-threatening situations;
- risks from casualty care (for example, transfusion-related hepatitis C);

- physiological and psychological stressors, including long working hours, sleep deprivation, inadequate nutrition, heavy manual labor, exposure to industrial chemicals (for example, solvents or pesticides); and exposure to extremes of human suffering or death of military members and civilians;
- endemic infectious diseases, including food- and water-borne diseases (for example, hepatitis A, bacterial diarrheas, typhoid fever, schistosomiasis); vector-borne diseases (for example, malaria, Dengue fever, plague, typhus); and from contact with displaced persons and prisoners of war (for example, tuberculosis);
- medical countermeasures to biological warfare agents (such as anthrax vaccine and smallpox vaccine); medical countermeasures to chemical warfare agents (such as pyridostigmine bromide); and medical countermeasures to endemic infectious diseases, including vaccinations and malaria prophylaxis;
- austere living conditions, including regions without electricity or running water;
- and worries about home, financial, or family problems; new onset or exacerbation of existing family problems and strains on family relationships; heightened interpersonal problems as a result of sudden changes within the family, both at the time of deployment and return.

The possible long-term health effects of each deployment are different, but there are some recurring patterns of illness. The sequelae from chronic infectious diseases, traumatic injuries, and chronic physical and psychological symptoms can lead to significant long-term disability. Several recent deployments have led to risks of endemic infectious diseases, including the Gulf War, Bosnia, and Afghanistan. Infectious diseases with a chronic course or delayed onset include malaria, tuberculosis, hepatitis B or C, leishmaniasis, and schistosomiasis. Emerging infectious diseases are reported each year that could cause deployment-related illnesses, and improved surveillance with new techniques is needed to better understand and treat symptomatic and occult infections. In addition, veterans have raised concerns about the long-term health effects of medical countermeasures, such as the use of pyridostigmine bromide during the Gulf War, the use of anthrax vaccine during subsequent deployments to Southwest Asia, the use of tick-borne encephalitis vaccine in Bosnia, and the use of Lariam (mefloquine) during the deployment to Afghanistan.

Serious trauma can result from combat, peacekeeping activities, such as removal of landmines, and non-battle injuries, such as a helicopter or truck crash. Chronic physical symptoms, which have been medically-unexplained, have been documented after each conflict for more than a century. In 1996, a historical review of the medical literature was published, which described illnesses after wars since the U.S. Civil War. Veterans of the Civil War, World War I, and World War II frequently reported several central nervous system symptoms, including fatigue, headaches, dizziness, disturbed sleep, forgetfulness, and difficulty concentrating. The rates of chronic fatigue syndrome and fibromyalgia, two poorly-understood illnesses, have been significantly increased in Gulf War veterans in several studies. Chronic psychological symptoms also have been documented after several wars, including posttraumatic stress disorder (PTSD), major depression, anxiety disorders, and alcohol and substance abuse.

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VA currently funds many research projects that are related to military occupational and environmental exposures. For example, VA has a long history of rehabilitation research to improve treatment for veterans with traumatic injuries, such as amputations or spinal cord injuries. Several research programs focus on endemic infectious diseases such as drug-resistant malaria, multiple-drug-resistant tuberculosis, hepatitis B and C, leishmaniasis, and schistosomiasis. These programs include the development of more sensitive or more rapid diagnostic methods, and new treatments. Also, many projects focus on the psychological effects of combat, including PTSD and major depression.

VA, DoD and the Department of Health and Human Services (HHS) have collaborated extensively on research related to illnesses in Gulf War veterans since 1994. VA, DoD, and HHS have funded 224 research projects, at a cumulative expenditure of \$213 million for fiscal years 1994 to 2002. As of September 30, 2002, 159 (71%) of these projects have been completed. All projects and their progress to date have been described in detail in *Annual Reports to Congress*, for the years 1994 to 2001. Reports for the years 1997 to 2001 can be accessed on the Internet at www.va.gov/resdev

Because of the maturity of the Gulf War illnesses portfolio, some definitive conclusions can be drawn related to several research questions, based on the integration of results of many completed projects. For example, there is no general increase in the rates or types of serious illnesses that would lead to hospitalizations in Gulf War veterans, compared to non-deployed veterans. These conclusions are listed in Appendix B. However, several key research questions remain to be fully answered. For example, some Gulf War veterans have reported symptoms of memory problems, difficulty in concentration, and mood changes. A few studies have used comprehensive neurological testing to evaluate these symptoms; however, additional, detailed clinical studies are warranted. (See section 5.c. below.)

Very little or no research has been published about several other potentially hazardous deployments, including deployment to Southwest Asia since the end of the Gulf War (more than 200,000 veterans). Project SHAD was conducted from 1962 to 1973 to identify warship vulnerabilities to attack with chemical or biological agents and to develop protective procedures. Project SHAD was not a recent operation, however, some veterans have recently expressed concern that they may have been exposed to harmful substances during the tests. A few research studies have been published about illnesses that were diagnosed in military hospitals during the deployments to Bosnia and Kosovo. However, there are almost no studies that have investigated the longer-term health of these veterans, after their return home (more than 160,000 veterans). Veterans are already returning from Afghanistan, but there is, as yet, no information about their health status. Appendix B contains information about the potential hazards of these deployments. Also, there have been several smaller, recent deployments, such as to Panama, Haiti, and Somalia, for which very little is known about long-term effects.

ORD offers this solicitation as a unique opportunity for investigators to build upon existing knowledge by identifying gaps, and by building on previous work funded by

VA, DoD, and HHS. Proposals that include collaboration with DoD investigators are encouraged, particularly for studies that require the acquisition of DoD data for subject selection or exposure assessment.

Studies that provide early results are particularly valuable (as the final product or as an intermediate product, in addition to longer-term findings). Studies are encouraged that result in “action items” or specific clinical or policy recommendations within a short timeframe (12 to 18 months). The focus should be on results that can be disseminated quickly to decision-makers within VA and DoD for implementation and rapid evaluation.

5. Sample Research Issues. ORD will support a broad spectrum of research that focuses on deployment health and force health protection. ORD recognizes five major categories of research priorities.

a. Long-term health impacts of hazardous deployments

This solicitation encourages the submission of proposals, which focus on potential long-term health effects of exposures and risk factors among veterans of hazardous deployments, such as the Gulf War, deployment to Southwest Asia since the end of the Gulf War, Project SHAD, Bosnia/Kosovo, or Afghanistan. Key requirements for such epidemiology studies should include the following, whenever feasible:

- Identification of a cohort of service members involved in a hazardous deployment, including names and personal identifiers (requires consultation with DoD); identification of an appropriate comparison group of veterans who were not deployed;
- Long-term follow-up, using tracing and location procedures to obtain as complete ascertainment as possible of current health status of veterans;
- Careful reconstruction of exposures to individual service members or to their military units, whenever possible (requires consultation with DoD); use of existing DoD location and exposure databases, whenever possible; these exposures and databases are listed in Appendix B;
- Focus on health outcomes with direct relevance to specific exposures, whenever possible (such as, asthma related to oil well fire smoke in Gulf War or to industrial air pollution in Bosnia);
- Use of objective biomarkers, such as, pulmonary function tests or urinary uranium levels (not just self-reported symptoms or self-reported exposures); examples of biomarkers are listed in Appendix B; and
- Use of existing health databases, if possible (such as, databases on in-theater hospitalizations during the Gulf War or in Bosnia, or national VA and DoD hospitalization databases); examples of health databases are listed in Appendix B.

