Department of Veterans Affairs

ANNUAL REPORT TO CONGRESS

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2002

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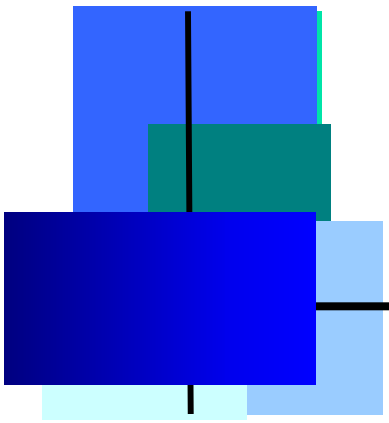
Deployment Health Working Group Research Subcommittee



Annual Report to Congress – 2002

Research on Gulf War Veterans' Illnesses

DEPLOYMENT HEALTH WORKING GROUP
RESEARCH SUBCOMMITTEE MEMBERS

Department of Veterans Affairs:
Kelley Ann Brix, M.D., M.P.H. (VA Co-Chair)
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K. Craig Hyams, M.D., M.P.H.
Roberta White, Ph.D.

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Karl Friedl, Ph.D., Col, USA
Carol Linden, Ph.D.

Department of Health and Human Services:
Drue Barrett, Ph.D., CDR, USPHS

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EXECUTIVE SUMMARY

I. INTRODUCTION

The Secretary of Veterans Affairs is required by Section 707 of Public Law 102-585 as amended by Section 104 of Public Law 105-368, to submit to the Senate and House Veterans' Affairs Committees an annual report on the results, status, and priorities of research activities related to the health consequences of military service in the Gulf War. The Research Subcommittee of the interagency Deployment Health Working Group (DHWG) prepared this *2002 Annual Report to Congress*, which is the ninth report on research and research activities. (PGVCB, 1995a; 1996a; 1997; 1998a; 1999a; 2001; MVHCB, 2001a; 2002; DHWG, 2003) The DHWG tracks all Federally-funded research projects related to Gulf War veterans' illnesses.

This Annual Report is divided into five sections. Section I is an introduction. Section II highlights and summarizes research progress since the last Annual Report. Section III is an analysis of the Federal Government's portfolio of research on Gulf War veterans' illnesses. Section IV highlights significant new research projects and initiatives since the last Annual Report. Section V discusses priorities established for future research in 1995, 1996, and 1998, and highlights the progress made to date.

II. RESEARCH RESULTS IN 2002

In 2002, several research studies have yielded results that provide new and expanded information on the health problems of Gulf War veterans. Section II provides brief summaries of research projects for which results were published from January 2002 to December 2002. As in previous Annual Reports, the research reports summarized in Section II are grouped according to ten focus areas: symptoms and general health status, brain and nervous system function, diagnosis, immune function, prevention, environmental toxicology, depleted uranium, chemical weapons, pyridostigmine bromide, and interactions of exposures.

1. Symptoms and General Health Status:

Thirteen large studies published in 2002 focused on symptoms and general health. (Gray, et al., 2002b; McCauley, et al., 2002a; McCauley, et al., 2002b; Shapiro, et al., 2002; Kang, et al., 2002; Unwin, et al., 2002; Higgins, et al., 2002; Hull, et al., 2002; Smith, et al., 2002b; Richardson, et al., 2002; Voelker, et al., 2002; Wolfe, et al., 2002; Jones, et al., 2002) These publications included the results of studies conducted at five Federally-funded research centers in San Diego, Portland, Oregon, Iowa City, Boston, and London, UK. Each of the publications included data on hundreds to thousands of individuals. Six of these studies were population-based, which means that the results of these studies may have implications for the overall population of 697,000 Gulf War veterans. (McCauley, et al., 2002a; Kang, et al., 2002; Unwin, et al., 2002; Higgins, et al., 2002; Hull, et al., 2002; Voelker, et al., 2002)

The objective of the first study was to compare the rates of self-reported symptoms among veterans who deployed to the Gulf War (Gulf War Seabees), veterans who deployed to another foreign country (Seabees deployed elsewhere), and veterans who did not leave the U.S. (non-deployed Seabees). The Seabees were active-duty and Reserve personnel who served in seven Naval Mobile Construction Battalions. (Gray, et al., 2002b)

The objectives of the second and third study were linked, and were based on an investigation of three groups of veterans: 653 Gulf War veterans who had deployed within 50 km of Khamisiyah, Iraq in March 1991; 610 Gulf War veterans who were distant from Khamisiyah; and 516 non-deployed veterans. The objectives of the second study were to examine the relationships between possible low-level exposure to organophosphate nerve agents and subsequent health effects, including medical diagnoses, hospitalizations, and disability. (McCauley, et al., 2002b) The objectives of the third study were to determine if a unique pattern of symptoms was present in veterans located near Khamisiyah; and if so, to determine if the pattern differed from that of veterans located farther away from Khamisiyah, or from that of non-deployed veterans. (Shapiro, et al., 2002)

The objective of the fourth study was to use factor analysis to determine if patterns of reported symptoms were similar in Gulf War veterans, compared to patterns of reported symptoms in non-deployed veterans, based on data from the VA National Health Survey. (Kang, et al., 2002)

The objective of the fifth study was to examine the clinical characteristics of Gulf War veterans with chronic fatigue syndrome (CFS), compared to healthy Gulf War veterans. (McCauley, et al., 2002a)

The objectives of the sixth, seventh, and eighth studies were linked, and were based on an investigation of three groups of British veterans: Gulf War veterans, Bosnia veterans, and non-deployed veterans. The objective of the sixth study was to compare the health outcomes of British service women who served in the Gulf War with women who served in Bosnia and women who were in the service, but who did not leave Great Britain (era veterans). (Unwin, et al., 2002) The objectives of the seventh study were to compare the nature and prevalence of skin disease in Gulf War veterans with Bosnia and era veterans. (Higgins, et al., 2002) The objective of the eighth study was to compare the characteristics of veterans who participated in the British Gulf War registry program, with veterans who did not, particularly in regard to their rates of ill health and health attributions. (Hull, et al., 2002)

The objective of the ninth study was to identify demographic and military factors and occupational and environmental exposures that were associated with registry participation, among 100,000 American veterans who were enrolled in the VA and DoD Gulf War registries. (Smith, et al., 2002b)

The objective of the tenth study was to compare Gulf War veterans seeking primary care at two different settings, at the Seattle VA Medical Center and Walter Reed Army Medical Center, on measures of physical symptoms, psychiatric distress, functional status, and employment status. (Richardson, et al., 2002)

The objectives of the eleventh study were to compare the health-related quality of life (HRQL) of Gulf War veterans with non-deployed veterans, and to identify potential risk factors for poorer HRQL, before and during deployment, among 3,695 veterans from the state of Iowa. (Voelker, et al., 2002)

The objective of the twelfth study was to determine if self-reported environmental exposures and psychological distress were associated with chronic multisymptom illness among 1,290 members of the Fort Devens, Massachusetts cohort. (Wolfe, et al., 2002)

The objectives of the thirteenth study were to determine if post-combat syndromes have existed after modern wars and what their relationships were to each other, based on British medical records from the Boer War to World War II. (Jones, et al., 2002)

2. Brain and Nervous System Function:

Five studies published in 2002 focused on brain and nervous system function. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Barrett, et al., 2002; Orcutt, et al., 2002) These publications included results of studies conducted at three Federally-funded research centers in Iowa City, Boston, and in London, U.K. Four of these studies included data on hundreds to thousands of individuals. (Ismail, et al., 2002; David, et al., 2002; Barrett, et al., 2002; Orcutt, et al., 2002) Three studies relied upon psychiatric, neuropsychological, or neurological evaluations, rather than relying solely on self-administered surveys. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002) Four of these studies were population-based, which means that the results of these studies may have implications for the overall population of 697,000 Gulf War veterans. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Barrett, et al., 2002)

The objectives of the first, second, and third studies were linked, and were based on an investigation of three groups of British veterans: disabled Gulf War veterans, healthy Gulf War veterans, and disabled veterans who did not deploy to the Gulf War. The objectives of the first study were: to determine the relationship between reported physical disability and psychiatric disorders in Gulf War veterans, using structured psychiatric interviews; and to determine if Gulf War veterans who reported physical disability were more likely to have psychiatric disorders, than the two comparison groups of veterans. (Ismail, et al., 2002) The objectives of the second study were to determine whether the pattern of neuropsychological deficits, if any, differed across symptomatic veterans from different deployments; and whether such deficits could be specifically attributed to Gulf War deployment vs. any overseas deployment. (David, et al., 2002) The objectives of the third study were to determine if

the neuromuscular symptoms reported by some Gulf War veterans were related to objective abnormalities of peripheral nerves, skeletal muscles, or neuromuscular junctions; and to compare the rates of neurological abnormalities among Gulf War veterans, Bosnia veterans and non-deployed veterans. (Sharief, et al., 2002)

The objective of the fourth study was to examine the relationship between posttraumatic stress disorder (PTSD) and perceived physical health and health-related quality of life in a representative sample of 3,682 Gulf War and non-deployed veterans from the state of Iowa. (Barrett, et al., 2002)

The objectives of the fifth study were to examine the relationship between exposure to combat during the Gulf War and exposure to traumatic life events in the two years after the war among 2,313 members of the Fort Devens, MA cohort; and to determine if PTSD symptoms were potential mediators between combat exposure and the risk of subsequent exposure to traumatic events. (Orcutt, et al., 2002)

3. Diagnosis:

One study published in 2002 focused on the diagnosis of anatomical abnormalities; and the objective was to describe the types and frequencies of pathological findings in head and neck specimens from Gulf War veterans, which were studied at the Armed Forces Institute of Pathology (AFIP). (Ladich, et al., 2002)

4. Immune Function:

One study published in 2002 focused on immune function; and the objective was to systematically evaluate components of the acquired immune system in ill Gulf War veterans, healthy Gulf War veterans, and ill non-deployed veterans. (Everson, et al., 2002)

5. Prevention:

Six articles published in 2002 focused on general topics in prevention of illness, and four articles focused on potential health effects of the anthrax vaccine, a preventive measure.

The objective of the first general study was to describe the Defense Medical Surveillance System, which serves as the central repository of medical surveillance data for the U.S. armed forces. (Rubertone and Brundage, 2002)

The objective of the second general study was to describe the Recruit Assessment Program, a DoD program designed to routinely collect demographic, medical, psychosocial, occupational, and health risk factor data from all US military personnel at the time of recruitment. (Hyams, et al., 2002)

The objectives of the third and fourth general studies were linked. The objective of the third study was to investigate one-year Navy attrition in relation to factors assessed by the Sailors' Health Inventory Program (SHIP) questionnaire, a medical and psychosocial history completed by all Navy recruits. (Booth-Kewley, et al., 2002) The objective of the fourth study was to examine the predictive accuracy and practical usefulness of items from the SHIP questionnaire for identifying Navy personnel at risk for attrition during basic training. (Larson, et al., 2002)

The objective of the fifth general study was to describe the goals and methods of the Millennium Cohort Study, which are to determine if risk factors related to military service, such as occupational specialty, deployment history, service type, and other exposures are associated with the development of chronic disease. (Gray, et al., 2002a)

The objectives of the sixth general study were to describe the psychological screening program for U.S. military personnel in different operations; present key findings from the psychological screening program; and highlight some of the lessons learned when implementing a psychological screening program. (Wright, et al., 2002)