VA and DoD maintain many health databases that could be utilized in epidemiology studies. Research proposals should use these databases whenever possible. These databases have been used in several studies; however, they have not been utilized as extensively as would be optimal. The development and evaluation of innovative methods

to link environmental exposure databases with clinical surveillance systems are encouraged. For example, data on soldiers in military units located in areas of Bosnia that have high levels of industrial air pollution could be linked with data on VA and DoD ambulatory care visits for asthma.

Some health databases are readily accessible to VA investigators. Access to others, such as the National Death Index, requires the resources of HHS. Several databases are accessible through collaboration with various offices of DoD. Investigators who propose to obtain data from non-VA databases must demonstrate appropriate plans for collaboration with the relevant offices within DoD or HHS. Upon request, ORD staff can assist VA investigators in the identification of the appropriate DoD offices and points of contact for access to specific health and exposure databases.

Studies are encouraged that investigate more effective uses of clinical surveillance systems to promote early recognition of trends of specific illnesses after deployments. A recent example is the investigation of a malaria death in a Special Forces soldier in Puerto Rico, which led to the discovery of multiple malaria cases in his unit. This raised concern that this outbreak was due to drug-resistant parasites. In fact, it was eventually linked to poor compliance with malaria prophylaxis in that unit, during a recent deployment to Nigeria. This finding identified the need for improved health risk communication about the necessity for prophylaxis.

Studies that use other methods, that do not use existing databases to assess health outcomes, are also encouraged. However, health outcomes must be objectively measured, such as with the use of pulmonary function tests to assess rates of asthma, rather than on the sole use of self-reported symptoms.

Proposals are encouraged that systematically compare veterans of hazardous deployments with veterans who were not deployed. The goal would be to determine if there are predictable differences in the characteristics of deployed veterans, such as:

- Demographic and lifestyle factors;
- Military and civilian occupational histories, including exposures;
- Rates and types of medical and psychiatric diagnoses;
- Rates of disability (for example, unemployment, service-connected disability, or medical retirement from military);
- Health-related quality of life (for example, use of the Medical Outcomes Study Short Form-36V);
- Rates of health care utilization;
- Compliance with recommended treatments, including continuity of care; and
- Patient satisfaction with VA medical care.

One important research question focuses on the identification of pre-war risk factors for post-war morbidity. Could pre-deployment factors be identified, which increase the risk of adverse outcomes after combat or other hazardous deployments? For example, some service members could be at greater risk for the development of PTSD or depression after combat. Conversely, there may be protective factors, which reduce the risk of developing

PTSD or depression after combat. DoD could use information on risk factors or protective factors to develop preventive measures, such as longer training before deployments to increase the hardiness of soldiers who are at higher risk.

Some studies are following Gulf War veterans over time and are collecting data on treatments and changes in health status, including the VA National Health Survey, the Iowa follow-up study, and the Fort Devens study. The Millennium Cohort Study (MCS) is following a cohort of 140,000 veterans for as long as 21 years, starting in 2001. However, the number and types of health outcomes that will be assessed in the MCS are limited, by necessity. Proposals are encouraged that provide more detailed longitudinal follow-up of veterans of recent deployments in Bosnia/Kosovo or Afghanistan.

b. Health impacts of specific military occupational and environmental exposures

This solicitation encourages the submission of proposals, which focus on potential long-term health effects of specific occupational and environmental exposures, such as combat, environmental and climatic extremes, endemic infectious diseases, and toxic environmental exposures. Key requirements for such studies should include the following, whenever feasible: 1) careful reconstruction of exposures to individual service members or to their military units; and/or 2) use of objective biomarkers, such as, pulmonary function tests or urinary uranium levels.

Examples of specific exposures include potential exposure to depleted uranium during the Gulf War, exposure to simulants of chemical or biological warfare agents during Project SHAD, exposure to air pollution during deployment to Bosnia/Kosovo, and exposure to hepatitis and tuberculosis in Afghanistan. Appendix B lists hazardous exposures during each deployment, as well as relevant examples of objective biomarkers.

c. Improvements in evaluation and diagnosis of deployment-related illnesses

This solicitation encourages the submission of proposals, which focus on improvements in the evaluation and diagnosis of deployment-related illnesses. The goal of such studies would be to develop, implement, and evaluate improved diagnostic techniques for illnesses that are often deployment-related.

In many studies, Gulf War veterans have reported increased frequencies of symptoms, compared to non-deployed veterans, including chronic fatigue, headaches, memory and concentration problems, sleep disturbances, depression, and musculoskeletal problems. Population studies that included medical evaluations have demonstrated increased frequencies of specific diagnoses in Gulf War veterans, including amyotrophic lateral sclerosis (ALS), chronic fatigue syndrome, posttraumatic stress disorder (PTSD), other anxiety disorders, major depression, and fibromyalgia. Each of these diagnoses is related to central nervous system (CNS) dysfunction. Even fibromyalgia primarily appears to be a manifestation of abnormal pain processing in the brain, based on recent research.

Because of the prevalence of these conditions, the Federal government has aggressively pursued studies of brain and nervous system in Gulf War veterans. This solicitation re-emphasizes the research need to improve diagnostic techniques in veterans with CNS symptoms. A few studies have included detailed neurological testing in Gulf War veterans; however, these usually included small numbers of highly-symptomatic veterans. Little is known about the neurological status of the overall population of veterans.

During the Gulf War, some service members were exposed to a number of potential neurotoxins. In particular, they were exposed to chemicals that can inhibit acetylcholine, a neurotransmitter. As a result, acetylcholine dysregulation and related pathology has been a high research priority. Many projects have focused on chemicals that affect acetylcholine regulation, including pyridostigmine bromide, organophosphate nerve agents, such as sarin, and organophosphate pesticides, such as chlorpyrifos.

In 1996, a historical review of the medical literature was published, which described illnesses after wars since the U.S. Civil War. Veterans of the Civil War, World War I, and World War II frequently reported several CNS symptoms, including fatigue, headaches, dizziness, disturbed sleep, forgetfulness, and difficulty concentrating. In 2002, a historical review was published, which summarized medical records related to British war pensions. Veterans of the Boer War, World War I, and World War II frequently reported several CNS symptoms, including fatigue, dizziness, headaches, depression, anxiety, and difficulty sleeping. Clearly, these CNS symptoms are a recurring phenomenon after hazardous deployments. Little or no information is available about the rates of symptoms and diagnoses in recent hazardous deployments in Bosnia/Kosovo or Afghanistan.

Further research is justified to determine whether objective markers can provide information on the pathophysiology of illnesses in veterans of hazardous deployments. Such markers include evaluations of subtle neurological function. Some studies in Gulf War veterans have used the following tests:

- neuropsychological testing;
- nerve conduction studies and electromyography;
- tests of audiovestibular function;
- neurophysiological measurements of the autonomic nervous system, including assessments of the regulation of the cardiovascular system;
- tests of neuroendocrine function; and
- various neuroimaging techniques.