Four articles published in 2002 focused on potential health effects of the anthrax vaccine. The objective of the first study was to monitor anthrax vaccine safety by comparing the rates of hospitalizations among anthrax-immunized and non-immunized U.S. military personnel on active duty in 1998. (Sato, et al., 2002)

The objective of the second vaccine study was to assess the safety of the anthrax vaccine given to nearly 400,000 military personnel in 1998 and 1999, through the evaluation of reports of adverse events submitted to the Vaccine Adverse

Event Reporting System (VAERS). (Sever, et al., 2002)

The objective of the third vaccine study was to compare the rates of ambulatory medical care among deployed persons who received the anthrax vaccine, with the rates in deployed persons who were not vaccinated. (Rehme, et al., 2002)

The objectives of the fourth vaccine study were to determine if anthrax vaccination would result in a measurable decrease in pregnancy rates, and to measure its effects on fetal loss and adverse birth outcomes. (Wiesen, et al., 2002)

6. Environmental Toxicology:

Two studies published in 2002 focused on environmental toxicology, specifically, the health effects of the oil well fire smoke. The objective of the first study was to explore the relationships between modeled exposures to contaminants released as a result of the Kuwaiti oil fires and rates of hospitalization due to any cause; hospitalization rates due to a diagnosis in one of 15 major categories; and hospitalization rates due to one of nine diagnoses that could be related to smoke exposure. (Smith, et al., 2002a) The objectives of the second study were to explore the relationship between symptoms of respiratory illness reported by Gulf War veterans and modeled exposures to contaminants released as a result of the Kuwait oil fires, as well as to self-reported smoke exposures. (Lange, et al., 2002)

7. Depleted Uranium:

Two studies published in 2002 focused on the health effects of depleted uranium. The objective of the first study was to describe the initial results of a uranium bioassay program for active and retired Canadian Forces personnel. (Ough, et al., 2002) The objective of the second study was to investigate potential mechanisms of carcinogenicity of depleted uranium (DU) fragments implanted in the soft tissue of rats. (Hahn, et al., 2002)

8. Chemical Weapons:

Six studies published in 2002 focused on the health effects of sarin in laboratory animals (rats and guinea pigs). (Mioduszewski, et al., 2002; Hulet, et al., 2002; Abdel-Rahman, et al., 2002; Henderson, et al., 2002; Conn, et al., 2002; Kalra, et al., 2002)

The objective of the first study was to develop a model for predicting dose-response effects of lethal vapor concentrations of sarin, as a function of duration, for a range of five minutes to six hours of exposure. (Mioduszewski, et al., 2002)

The objective of the second study was to determine a dose of injected sarin that could be given over a two-week period of daily exposures without causing severe, easily identifiable cholinergic symptoms such as tremors, seizures, or death. (Hulet, et al. 2002)

The objective of the third study was to investigate early neuropathological changes in the rat brain following a single exposure to different doses of injected sarin. (Abdel-Rahman, et al., 2002)

The fourth, fifth, and sixth studies were related to a single set of experiments. The objective of the fourth study was to determine whether single or repeated inhalation exposures to sub-clinical doses of sarin could result in subtle, adverse health effects in rats, that persisted as long as 30 days after the exposures ended. (Henderson, et al., 2002) The objective of the fifth study was to determine if single or repeated inhalation exposures to sub-clinical doses of sarin could impair regulation of body temperature and locomotor activity in rats, particularly under conditions of heat stress. (Conn, et al., 2002) The objective of the sixth study was to determine the effects of inhalation exposures to sub-clinical doses of sarin on immune function in the rat and to determine the possible mechanisms for such effects. (Kalra, et al., 2002)

9. Pyridostigmine Bromide:

One study published in 2002 focused on the health effects of pyridostigmine bromide (PB) in humans; and the objective was to evaluate the physiological and behavioral effects of PB in healthy, young volunteers, in particular, at the dosage of 30 mg three times a day, which DoD recommends for prophylaxis for nerve agent exposure. (Cook, et al., 2002)

10. Interactions of Exposures:

Seven laboratory studies published in 2002 focused on the effects of pyridostigmine bromide

(PB), in combination with stress or other chemicals. Two studies focused on the effects of PB in combination with stress (forced swimming, forced running, or restraint). (Tian, et al., 2002; Song, et al., 2002)

The objectives of the first study were to evaluate the effects of physical stress (forced swimming or forced running) on the short-term toxicity of pyridostigmine bromide (PB) in rats; and to determine if PB could cross the blood-brain barrier (BBB) and disrupt central nervous system function under conditions of physical stress. (Tian, et al. 2002)

The objective of the second study was to determine if stress modifies pyridostigmine (PB) neurotoxicity in rats, by evaluating the effects of single and repeated restraint stress on PB-mediated cholinergic toxicity and inhibition of cholinergic activity in blood and brain tissues. (Song, et al., 2002)

Five studies focused on the effects of PB in combination with other chemicals (DEET, permethrin, sarin, or organophosphate pesticides). (Abou-Donia, et al., 2002; Chaney, et al., 2002; Wilson, et al., 2002; Usmani, et al., 2002; Vogel, et al., 2002)

The objective of the first study was to evaluate how exposure to sarin and pyridostigmine bromide (PB), alone or in combination, could affect sensorimotor performance as well as the central cholinergic system in rats. (Abou-Donia, et al., 2002)

The objective of the second study was to explore the immediate lethal interaction between pyridostigmine bromide (PB) and DEET when administered in combination at high doses to rats, to determine the possible biological mechanism for this interaction. (Chaney, et al., 2002)

The objective of the third study was to determine if combined exposure to PB, sarin, and/or diisopropyl phosphofluoridate (DFP) is more neurotoxic to chickens than if given separately, by examining inhibition of two enzymes. (Wilson, et al., 2002)