Several studies have used neuropsychological testing in Gulf War veterans; however, most studies have included small numbers of veterans. These have generally demonstrated few or no significant abnormalities. A few studies have included neurophysiological tests, but very little has been published, to date. Several studies have used neuroimaging techniques, including: conventional MRI, functional MRI, magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission computed tomography (SPECT). Again, very little has been published.

Most of the studies that utilized sophisticated tools to investigate neurological function evaluated small numbers of highly-symptomatic veterans. In some studies, there was little effort to correlate clinical diagnoses, such as PTSD, major depression, or peripheral neuropathy, with abnormalities on the tests of subtle neurological function, such as abnormalities on MRS or nerve conduction studies and electromyography. This lack of clinical correlation causes difficulties in interpretation of the subtle tests, and makes it very difficult to generalize to the larger population of veterans.

In addition, further research is justified to determine whether objective markers can provide information on mechanisms of illness in Gulf War veterans. Such markers could include indicators of individual susceptibility or vulnerability, for example, enzymes such as paraoxonase (PON1), butyrylcholinesterase (BChE), or acetylcholinesterase (AChE). A few studies have determined enzyme activity levels in Gulf War veterans, however, they were limited by small sample size and lack of clinical correlation.

In summary, additional work is warranted to evaluate CNS symptoms in representative samples of ill and healthy veterans, with a focus on diagnoses with increased prevalence in deployed veterans. Using careful clinical correlation, one goal would be to develop a set of objective neurophysiology, neuropsychology, or neuroimaging tests with proven clinical relevance to diagnosis and treatment. The utility of these tests as screening tools should be determined, based on the detection of subclinical abnormalities that have validated predictive value in the natural history of well-recognized clinical diseases.

d. Improvements in treatment of deployment-related illnesses

This solicitation encourages the submission of proposals for treatment trials, either small-scale, single-site trials or larger-scale trials, for veterans of hazardous deployments, who have deployment-related illnesses. Note, that in addition to this current solicitation, the VA Cooperative Studies Program has issued two solicitations that focus on treatment trials in Gulf War veterans, which continue to be open for applications.

In July 2001, the Institute of Medicine (IOM) published *Gulf War Veterans: Treating Symptoms and Syndromes*. IOM concluded that difficult-to diagnose symptoms experienced by some Gulf War veterans have a large overlap with the following seven diagnoses: chronic fatigue syndrome (CFS), depression, fibromyalgia, headache, irritable bowel syndrome, panic disorder, and PTSD. The major focus of this report was on the evaluation of proven treatments for these diagnoses, and recommendations for improving health care for patients. There is a detailed discussion of each condition, including diagnostic criteria; evaluation of therapies, describing benefits and harms; and recommendations for effective treatments, based on the strength of the evidence.

IOM evaluated certain therapies as definitely or likely to be beneficial for multiple conditions. Cognitive behavior therapy was evaluated as definitely or likely beneficial for six of the conditions (inadequate data for fibromyalgia). Exercise therapy was evaluated as likely beneficial for CFS, depression, and fibromyalgia. Antidepressant

medication was definitely or likely beneficial for six conditions (inadequate data for CFS). VA and DoD recently completed a randomized clinical trial of Gulf War veterans with symptoms similar to CFS and fibromyalgia. Cognitive behavior therapy and aerobic exercise were shown to improve symptoms of chronic fatigue and memory problems.

This solicitation encourages the submission of proposals, which focus on innovative treatment methods for the seven conditions highlighted by IOM, using treatment methods for which the evidence shows a definite or likely benefit. Clearly, these conditions are not only prevalent in Gulf War veterans, but also in veterans of other wars.

VA has published clinical practice guidelines for several diseases that are prevalent in veterans. The guidelines that are particularly relevant to deployment-related illnesses are those for chronic fatigue, chronic pain (such as in fibromyalgia), depression, and PTSD. Proposals are encouraged that would evaluate how VA clinicians have utilized these guidelines; that is, how have the guidelines influenced changes in clinical practice. In addition, the clinical improvement of patients could be evaluated, in response to the treatments recommended in the guidelines. One method to identify VA patients with these disorders would be to use the existing health databases that are outlined in Appendix B.

This solicitation encourages the submission of proposals for innovative approaches to treating war veterans with complex, disabling medical conditions, or with complex psychosocial problems, such as substance abuse or unemployment. Two recent studies demonstrated complex medical and psychosocial problems in Gulf War veterans who attended VA clinics in Seattle, Washington and in Cincinnati or Cleveland, Ohio. The following are examples of questions that could be addressed:

- impact of case management on improvement of medical and psychiatric diseases and/or patient satisfaction;
- impact of comorbidity on approaches to effective treatment;
- impact of multidisciplinary approach to treatment, with effective integration of primary care medicine and behavioral medicine/psychiatry; and
- development of improved methods of patient education to increase self-management of chronic symptoms, similar to chronic pain management programs.

ORD particularly encourages research focused on optimizing rehabilitative health care for veterans with disabilities. The Rehabilitation Research and Development Service funds research emphasizing amputation management, prosthetic and orthotic development, neurological impairments including spinal cord injury, vision and hearing impairments, and other combat-related disabilities. Proposals are also invited that enhance the treatment of medical complications that arise from chronic impairment. Current priorities seek to take advantage of medical and technological advances promising the possibility of genuine recovery after traumatic injuries, refined assistive devices, and improved delivery of care and medical equipment. Examples of such studies include the development of computer chips for implanting in the retina of blind veterans, new generations of functional electrical stimulation for activating paralyzed muscles, and improved robotics for delivering intensive, precise therapies.

e. Health risk communication for veterans and health care providers

This solicitation encourages the submission of proposals, which focus on research that would lead to improved methods of health risk communication for veterans and their health care providers. The goal is to develop, implement, and evaluate communication strategies, in order to provide more timely, understandable and effective communications. The need to improve health risk communication methods for veterans and health care providers has been highlighted in reports related to deployment health, including:

- Presidential Advisory Committee on Gulf War Veterans' Illnesses (1996);
- National Science and Technology Council of the Executive Office of the President (1998);
- Centers for Disease Control and Prevention (2000); and
- Institute of Medicine Committee on Strategies to Protect the Health of Deployed U.S. Forces (2000).

Research is needed that would identify effective methods or tools of delivering information to target audiences on a variety of health risk topics, with an aim to developing general guiding principles. The effectiveness of the delivery of the health risk message on the target audience must be assessed. Target audiences may be veterans or health care providers. Outcomes of the communication strategy must be assessed, which could include measures of target audience understanding or acceptance of the intended message; health-related behavioral changes, in response to the message; or change in health status, in response to the message.

Proposals are encouraged that consider how military personnel and veterans think about deployment-related risks, in terms of knowledge, attitudes, and beliefs. Veterans have expressed concerns about long-term health impacts of numerous deployment-related exposures, for example:

- use of pyridostigmine bromide during the Gulf War;
- use of anthrax vaccine during subsequent deployments to Southwest Asia;
- use of munitions containing depleted uranium in Kosovo; and
- use of malaria prophylaxis in Afghanistan.

Compliance with malaria prophylaxis continues to be an occasional problem, leading to preventable cases of malaria. Clearly, these military personnel think about the risks and benefits of the disease vs. the medication differently than a physician would. Service members who choose to face court martial, because they are concerned about allegations of long-term reproductive risks due to the anthrax vaccine, also think about the risks and benefits differently than a physician would.

VA and DoD have developed many products to educate Gulf War veterans, including fact sheets, booklets, notification letters, and web sites. Investigators could systematically review these products to develop improved products for veterans of more recent deployments. VA and DoD have also developed relevant products for health care providers, which would be useful for investigators to review. For example, an on-line

course has been developed on illnesses in Gulf War veterans, entitled *A Guide to Gulf War Veterans Health*. Continuing medical education (CME) credits are awarded to VA physicians upon completion of the course. Similarly, another on-line course has been developed for CME, entitled *Post-Traumatic Stress Disorder: Implications for Primary Care*. Clinicians value the ease of accessibility of these products, as well as the provision of information that is directly relevant to clinical practice.

Proposals need to describe key elements that form the basis of the research, as follows:

- description of target audience;
- plans for developing messages;
- plans for selecting tools for message delivery;
- expected objectives of target audience understanding, acceptance, and/or actions, in response to the message;
- plans for implementation; and
- plans for evaluation.

6. Letter of Intent. All applicants must first submit a Letter of Intent (LOI) in the format specified by the appropriate service. LOIs will be reviewed for scientific merit, and for relevance to this announcement on deployment health. This solicitation follows established procedures for the ORD Merit Review Award program.

Based on the focus of their proposals, investigators should determine the most appropriate research service for their applications. Applicants may consult with service staff identified in Section 10. to determine the most appropriate service for their proposal. Examples of the appropriate services for specific topics include, but are not limited to:

- Long-term health impacts of hazardous deployments (epidemiology, clinical studies, health care utilization, etc.)-MRS, HSRD, CSP
- Health impacts of specific military occupational and environmental exposures (epidemiology, clinical studies, etc.)-MRS
- Improvements in evaluation and diagnosis of deployment-related illnesses (epidemiology, clinical studies, etc.)-MRS, HSRD
- Improvements in treatment of deployment-related illnesses (single-site clinical trials, larger-scale clinical trials, evaluation of clinical practice guidelines, rehabilitation research, etc.)-MRS, CSP, HSRD, RRDS
- Health risk communication for veterans and health care providers (health education for veterans or health care providers, etc.)-HSRD

Letters of Intent will be evaluated by the appropriate service. Only applicants with an approved Letter of Intent may submit a full research proposal. Detailed instructions for Letter of Intent, Proposal Preparation and Submission, and other guidelines on applications have been published by each service on the Internet at www.va.gov/resdev/fr/funding.cfm

Medical Research Service:

Specific instructions for Letters of Intent for MRS applications are provided at www.va.gov/resdev/directive/1202_Merit_Review_Handbook_JIT.doc

For this solicitation, MRS requires that LOIs specifically include the following:

- Objectives of the proposed research, including hypotheses to be tested and specific aims
- Description of the study type (e.g., epidemiology, clinical trial, etc.)
- Importance of the study
- Scientific background and preliminary data to support validity
- Description of study design, including, as appropriate:
 - Study populations
 - Recruitment procedures
 - Sampling methods
 - Experimental measures to be evaluated
 - Follow-up procedures
 - General analytical plan, including statistical analyses
 - Feasibility statement
 - Resources available, estimated cost, and estimated duration

Health Services Research and Development Service:

Specific instructions for Letters of Intent for HSRD applications are provided at www.hsrp.research.va.gov/for_researchers/funding/application/guidelines/

Also, there is a related HSRD solicitation, entitled “Terrorism: Health Services Research (HSR) Studies Relevant to Preparation for and Response to Nuclear, Chemical, Biological, or Explosive Attacks.” This solicitation can be accessed at www.hsrp.research.va.gov/for_researchers/funding/solicitations/TerrorismSolicitation1-30-02.pdf

Rehabilitation Research and Development Service:

Specific instructions for Letters of Intent for RRDS applications are provided at www.vard.org/guid/procedur.htm

Cooperative Studies Program:

Specific instructions for Letters of Intent for CSP applications are provided at www.va.gov/resdev/ps/pscsp/cspplan.cfm

7. Proposal Preparation and Submission. Only applicants with an approved Letter of Intent may submit a full research proposal to the relevant Service. Preparation and submission of proposals should follow the guidelines of the individual Service to which the application is made.

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This is an ongoing announcement with multiple receipt dates. Until further notice, Letters of Intent and research proposals may be submitted for any of the regular receipt dates established by the relevant Service.

Medical Research Service:

Specific instructions for Proposal Preparation for MRS applications are provided at www.va.gov/resdev/directive/1202_Merit_Review_Handbook_JIT.doc

Health Services Research and Development Service:

Specific instructions for Proposal Preparation for HSRD applications are provided at www.hsrp.research.va.gov/for_researchers/funding/application/guidelines/

Also, there is a related HSRD solicitation, entitled "Terrorism: Health Services Research (HSR) Studies Relevant to Preparation for and Response to Nuclear, Chemical, Biological, or Explosive Attacks." This solicitation can be accessed at www.hsrp.research.va.gov/for_researchers/funding/solicitations/TerrorismSolicitation1-30-02.pdf

Rehabilitation Research and Development Service:

Specific instructions for Proposal Preparation for RRDS applications are provided at www.vard.org/guid/procedur.htm

Cooperative Studies Program:

Specific instructions for Proposal Preparation for CSP applications can be obtained from CSP staff. (Joseph Gough; 202-565-8274)

8. Review. Proposals will be reviewed by the appropriate Service in the normal cycle. Proposals will be evaluated on the basis of scientific quality, significance and innovation of the research question(s), rigor of the methodological approach, feasibility, and relevance to this announcement on deployment health.

Medical Research Service:

Specific details on Review of MRS applications are provided at www.va.gov/resdev/directive/1202_Merit_Review_Handbook_JIT.doc

MRS is especially soliciting pilot projects that will approach existing problems from a new perspective and/or use new avenues of investigation. These pilot projects differ from traditional merit review proposals in that preliminary data, while useful, is not required. However, these pilot proposals should be based on a rational hypothesis derived from critical review and analysis of the literature and/or logical reasoning.

For MRS, Merit Review subcommittees will conduct the review of proposals submitted in response to this announcement within their regularly scheduled sessions and within their specified purview. Purview of each subcommittee is provided in Appendix H, at www.va.gov/resdev/directive/1202_Merit_Review_Handbook_JIT.doc

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Health Services Research and Development Service:

Specific details on Review of HSRD applications are provided at www.hsrdr.research.va.gov/for_researchers/funding/application/guidelines/

Rehabilitation Research and Development Service:

Specific details on Review of RRDS applications are provided at www.vard.org/guid/procedur.htm

RRDS Merit Review will be conducted within their regularly scheduled sessions with proposals assigned to the appropriate review panel, based on the specific area within rehabilitation.