The objectives of the fourth study were to quantify the metabolism of DEET by human microsomes, extracted from donated liver specimens; to identify the human P450 isoenzymes responsible for the metabolism of DEET; and to investigate the potential for inhibition or activation of DEET metabolism, in combination with chlorpyrifos, permethrin, or pyridostigmine bromide. (Usmani, et al., 2002)

The objective of the fifth study was to use accelerator mass spectrometry (AMS) to quantify radio-labeled diisopropylfluorophosphate (DFP) as a tracer at attomolar levels (10^{-18} molar), after co-exposures to two different classes of pesticides in mice, alone or in combination. (Vogel, et al., 2002)

III. RESEARCH FUNDING TRENDS

The Gulf War Veterans' Illnesses research portfolio currently includes 239 projects. It was last updated during the first quarter of Fiscal Year 2003 (through December 31, 2002). These 239 Federal research projects are sponsored by the Departments of Veterans Affairs (VA), Defense (DoD), or Health and Human Services (HHS). The scope of the Federal research portfolio is broad, from small pilot studies to large-scale epidemiology studies involving large populations and major research center programs. From FY94 through FY02, Federal Government funding for the direct costs of Gulf War research exceeded $227 million. The total does not include indirect costs of conducting the research such as facility, administrative and operational costs because indirect costs can be computed only by facility and not by project. Estimates of these indirect costs approach $70 million. As of September 30, 2002, 152 projects were completed (64% of total), and 87 projects were ongoing. The overall emphasis of research has been greatest in the focus areas of Symptoms and General Health Status, and Brain and Nervous System Function. The numbers of projects in each focus area are described in more detail in Section III.

IV. NEW RESEARCH PROJECTS AND INITIATIVES

Besides new research findings appearing in the published scientific literature, there have been several important events since last year's *Annual Report to Congress* that deserve discussion. These include the awarding of new research projects and the development of new research initiatives. This section also updates important accomplishments of key research projects and initiatives in 2002.

A. NEW RESEARCH PROJECTS

1. VA Program Announcement on Deployment Health Research

VA places a high priority on the development of improved methods of diagnosis, treatment, and prevention of illnesses related to hazardous deployments, such as the Gulf War, Bosnia/Kosovo, Afghanistan, and the current war in Iraq. In 2002, VA released a Program Announcement on Deployment Health Research to expand its research portfolio. The complete Program Announcement can be accessed at: www.va.gov/resdev/fr/ProgramAnnouncementDeploymentHealthIssues.pdf
VA recognizes five major research 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

2. National Registry of Veterans with Amyotrophic Lateral Sclerosis (Project VA-89)

Amyotrophic lateral sclerosis (ALS) is a rapidly fatal neuromuscular disease of unknown etiology. In December 2001, VA and DoD released the preliminary results of a study of ALS in Gulf War veterans (VA-61/DoD-118). The incidence of ALS was increased almost two-fold in Gulf War veterans, compared to non-deployed veterans. Therefore, VA determined that systematic identification and tracking of veterans with ALS was a high research priority. Accordingly, in 2002, VA funded a National Registry of veterans diagnosed with ALS (VA-89). ALS is a very rare disease, therefore it is very difficult to identify and enroll adequate numbers of patients in clinical trials of promising new treatments. This National Registry is the first step to develop the capability to set up national treatment trials. There are three objectives for this Registry:

- to provide VA with data on the current number and characteristics of veterans with ALS, as well as the ongoing identification of new cases;
- to provide VA with an important data resource for future studies examining the causes and treatment of ALS; and
- to provide a mechanism for VA to inform veterans with ALS about treatment trials and other studies for which they may be eligible.

3. DoD Broad Agency Announcement on Low-Level Chemical Exposures in Gulf War Veterans

In the summer of 2002, the U.S. Army Medical Research and Materiel Command released a solicitation (Broad Agency Announcement) for research proposals on persons who served on active duty in the Southwest Asia theatre of operations during the Gulf War. The focus of this solicitation was research on: 1) possible health effects of exposures to low-levels of hazardous chemicals; and 2) individual susceptibility of humans to such exposures under environmentally controlled conditions. After independent review by scientific experts, one proposal was recommended for funding on the basis of scientific merit and highest relevance to the Congressional law. In 2003, this four-year project will start at Rutgers University, focusing on the effects of diesel exhaust and stress on symptoms in chemically intolerant individuals.

B. 2002 UPDATE OF KEY RESEARCH PROJECTS AND INITIATIVES

1. Deployment Health Working Group

In 2002, the Deployment Health Working Group (DHWG) was chartered to provide interagency coordination regarding the health of active-duty service personnel and veterans, related to past, current, and future deployments. The DHWG replaced the Military and Veterans Health Coordinating Board, and it has a broader mission. The DHWG charter outlines its responsibilities, which include: "collaboration between VA, DoD and HHS on a broad range of military and veterans' health matters to achieve the nation's commitment to maintain, protect and preserve the health of the men and women who serve in the U.S. Armed Forces. . . The work group provides recommendations and coordination for deployment health research activities, health risk communication efforts, and

other matters related to deployment health as they arise."

2. VA Research Advisory Committee on Gulf War Veterans' Illnesses

In January 2002, the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) was appointed. This Committee was established by Congress to provide advice on research studies to the Secretary of the VA on a regular basis. The VA approved the charter for the RACGWVI in January 2002. The charter defines its scope of activity as follows: "The VA RACGWVI shall provide advice and make recommendations to the Secretary of the VA on proposed research studies, research plans, and research strategies relating to the health consequences of military service in the Southwest Asia theater of operations during the Persian Gulf War."