Cooperative Studies Program:

Specific details on Review of CSP applications can be obtained from CSP Staff. (Joseph Gough; 202-565-8274)

9. Funding. Proposals may request up to the maximum number of years of funding allowed by the relevant Service. Each service sets its own limit on project cost. The research design is expected to be appropriate and efficient, with all budget categories well justified. In planning project budgets, applicants are reminded to adhere to ORD guidelines regarding allowable use of research funds for specific items.

Medical Research Service:

MRS proposals will be limited to an annual budget of \$150,000 per year, and a maximum of three years duration. In addition, MRS will not cover the Principal Investigators' salaries on these proposals, if they are already salaried from another VA source.

Health Services Research and Development Service:

Specific details on Funding of HSRD applications are provided at www.hsrdr.research.va.gov/for_researchers/funding/application/guidelines/

Rehabilitation Research and Development Service:

RRDS Merit Proposal guidelines currently set a limit of three years of funding at a maximum of \$250,000 per year.

Cooperative Studies Program:

There is no preset limit on CSP project costs, but proposals must include appropriate justification.

10. Inquiries. Please direct questions about this solicitation to the appropriate Service staff, as follows:

Medical Research Service:

Letter of Intent: Adam Richman; 202-408-3603

Proposal Preparation and Submission: Leroy Frey; 202-408-3636

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Health Services Research and Development Service:

Letter of Intent: Caryn Cohen; 202-408-3671

Proposal Preparation and Submission: Martha Bryan; 202-408-3665

Rehabilitation Research and Development Service:

Letter of Intent or other inquiries: Patricia Dorn; 202-408-3672

Cooperative Studies Program:

Letter of Intent or other inquiries: Joseph Gough; 202-565-8274

[signed]

James F. Burris, M.D.

Acting Chief Research and Development Officer

Attachments:

Appendix A includes general references related to research needs on deployment health and force health protection.

Appendix B includes summaries of the potentially hazardous exposures and relevant databases related to five deployments, as well as selected references. These are the Gulf War, deployments to Southwest Asia since the end of the Gulf War, Project SHAD, Bosnia/Kosovo, and Afghanistan.

APPENDIX A

GENERAL REFERENCES RELATED TO RESEARCH NEEDS ON DEPLOYMENT HEALTH AND FORCE HEALTH PROTECTION

1. General reports:

Presidential Advisory Committee on Gulf War Veterans' Illnesses. *Final Report*. Washington, DC: US Government Printing Office; December 1996. Accessed at www.gwvi.ncr.gov

Senate Veterans' Affairs Committee. *Report of the Special Investigation Unit on Gulf War Illnesses*. Washington, DC: US Government Printing Office; September 1998. Accessed at <http://veterans.senate.gov/Reports/siu.htm>

National Science and Technology Council. *Presidential Review Directive 5: A National Obligation-Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments*. Washington, DC: Executive Office of the President, Office of Science and Technology Policy; 1998. Accessed at www.mvhcb.gov/mvhcb_13h/PRD-5.htm

Joint Chiefs of Staff, Medical Readiness Division. *Force Health Protection: Healthy and Fit Force, Casualty Prevention, and Casualty Care and Management*. Washington, DC: DoD; 1999. Accessed at www.ha.osd.mil/forcehealth/library/main.html

Institute of Medicine. *Protecting Those Who Serve: Strategies to Protect the Health of Deployed U.S. Forces*. Washington, DC: National Academy Press; 2000. Accessed at www.gulflink.osd.mil/medical/ptws.pdf

Research Advisory Committee on Gulf War Veterans' Illnesses. *Interim Report*. Washington, DC: VA; June 25, 2002. Accessed at www.va.gov/rac-gwvi/docs/finalinterimreport.doc

President's Task Force to Improve Health Care Delivery for Our Nation's Veterans. *Interim Report*. Washington, DC: July 31, 2002. Accessed at www.presidentshealthcare.org/pdffiles/InterimReport.pdf

2. Internet web sites and reports:

DeploymentLINK: DoD Deployment Health Support Directorate. Accessed at <http://deploymentlink.osd.mil>

DoD Deployment Information. Accessed at

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http://deploymentlink.osd.mil/deploy/info/info_intro.shtml

DoD Joint Staff Memorandum MCM-0006-02, 1 February 2002. Subject: Updated Procedures for Deployment Health Surveillance and Readiness. Accessed at: <http://deploymentlink.osd.mil/pdfs/dhsar01feb2002.pdf>

DoD Office of the Assistant Secretary for Health Affairs. Accessed at www.ha.osd.mil/

DoD Force Health Protection and Readiness. Accessed at www.ha.osd.mil/fhpr/

DoD Deployment Health Clinical Center. Accessed at www.pdhealth.mil/main.asp

US Army Center for Health Promotion and Preventive Medicine (USACHPPM). Deployment Resources. Accessed at <http://chppm-www.apgea.army.mil/deployment/deploymentlinks.asp>

USACHPPM
Staying Healthy Guides. Accessed at <http://chppm-www.apgea.army.mil//deployment/shg.asp>

USACHPPM
US Army Guide to Staying Healthy. Accessed at <http://chppm-www.apgea.army.mil/deployment/GTA%2008-05-062.pdf>

USACHPPM
A Soldier and Family Guide to Redeploying. Accessed at <http://chppm-www.apgea.army.mil//deployment/RedeploymentWeb.pdf>

USACHPPM
Deployment Medication Information Sheets (includes vaccines). Accessed at <http://chppm-www.apgea.army.mil/dmis/>

Clinical Practice Guidelines. U.S. Army MEDCOM Quality Management Office. Accessed at www.qmo.amedd.army.mil/HOME.HTM

Post-Deployment Health Management Guideline (jointly published by VA and DoD). Accessed at www.qmo.amedd.army.mil/redep/redep.htm

Clinical Practice Guidelines. Medically Unexplained Symptoms: Chronic Pain and Fatigue (jointly published by VA and DoD). Accessed at www.qmo.amedd.army.mil/mus/mus.htm

VA Clinical Practice Guidelines. Office of Quality and Performance. Accessed at

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www.oqp.med.va.gov/cpg/cpg.htm

VA Clinical Practice Guidelines. Major Depressive Disorder (MDD) (jointly published by VA and DoD). Accessed at

www.oqp.med.va.gov/cpg/MDD/MDD_Base.htm

VA Clinical Practice Guidelines. Biological, Chemical, and Radiation Induced Illnesses.

Accessed at www.oqp.med.va.gov/cpg/BCR/BCR_Base.htm

Millennium Cohort Study (joint DoD/VA long-term follow-up study of 140,000 service members). Accessed at

www.millenniumcohort.org

Armed Forces Press Service. Dead Men Do Tell Tales. August 27, 2002. Accessed at

www.defenselink.mil/news/Aug2002/

3. *Journal articles:*

Hyams, KC, Wignall, FS, and Roswell, R. War syndromes and their evaluation: from the U.S. Civil War to the Persian Gulf War. *Annals of Internal Medicine* 1996; 125(5):398-405.