The Committee held its first meeting in April 2002, and two more meetings in 2002. It released an *Interim Report* in June 2002, which contained seven recommendations for future research on illnesses in Gulf War veterans. This report is accessible at: www.appc1.va.gov/rac-gwvi/

3. Medsearch: Gulf War Veterans Medical Library Web Site

DoD, CDC, and VA have collaborated to create a web-based library of Gulf War-related research, entitled Medsearch. Accessible at http://www.gulflink.osd.mil/medsearch/, the library was developed to help service members, veterans, families, and the public learn about research efforts into health concerns related to service during the Gulf War. The Medsearch web site was launched on June 18, 2002. The three major sections of Medsearch contain descriptions of government funded research projects that link to abstracts of articles published in peer-reviewed journals; explanations of the major research areas such as exposure to low-level chemical weapons; and a compilation of the most important, relevant government reports.

4. Conference on Post-Deployment Care: Risk Communication and Terrorism-New Clinical Approaches

On September 9 to 11, 2002, a conference was held in Alexandria, VA, entitled: Conference on Post-Deployment Care: Risk Communication and Terrorism-New Clinical Approaches. The purpose was to provide cutting-edge information on clinical risk communication to strengthen health provider-patient relationships. Four initiatives funded by VA and CDC, specifically related to illnesses in Gulf War veterans, were highlighted during this conference. In 2001, VA funded two War-Related Illness and Injury Study Centers at the East Orange, NJ VAMC and the Washington, DC VAMC. Both Centers have developed new research initiatives on risk communication. In 2001, CDC funded two new research projects focusing on the development of improved methods of risk communication, at Rutgers University and at Walter Reed Army Medical Center. Detailed information about this conference, including the agenda, is accessible at www.pdhealth.mil/education/conference.asp

V. RESEARCH PRIORITIES

The Federal government identified three sets of research priorities in 1995, 1996, and 1998 (PGVCB, 1995b; 1996b; 1999a). Substantial progress has been made on each of these sets of priorities, which is detailed in Section V.

I. INTRODUCTION

On August 31, 1993, in response to section 707 of Public Law 102-585, President William J. Clinton named the Secretary of Veterans Affairs (VA) to coordinate research activities undertaken or funded by the Executive Branch of the Federal Government into the health consequences of service in the Gulf War. Section 104 of Public Law 105-368 (1998) expanded the range of activities to be coordinated. VA carries out its coordinating role through the auspices of the Research Subcommittee of the interagency Deployment Health Working Group (DHWG). The VA Under Secretary of Health and the Department of Defense (DoD) Assistant Secretary for Health Affairs chair the DHWG.

As part of its coordination role, VA is required to submit an annual report on the results, status, and priorities of research activities to the Senate and House Veterans' Affairs Committees. This document, the 2002 *Annual Report to Congress*, is the ninth report on research and research activities. (PGVCB, 1995a; 1996a; 1997; 1998a; 1999a; 2001; MVHCB, 2001a; 2002; DHWG, 2003) The 2002 *Annual Report to Congress* describes research funded by Federal and non-federal institutions. All new peer-reviewed reports of high quality research add to existing knowledge, regardless of funding source.

This Annual Report is divided into five Sections. Following this introductory Section, Section II highlights and summarizes research progress since the last Annual Report. Section III is an analysis of the Federal Government's portfolio of research on Gulf War veterans' illnesses. Section IV highlights significant research projects and initiatives since the last Annual Report. Section V discusses priorities established in 1995, 1996, and 1998 for future new research, and highlights the progress made to date.

II. RESEARCH RESULTS IN 2002

In the past year, there have been several research studies that have yielded results that provide new and expanded information on the health problems of Gulf War veterans. This Section provides brief summaries of research projects for which results were published from January 2002 to December 2002. Because all scientifically peer-reviewed research must be considered in assessments of Gulf War veterans' illnesses, these summaries are inclusive of both Federally funded and non-federally funded research. The Deployment Health Working Group tracks all Federally-funded research projects related to Gulf War veterans' illnesses. These are described in Appendix A.

All research studies have strengths and limitations. The presence of limitations in a particular study does not necessarily invalidate its findings or conclusions, but must be taken into account in evaluating a study's overall weight and impact. For this reason, the strengths and limitations of each of the new reports of study findings are cited as a guide for the reader. Among the limitations, epidemiological studies are frequently subject to a variety of biases. For example, studies that rely on self-reported symptoms and exposures are subject to recall bias, and studies that rely on self-selected cohorts (such as registry participants) are subject to selection bias. Other factors potentially affecting epidemiological outcomes include sample size and response rate.

Research using animal models is also subject to limitations in its applicability to a specific situation for humans. Sources of limitations include extrapolation of biological processes from one animal species to another, and extrapolation of experimental dosing regimens (route of administration, amount, and duration) from animal experiments to real human exposure situations. Experiments utilizing whole laboratory animals are less difficult to extrapolate to humans than studies performed in test tubes; therefore, studies of whole animals are emphasized in this report.

As in previous reports to Congress, research has been categorized according to the particular focus of the research. The research reports summarized below are grouped in ten focus areas: symptoms and general health status, brain and nervous system function, diagnosis, immune function, prevention, environmental toxicology, depleted uranium, chemical weapons, pyridostigmine bromide, and interactions of exposures.

A. Symptoms and General Health Status

Overview:

Thirteen large studies published in 2002 focused on symptoms and general health. (Gray, et al.,

2002b; McCauley, et al., 2002a; McCauley, et al., 2002b; Shapiro, et al., 2002; Kang, et al., 2002; Unwin, et al., 2002; Higgins, et al., 2002; Hull, et al., 2002; Smith, et al., 2002b; Richardson, et al., 2002; Voelker, et al., 2002; Wolfe, et al., 2002; Jones, et al., 2002) These publications included the results of studies conducted at five Federally-funded research centers in San Diego, Portland, Oregon, Iowa City, Boston, and London, UK. Each of the publications included hundreds to thousands of individuals. Six of these studies were population-based, which means that the results of these studies may have implications for the overall population of 697,000 Gulf War veterans. (McCauley, et al., 2002a; Kang, et al., 2002; Unwin, et al., 2002; Higgins, et al., 2002; Hull, et al., 2002; Voelker, et al., 2002)

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The objectives of the second and third study were linked, and were based on an investigation of three groups of veterans: 653 Gulf War veterans who had deployed within 50 km of Khamisiyah, Iraq in March 1991; 610 Gulf War veterans who were distant from Khamisiyah; and 516 non-deployed veterans. The objectives of the second study were to examine the relationships between possible low-level exposure to organophosphate nerve agents and subsequent health effects, including medical diagnoses, hospitalizations, and disability. (McCauley, et al., 2002b) The objectives of the third study were to determine if a unique pattern of symptoms was present in veterans located near Khamisiyah; and if so, to determine if the pattern differed from that of veterans located farther away from Khamisiyah, or from that of non-deployed veterans. (Shapiro, et al., 2002)

The objective of the fourth study was to use factor analysis to determine if patterns of reported symptoms were similar in Gulf War veterans, compared to patterns of reported symptoms in non-deployed veterans, based on data from the VA National Health Survey. (Kang, et al., 2002)

The objective of the fifth study was to examine the clinical characteristics of Gulf War veterans with chronic fatigue syndrome (CFS), compared to healthy Gulf War veterans. (McCauley, et al., 2002a)

The objectives of the sixth, seventh, and eighth studies were linked, and were based on an investigation of three groups of British veterans: Gulf War veterans, Bosnia veterans, and non-deployed veterans. The objective of the sixth study was to compare the health outcomes of British service women who served in the Gulf War with women who served in Bosnia and women who were in the service, but who did not leave Great Britain (era veterans). (Unwin, et al., 2002) The objectives of the seventh study were to compare the nature and prevalence of skin disease in Gulf War veterans with Bosnia and era veterans. (Higgins, et al., 2002) The objective of the eighth study was to compare the characteristics of veterans who participated in the British Gulf War registry program, with veterans who did not, particularly in regard to their rates of ill health and health attributions. (Hull, et al., 2002)

The objective of the ninth study was to identify demographic and military factors and occupational and environmental exposures that were associated with registry participation, among 100,000 American veterans who were enrolled in the VA and DoD Gulf War registries. (Smith, et al., 2002b)

The objective of the tenth study was to compare Gulf War veterans seeking primary care at two different settings, at the Seattle VA Medical Center and Walter Reed Army Medical Center, on measures of physical symptoms, psychiatric distress, functional status, and employment status. (Richardson, et al., 2002)

The objectives of the eleventh study were to compare the health-related quality of life (HRQL) of Gulf War veterans with non-deployed veterans, and to identify potential risk factors for poorer HRQL, before and during deployment, among 3,695 veterans from the state of Iowa. (Voelker, et al., 2002)

The objective of the twelfth study was to determine if self-reported environmental

exposures and psychological distress were associated with chronic multisymptom illness, among 1,290 members of the Fort Devens, Massachusetts cohort. (Wolfe, et al., 2002)

The objectives of the thirteenth study were to determine if post-combat syndromes have existed after modern wars and what their relationships were to each other, based on British medical records from the Boer War to World War II. (Jones, et al., 2002)

Gulf War veterans have consistently reported increased frequencies of symptoms, compared to non-deployed veterans, related to a wide variety of organ systems. Large population-based studies in the US, UK, and Canada have shown increased rates of self-reported illnesses in GWV, including chronic fatigue, memory problems, posttraumatic stress disorder, depression, musculoskeletal problems, and asthma. (Iowa Persian Gulf Study Group, 1997; Kang, et al., 2000; Goss Gilroy, 1998; Unwin, et al., 1999; Unwin, et al., 2002; Cherry, et al. 2001a) Other large studies that were not population-based have also shown the same pattern of increased symptom reporting in Gulf War veterans. (Pierce, 1997; Fukuda, et al., 1998; Gray, et al., 1999a; Gray, et al., 2002b; Wolfe, et al., 1999b; Steele, 2000) In several studies, Gulf War veterans have reported increased frequencies of almost all symptoms included in the questionnaires. For example in the Iowa study, Gulf War veterans reported significantly higher rates of 123 of 137 symptoms (90%) during the past year, compared to non-deployed veterans. These symptoms were related to all organ systems. The authors concluded that the increased prevalence in Gulf War veterans of nearly every symptom is "difficult to explain pathophysiologically as a single condition." (Iowa, 1997; Doebbeling, et al., 2000) Similar patterns of symptom reporting in many organ systems were found in other studies, including two large 2002 studies. (Kang, et al., 2000; Gray, et al., 1999a; Gray, et al., 2002b; Steele, 2000; Unwin, et al., 1999; Unwin, et al., 2002; Cherry, et al., 2001a)

Seven large, controlled studies have used factor analysis, and each study has shown that Gulf War veterans do not suffer from a unique, previously unrecognized "Gulf War syndrome." Thousands of Gulf War veterans and non-deployed veterans have been evaluated in these studies, including: the US Air Force; the US Navy; the U.S. Army; all three services in the US, in two independent studies; and all three services in Great Britain, in two independent studies. (Fukuda, et al., 1998; Knoke, et al., 2000; Shapiro, 2002; Doebbeling, et al., 2000; Kang, et al., 2002; Ismail, et al., 1999; Cherry, et al., 2001a) In all seven studies, the patterns of symptoms reported by Gulf War veterans were similar to the patterns reported by non-deployed veterans. In general, Gulf War veterans reported higher rates of the patterns of symptoms than non-deployed veterans. (Kang, et al., 2002) However, in some studies, non-deployed veterans reported higher rates of some of the patterns of symptoms. (Knoke, et al., 2000; Cherry, et al., 2001a)