Jones, E, Hodgins-Vermaas, R, McCartney, H, Everitt, B, Beech, C, Poynter, D, Palmer, I, Hyams, K, and Wessely, S. Post-combat syndromes from the Boer War to the Gulf War: a cluster analysis of their nature and attribution. *British Medical Journal* 2002 February 9; 324(7333):321-324.

Prigerson, HG, Maciejewski, PK, and Rosenheck, RA. Population-attributable fractions of psychiatric disorders and behavioral outcomes associated with combat exposure among US men. *American Journal of Public Health* 2002 January; 92(1):59-63.

Hoge, CW, Lesikar, SE, Guevara, R, Lange, J, Brundage, JF, Engel, CC, Messer, SC, and Orman, DT. Mental disorders among U.S. military personnel in the 1990s: association with high levels of health care utilization and early military attrition. *American Journal of Psychiatry* 2002 September; 159(9):1576-1583.

Talcott, GW, Haddock, CK, Klesges, RC, Lando, H, and Fiedler, E. Prevalence and predictors of discharge in United States Air Force basic military training. *Military Medicine* 1999; 164:269-274.

Booth-Kewley, S, Larson, GE, and Ryan, MA. Predictors of Navy attrition. I. Analysis of 1-year attrition. *Military Medicine* 2002 September; 167(9):760-769.

Larson, GE, Booth-Kewley, S, and Ryan, MA. Predictors of Navy attrition. II. A demonstration of potential usefulness for screening. *Military Medicine* 2002 September; 167(9):770-776.

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Gray, GC, Chesbrough, KB, Ryan, MA, Amoroso, P, Boyko, EJ, Gackstetter, GD, Hooper, TI, and Riddle, JR. The Millennium Cohort Study: a 21-year prospective cohort study of 140,000 military personnel. *Military Medicine* 2002 June; 167(6):483-488.

Trump, DH, Mazzuchi, JF, Riddle, J, Hyams, KC, and Balough, B. Force health protection: 10 years of lessons learned by the Department of Defense. *Military Medicine* 2002 March; 167(3):179-185.

APPENDIX B

SUMMARIES AND REFERENCES ON INDIVIDUAL DEPLOYMENTS

I. Gulf War

Because of the maturity of the research portfolio on Gulf War illnesses, some definitive conclusions can be drawn related to several research questions, based on the integration of results of many completed projects. Research results are described in detail each year, in an *Annual Report to Congress*, which can be accessed on the Internet at

www.va.gov/resdev

Key conclusions, to date, include:

- Illnesses in Gulf War veterans are real. In many studies, Gulf War veterans have reported increased rates of symptoms, compared to non-deployed veterans. These include chronic fatigue, musculoskeletal problems, asthma, PTSD, depression, and memory problems.
- There appears to be almost a two-fold increase in the rate of amyotrophic lateral sclerosis (ALS) in Gulf War veterans, compared to non-deployed veterans.
- A national treatment trial, funded jointly by VA and DoD, demonstrated that symptoms of chronic fatigue and memory problems in Gulf War veterans were improved using aerobic exercise and cognitive behavioral therapy.
- A national treatment trial, funded jointly by VA and DoD, was performed in response to suggestions by some physicians and veterans that long-term treatment with antibiotics could alleviate unexplained illnesses in some Gulf War veterans. The results of this trial were definitive, showing that a 12-month course of antibiotics (doxycycline) did not improve chronic symptoms of fatigue, pain, or memory problems.
- There is no difference in mortality rates between Gulf War veterans and non-deployed veterans. The mortality rate in Gulf War veterans is 40% of the mortality rate in the general U.S. population (less than half).
- There is no general increase in the rates or types of serious illnesses that would lead to hospitalizations in Gulf War veterans, compared to non-deployed veterans.
- There is no difference in the rates of medically-confirmed birth defects among offspring of Gulf War veterans and offspring of non-deployed veterans.
- There is no clinical evidence of adverse effects of depleted uranium exposure.
- The rates and patterns of infectious diseases in Gulf War veterans have been unremarkable.

However, several key research areas remain to be fully addressed, for example:

- longitudinal follow-up of Gulf War veterans who have already undergone thorough clinical evaluations;
- comprehensive studies of CNS symptoms, including the use of neuropsychological testing, nerve conduction studies and electromyography, tests

- of autonomic nervous system function, tests of audiovestibular function, neuroendocrine testing, and neuroimaging;
- improved diagnostic techniques for deployment-related illnesses; and
- improved treatments of deployment-related illnesses.

In addition to studies on veterans' health, proposals that focus on the health of their spouses and children are encouraged. Proposals that include collaboration with DoD investigators are encouraged, particularly for studies that require the acquisition of DoD data for subject selection or exposure assessment.

Databases on medical conditions in veterans of the Gulf War and subsequent deployments to Southwest Asia include:

- list of all 28,000 individuals who were known to be hospitalized in military hospitals during the Gulf War, including discharge diagnoses;
- list of all individuals hospitalized in military hospitals during later deployments to Southwest Asia, including discharge diagnoses;
- DoD Comprehensive Clinical Evaluation Program database;
- VA Persian Gulf War Registry database;
- VA National Survey of Persian Gulf Veterans (database of 21,000 veterans);
- Veterans Benefits Administration database on compensation claims, including diagnoses;
- DoD database on medical retirements, including diagnoses;
- National Death Index of the National Center for Health Statistics;
- Social Security Administration database;
- VA Beneficiary Identification and Records Locator Subsystem;
- national database of DoD ambulatory care visits;
- hospitalization database from all DoD hospitals nationwide;
- national database of VA ambulatory care visits; and
- hospitalization database from all VA hospitals nationwide.

Most of these health databases were utilized in relevant journal articles listed below, in which the databases are described in some detail. Some health databases are readily accessible to VA investigators. Access to others, such as the National Death Index, requires the resources of HHS. Several databases are accessible through collaboration with various offices of DoD. Investigators who propose to obtain data from non-VA databases must demonstrate appropriate plans for collaboration with the relevant offices within DoD or HHS. Upon request, ORD staff can assist VA investigators in the identification of the appropriate DoD offices and points of contact for access to specific health and exposure databases.

There are several available resources related to potentially hazardous exposures during the Gulf War. Most of these resources are described in web site reports listed below. These include, but are not limited to:

- Studies on the health effects of potential sarin exposure due to the demolitions of munitions at Khamisiyah, Iraq, using DoD data on unit locations and modeled air concentrations.
- Studies on exposure to oil well fire smoke, using DoD data on unit locations and exposures, based on extensive air sampling.
- Interview data on exposure histories from 104 veterans exposed to depleted uranium in friendly fire incidents.
- Interview data on exposure histories from about 700 preventive medicine specialists with relatively defined, higher-level exposures to pesticides.
- Accurate, but incomplete, list of anthrax vaccine and botulinum toxoid recipients.
- List of veterans in military units that had the greatest contact with Iraqi prisoners of war (which could have increased the risk of infectious diseases, such as viral hepatitis or tuberculosis).
- List of veterans in specific military units or Military Occupational Specialties that were most likely to be involved in direct combat.

Identification of objective markers in ill Gulf War veterans and investigation of linkages between markers, exposures, and health status have been a high research priority. Possible markers of illness include blood tests of immune function, which have been used in several studies. Objective markers of exposures include detection of infectious organisms or chemicals in blood or urine. Several studies in Gulf War veterans have used markers of exposure, such as:

- blood assays for *Mycoplasma* species in the Antibiotic Treatment Trial and several other studies;
- blood assays for several infectious diseases in the CDC Air Force study;
- blood lead concentrations in the Amyotrophic Lateral Sclerosis study; and
- urinary uranium concentrations in veterans exposed to depleted uranium in friendly fire incidents.

References for Gulf War

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Military and Veterans Health Coordinating Board (MVHCB). *Annual Report to Congress: Federally Sponsored Research on Gulf War Veterans' Illnesses for 2001*. Washington, DC: VA; March 2002. Accessed at www.va.gov/resdev/prt/gulf_war_2001/

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Persian Gulf Veterans Coordinating Board. *A Working Plan for Research on Persian Gulf Veterans' Illnesses, First Revision*. Washington, DC: VA; 1996. Accessed at www.gulflink.osd.mil/medical/96RESPLA.htm

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IOM. *Gulf War and Health: Volume 1. Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines*. Washington, DC: National Academy Press; Sept. 2000. Accessed at www.nap.edu/catalog/9953.html

IOM. *The Anthrax Vaccine: Is It Safe? Does It Work?* Washington, DC: National Academy Press; March 2002. Accessed at www.nap.edu/catalog/10310.html

IOM. *Gulf War Veterans: Measuring Health*. Washington, DC: National Academy Press; 1999. Accessed at www.nap.edu/catalog/9636.html

Centers for Disease Control and Prevention (CDC). *The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference*. Atlanta: CDC; 2000. Accessed at www.cdc.gov/nceh/publications/gulfwar/report.pdf

2. Internet web sites and reports:

Medsearch: Interagency (CDC, DoD, & VA) Gulf War Medical Research Library. Accessed at www.gulflink.osd.mil/medsearch/

GulfLINK: DoD Office of the Special Assistant for Gulf War Illnesses. Accessed at www.gulflink.osd.mil/

VA Gulf War Illnesses Homepage. Accessed at www.va.gov/health/environ/persgulf.htm

VA Demonstration Projects for Treatment of Gulf War Illnesses. Accessed at www.va.gov/health/environ/persgulf.htm

Veterans Health Initiative: A Guide to Gulf War Veterans Health. Accessed at www.va.gov/VHI/

Veterans Health Initiative: Post-Traumatic Stress Disorder-Implications for Primary Care. Accessed at www.va.gov/VHI/

Office of the Special Assistant for Gulf War Illnesses (OSAGWI). *Depleted Uranium in the Gulf II Environmental Exposure Report*. Washington, DC: DoD; December 2000a. Accessed at www.deploymentlink.osd.mil/du_library/du_ii/

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www.gulflink.osd.mil/owf_ii/

OSAGWI. *Particulate Matter Environmental Exposure Report*. Washington, DC: DoD; July 2000c. Accessed at www.gulflink.osd.mil/pm/

OSAGWI. *Pesticides Environmental Exposure Report*. Washington, DC: DoD; March 2001. Accessed at www.gulflink.osd.mil/pesto/pest_exec_summary.htm.

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Araneta, MR, Destiche, DA, Schlangen, KM, Merz, RD, Forrester, MB, and Gray, GC. Birth defects prevalence among infants of Persian Gulf War veterans born in Hawaii, 1989-1993. *Teratology* 2000; 62(4):195-204.

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Bourdette, DN, McCauley, LA, Barkhuizen, A, Johnston, W, Wynn, M, Joos, SK, Storzbach, D, Shuell, T, and Sticker, D. Symptom factor analysis, clinical findings, and functional status in a population-based case control study of Gulf War unexplained

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II. Deployment to Southwest Asia since the End of Gulf War (April 1991) to Present

More than 200,000 American troops have been deployed to Southwest Asia continuously since the Gulf War ended in March 1991. The oil fires burned until the last one was

extinguished in November 1991. Some troops were exposed to depleted uranium during repair and cleanup operations after the war. For the past 11 years, U.S. troops have been exposed to a number of potential risk factors, which are similar to risk factors during the Gulf War. These have included:

- environmental hazards, including extreme climatic conditions (one of the hottest regions in the world), intermittently very high levels of particulates in the ambient air due to sand storms, and air pollution in urban areas due to petroleum refineries and chemical factories;
- the threat of terrorism, such as the attacks on Khobar Towers and the USS Cole;
- endemic infectious diseases, such as hepatitis A, bacterial diarrheas, typhoid fever, malaria, sandfly fever, and cutaneous leishmaniasis;
- medical countermeasures to biowarfare agents (anthrax vaccine) and to endemic infectious diseases, including vaccinations and malaria prophylaxis; and
- austere living conditions.

DoD databases that are relevant to exposures during deployments to Southwest Asia since the Gulf War are described in the references listed below. These include:

- studies on exposure to oil well fire smoke, using DoD data on unit locations and exposures, based on extensive air sampling;
- interview data on exposure histories from about 140 veterans exposed to depleted uranium during repair and cleanup operations after the war;
- list of recipients of anthrax vaccine, since DoD started the program in 1998; and
- list of veterans who were involved in the terrorist attacks at Khobar Towers and on the USS Cole.

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III. Project SHAD

The Shipboard Hazard and Defense (SHAD) program was a joint services program that was planned and conducted from 1962 to 1973, as part of a larger program known as Project 112. Project SHAD was not a recent operation, however, some veterans have recently expressed concern that they may have been exposed to harmful substances during the tests. The tests consisted of joint exercises involving the Army's Desert Test Center in Utah, Navy ships, Army ships, and Air Force aircraft. The tests were designed to identify warship vulnerabilities to attack with chemical or biological agents and to develop procedures to respond to such attacks. By learning how agents could disperse, procedures could be improved to protect crewmembers and to decontaminate the ships.

Since 2000, DoD has been actively searching for 40-year-old documents kept by different military services in different locations. DoD has expedited the declassification of relevant information for a total of 18 known chemical or biological tests conducted during Project SHAD. To date, DoD has published 16 fact sheets that describe ships and units involved in the tests, when the tests took place, and the possible exposures to the crews. Approximately 5,000 sailors were involved in these 16 tests, many of whom were in more than one test. DoD has provided VA with the names of these veterans, so that VA can attempt to locate these individuals and send them notification letters about the tests. DoD anticipates completion of declassification of relevant historical documents, and release of fact sheets on all SHAD tests by June 2003. Fact sheets include test date and location; purpose of the test; the use of simulants and live agents; and methods of decontamination. These fact sheets have been published on a DoD web site, listed below.