An analysis was performed to determine if post-combat syndromes have occurred after several wars. (Jones, et al., 2002) A previous historical study had concluded: "Poorly understood war syndromes have been associated with armed conflicts at least since the U.S. Civil War. Although these syndromes have been characterized by similar symptoms (fatigue, shortness of breath, headache, sleep disturbance, forgetfulness, and impaired concentration), no single recurring illness that is unrelated to psychological stress is apparent." (Hyams, et al., 1996) The current study utilized British war pension files as the primary data source. (Jones, et al., 2002) Records of 1,856 British veterans were randomly selected from war pension files starting in 1872, including from the Boer War (400 veterans), World War I (640), and World War II (367). In addition, medical records for 400 Gulf War veterans were abstracted from the Medical Assessment Program (the British Gulf War registry). Medical notes were detailed in the pension records, covering the veterans' histories from enlistment until death. The records of each veteran were abstracted, including a list of 25 symptoms. The 25 symptoms were subjected to cluster analysis, which yielded three groups of correlated symptoms. These were: a debility syndrome, without psychological or cognitive symptoms (including fatigue, difficulty completing tasks, shortness of breath, and weakness); a somatic syndrome focused on the heart (including rapid heartbeat, shortness of breath, fatigue, and dizziness); and a neuropsychiatric syndrome with a range of associated somatic symptoms (including fatigue, headaches, depression, anxiety, and difficulty sleeping). The era in which the war occurred was overwhelmingly the

best predictor of the particular group of symptoms that a given veteran would report. Most Gulf War cases fell into the neuropsychiatric group (54%), but Gulf War veterans were found in all three groups (37% debility, 10% somatic). The authors concluded: "the three syndromes are unrelated to any particular exposure as they occurred during several wars, albeit with different frequencies."

Two studies in Portland and New Jersey have highlighted the necessity of caution in the interpretation of surveys, if they are used as the sole source of health data. (McCauley, et al., 1999a; Bourdette, et al., 2001; McCauley, et al., 2002a; Pollet, et al., 1998; Lange, et al., 1999; Natelson, et al., 2001) In both studies, substantial proportions of potential cases were not included, due to exclusions for medical diagnoses made on clinical evaluation. Several large studies involve comprehensive evaluations to provide medical verification of self-reported symptoms and illnesses, including the VA National Health Survey, and studies in Portland, New Jersey, Pennsylvania, Iowa, and the UK. (McCauley, et al., 1999a; Storzbach, et al., 2000; Bourdette, et al., 2001; McCauley, et al., 2002a; Pollet, et al., 1998; Lange, et al., 1999; Natelson, et al., 2001; Lange, et al., 2001; Fukuda, et al., 1998; Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Higgins, et al., 2002)

Four groups of British veterans, who participated in a mail survey in 1997-98, were invited to undergo a one-day medical exam at King's College Hospital in London in 1999-2000. Four studies were published in 2002, based on these medical exams. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Higgins, et al., 2002) The four groups were randomly selected, based on their reported level of physical disability: 111 Gulf War veterans who reported disability; 98 Gulf War veterans who did not report disability; 54 veterans of the Bosnia conflict who reported disability; and 79 veterans who did not deploy outside the UK who reported disability (era veterans). The results of structured psychiatric interviews, standardized neuropsychological testing, detailed neurological evaluations, and dermatological exams were published. The risk of one or more concurrent psychiatric disorders was 2.4 times higher in ill Gulf War veterans, compared to healthy Gulf War veterans, including major depression, anxiety disorders, PTSD, and alcohol related disorders. (Ismail, et al., 2002) There was no evidence of objective neuropsychological impairment in ill or healthy Gulf War veterans, compared to Bosnia or era veterans. (David, et al., 2002) There was no evidence in Gulf War veterans of objective generalized neurologic or neuromuscular dysfunction, or abnormalities of the autonomic nervous system, compared to Bosnia and era veterans. (Sharief, et al., 2002) There were no increases in the rates of 19 types of skin conditions in Gulf War veterans, with one exception. Seborrheic dermatitis was twice as prevalent in both ill and healthy Gulf War veterans, compared to Bosnia and era veterans (Higgins, et al, 2002)

Several studies have evaluated the rates of three poorly-understood syndromes in Gulf War veterans-chronic fatigue syndrome (CFS), multiple chemical sensitivities (MCS), and fibromyalgia. Gulf War veterans have reported increased rates of symptoms of CFS and MCS, compared to non-deployed veterans. (Iowa, 1997; Black, et al., 1999; Black, et al., 2000; Goss Gilroy, 1998; Unwin, et al., 1999; Reid, et al., 2001; Proctor, et al., 2001b; Gray, et al., 2002b) Ill Gulf War veterans reported increased rates of symptoms of CFS and MCS, compared to healthy Gulf War veterans. (Kipen, et al., 1999; Bourdette, et al., 2001; McCauley, et al., 2002a) Gulf War veterans with CFS or MCS reported significantly higher rates of psychiatric disorders than control populations, a finding that has previously been reported in civilian populations with CFS or MCS. (Pollet, et al., 1998; Lange, et al., 1999; Lange, et al., 2001; Black, et al., 1999; Black, et al., 2000; Reid, et al., 2001; Proctor, et al., 2001b) Gulf War veterans also reported higher rates of symptoms of fibromyalgia (FM) than comparison veterans. (Iowa, 1997; Goss Gilroy, 1998; Smith, et al., 2000; Bourdette, et al., 2001) Several studies involve medical evaluations of veterans with symptoms of CFS, MCS, and FM, including the VA National Health Survey and studies in New Jersey, Portland, Iowa, and the UK. (Pollet, et al., 1998; Lange, et al., 1999; Lange, et al., 2001; Natelson, et al., 2001; McCauley, et al., 1999a; Storzbach, et al., 2000; Storzbach, et al., 2001; Bourdette, et al., 2001; Ford, et al., 2001; McCauley, et al., 2002a)