Simulants (chemicals with low toxicity or non-pathogenic bacteria) were used in most of the tests, but some tests used actual chemical or biological warfare agents. Laboratory animals were used as test subjects. The tests were designed to protect the sailors through the use of a shelter in an airtight compartment, or through the use of protective masks and clothing. Some chemicals used to decontaminate ships were potentially caustic or toxic. To date, the potential exposures in the 16 tests have included:

- Actual nerve agents (sarin or VX)
- Actual biological warfare agents (*Coxiella burnettii*, *Francisella tularensis*, or Staphylococcal enterotoxin type B)
- Simulants of nerve agents (sulfur dioxide or methylacetoacetate)
- Simulants of biological warfare agents (*Bacillus subtilis*, variant niger [also called *Bacillus globigii*]; *Serratia marcescans*; *Escherichia coli*; or zinc cadmium sulfide)
- Decontamination products (containing peracetic acid, potassium hydroxide, sodium hydroxide, sodium hypochlorite, or beta-propiolactone)

The biological agents used in Project SHAD are unlikely to produce long-term health effects without observable illnesses at the time of exposure, because these infectious agents do not cause chronic infections without symptomatic disease. Similarly, the chemical agents used are unlikely to cause long-term health effects, if they did not cause clinically significant illnesses at the time of exposure. Nonetheless, veterans of Project SHAD have expressed concern about possible long-term health risks. Research on the possible long-term health effects of Project SHAD will require the tracing and location of individuals four decades later, an especially difficult task. The first step is to determine the types of live agents and/or simulants that were used in each test. Then, the names of sailors involved in each test must be identified. DoD has already completed these two steps for about 5,000 sailors.

Long-term studies of mortality and morbidity among Project SHAD participants could utilize several of the health databases outlined above for Gulf War veterans. Mortality data are available for the entire follow-up period. However, computerization of DoD and VA data on hospitalizations and ambulatory care visits took place in the 1990s. Other methods would be required to evaluate morbidity during the time period of the 1960s to 1990s, such as interviews of subjects, followed by retrieval of medical records.

For the agents used in Project SHAD, no objective markers are known that would determine exposure decades later. There are also no specific medical tests that can be recommended for SHAD veterans. However, new research proposals to identify such markers and tests will be considered under this solicitation.

References for Project SHAD

DoD web site on Project SHAD (includes fact sheets about exposures in each test). Accessed at www.deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml

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IV. Bosnia/Kosovo

More than 160,000 U.S. troops have deployed to the Balkans from 1995 to the present. Potential hazards in Bosnia, Herzegovina, and Kosovo have included:

- climatic conditions (some areas have cold winters and up to 100 inches of rain per year);
- high altitude (defined as over 6,000 feet by DoD);
- “black winds” (severe dust storms along the Danube River valley in winter);
- localized areas of serious industrial pollution of air, water, and soil from Soviet period of industrialization; high levels of particulates in ambient air due to power plants and factories using coal; heavy metal contamination of soil, crops, and fish;

- risks of life-threatening situations during peacekeeping operations, including thousands of unmarked landmine fields;
- exposure to human suffering and death; “ethnic cleansing;” mass graves; displaced persons and refugee camps;
- endemic infectious diseases, including food- and water-borne diseases (for example, hepatitis A, bacterial diarrheas, typhoid fever); vector-borne diseases (for example, tick-borne encephalitis, hantavirus, typhus); and from contact with displaced persons and prisoners of war (for example, tuberculosis);
- medical countermeasures to endemic infectious diseases, including vaccinations (such as for tick-borne encephalitis); and
- austere living conditions; long-term loss of safe water supplies and electricity in some areas, from loss of infrastructure due to civil war.

Databases on medical conditions in Bosnia/Kosovo veterans include:

- list of all individuals who were hospitalized in-theater, including discharge diagnoses; and
- several of the health databases outlined above for Gulf War veterans.

DoD databases that are relevant to exposures in Bosnia/Kosovo include:

- results of extensive air monitoring program, documenting some areas with persistently high levels of industrial air pollution;
- veterans in military units that had the greatest contact with displaced persons and refugees (which could have increased the risk of infectious diseases, such as viral hepatitis or tuberculosis);
- list of personnel who received regionally-targeted medical countermeasures (such as, tick-borne encephalitis vaccine); and
- veterans in specific military units or Military Occupational Specialties that were likely to be involved in the most hazardous peacekeeping activities (such as, specialists in explosive ordnance demolition).

Most of these health and exposure databases are described in the references listed below.

Objective markers in veterans of Bosnia/Kosovo could include, for example:

- pulmonary function tests to evaluate long-term effects of industrial air pollution;
- urinary uranium levels in veterans who were in military units that were directly exposed to depleted uranium;
- tests for previous or current endemic infectious diseases (such as, viral hepatitis or tuberculosis); and
- tests for potential long-term effects of medical countermeasures (such as, antibodies to tick-borne encephalitis vaccine).

References for Bosnia/Kosovo

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V. Afghanistan

In October 2001, the U.S. began Operation Enduring Freedom to combat terrorism. This deployment is particularly hazardous because Afghanistan is one of the poorest countries in the world, and it has been torn by civil war since the Soviet invasion in 1979. Potential deployment hazards in central Asia include:

- extremes of climate (extremely hot summers and very cold winters);
- high altitude (defined as over 6,000 feet by DoD);
- severe sand and dust storms in the summer, with winds up to 110 miles per hour;
- risks of serious injury during combat and other life-threatening situations;
- widespread landmines and unexploded ordnance due to ongoing war since 1979;
- exposure to extremes of human suffering or death of military members and civilians;
- severe drought for four years leading to crop failures and mass malnutrition; almost one-third of population immigrated to Iran or Pakistan as displaced persons and refugees, due to crop failures and war;
- little or no infrastructure in most of country, therefore widespread sewage contamination of water and food, leading to cholera and typhoid outbreaks;
- endemic infectious diseases, including food- and water-borne diseases (for example, hepatitis A, bacterial diarrheas, amoebic dysentery, typhoid fever, leptospirosis); vector-borne diseases (for example, malaria, Dengue fever, typhus, cutaneous leishmaniasis); and from contact with refugee camps, displaced persons, and prisoners of war (for example, one of the highest rates of tuberculosis in the world);
- medical countermeasures to endemic infectious diseases, including vaccinations and malaria prophylaxis; and
- austere living conditions; almost entire country lacks electricity, running water, and paved roads.

Databases on medical conditions in Afghanistan veterans include:

- list of all individuals who were hospitalized in-theater, including discharge diagnoses; and
- several of the health databases outlined above for Gulf War veterans.

DoD databases that are relevant to exposures in Afghanistan are currently under development, and they could include:

- veterans in military units that had the greatest contact with refugees and prisoners of war (which could have increased the risk of infectious diseases, such as viral hepatitis, tuberculosis, or malaria);
- list of personnel who received regionally-targeted medical countermeasures (such as, malaria prophylaxis);
- veterans in specific military units or Military Occupational Specialties that were likely to be involved in the most hazardous non-combat activities (such as, specialists in explosive ordnance demolition); and
- veterans in specific military units or Military Occupational Specialties that were most likely to be involved in direct combat.

Objective markers in Afghanistan veterans could include, for example:

- tests for previous or current endemic infectious diseases (such as, viral hepatitis, malaria, or tuberculosis); and

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- tests for potential long-term effects of medical countermeasures (such as, antibodies to vaccines for regional diseases).

References for Afghanistan

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