In 2002, three studies evaluated the demographic, occupational, and clinical factors in Gulf War veterans that were related to seeking medical care. (Hull, et al., 2002; Smith, et al., 2002b; Richardson, et al., 2002) The VA Gulf

War registry started in 1992 and the DoD Gulf War registry started in 1994. The U.K. started a similar registry in 1993, the Medical Assessment Program (MAP). Among 3,529 British Gulf War veterans who participated in a 1997-98 mail survey, 173 (5%) veterans had participated in the MAP, and 3,356 (95%) veterans had not. (Hull, et al., 2002) The 173 veterans who participated in the MAP were significantly more likely to be older, female, unemployed, to have less education, and to have been medically discharged from the service. The 173 veterans in the MAP reported significantly higher numbers of symptoms (mean of 20.5 vs. 10.3 symptoms), and higher numbers of medical conditions (mean of 4.5 vs. 2.2 conditions). The authors concluded: "MAP patients are unrepresentative of the wider deployment to the Persian Gulf."

In the second study, the study population included 66,227 patients enrolled in the VA Gulf War Registry, and 29,721 patients enrolled in the DoD registry, who had been examined by September 1999. (Smith, et al., 2002b) Regression modeling was used to determine risk factors that were associated with participation in either registry. Enrollment was significantly associated with female gender; age 31 years or older in 1990; enlisted rank; Reserve and National Guard status vs. active-duty; and hospitalization in a military hospital in the 12 months before the war. Navy troops were least likely to enroll in the registries. In comparison to the Navy, the odds ratios for enrollment were 1.56 for the Air Force, 2.64 for the Marines, and 4.57 for the Army.

The objective of the third study was to compare Gulf War veterans seeking primary care at two different settings, at the Seattle VA Medical Center and Walter Reed Army Medical Center, on measures of physical symptoms, psychiatric distress, functional status, and employment status. (Richardson, et al., 2002) In 1998-99, 406 consecutive patients were included from the primary care clinics in Seattle (253 veterans) and in Washington, DC (153 active-duty or reservists). Compared to VA patients, DoD patients were more likely to be older, female, black, more educated, Army vs. other branches, reservists rather than active-duty before the Gulf War, currently employed, have an income more than $25,000 per year, and current non-smokers. Six percent of DoD patients were unemployed, compared to 29% of VA patients. VA patients reported significantly higher rates of anxiety and PTSD symptoms, compared to the DoD patients. Also, unemployed patients reported significantly higher rates of depression and PTSD symptoms, compared to employed patients. The authors commented: "Research findings based exclusively on one sample or the other may not generalize to the population of Gulf War veterans at large. In addition to the findings on site differences, employment status among Gulf War veterans was consistently and independently predictive of health functioning."

Several large studies have demonstrated a significant association between demographic, lifestyle, and occupational risk factors and increased reporting of symptoms among Gulf War veterans. Demographic and lifestyle factors consistently associated with increased symptoms include increasing age, female gender, lower education, current unemployment, and cigarette smoking. Military factors consistently associated with increased symptoms include Reserve/National Guard vs. active-duty status; enlisted vs. officer status; Army vs. other military branches; and discharged from vs. still serving in the military. (Iowa, 1997; Wolfe, et al., 1998; Sharkansky, et al., 2000; Fukuda, et al., 1998; Nisenbaum, et al., 2000; Kang, et al., 2000; Steele, 2000; Bourdette, et al., 2001; Gray, et al., 2002b; Unwin, et al., 1999; Ismail, et al., 2000; Chalder, et al., 2001; Reid, et al., 2001; Hull, et al., 2002; Cherry, et al., 2001a)

In a clinical study in Portland, Oregon, there were several differences between Gulf War veterans diagnosed with chronic fatigue syndrome (CFS) and healthy Gulf War veterans. (McCauley, et al., 2002a) Veterans with CFS were significantly more likely to be younger, female, previously in the Army vs. other service branches, currently unemployed, and a participant in the VA Gulf War registry. The objective of an Iowa study was to compare the health-related quality of life of Gulf War veterans with non-deployed veterans, as measured on the SF-36. (Voelker, et al., 2002) Lower (worse) scores on the SF-36 were significantly related to service in the Gulf War, service in the Army vs. other branches, cigarette smoking, and several pre-war medical and psychiatric conditions. The objective of a Boston study was to determine risk factors for chronic symptoms of fatigue, musculoskeletal pain, and cognitive symptoms in Gulf War veterans, compared to healthy Gulf War veterans. (Wolfe, et al., 2002) These symptoms

were significantly related to female gender, lower education, and psychological distress.

Five studies have evaluated the health effects of potential exposure to very low levels of sarin and cyclosarin, related to the demolition of munitions in Khamisiyah, Iraq in March 1991. (Kang and Bullman, 2001; Gray, et al., 1999c; McCauley, et al., 2002b; Shapiro, et al., 2002; Smith, et al., 2002b) The mortality rates of 48,281 Gulf War veterans who were potentially exposed to nerve agent were compared to mortality rates of 573,621 Gulf War veterans who were not exposed. There were no differences in the overall mortality rates, or in the rates of cause-specific mortality (all diseases, all cancers, motor accidents, and suicide.) (Kang and Bullman, 2001) Hospitalizations were compared between 124,487 veterans who were potentially exposed to nerve agents, and 224,804 veterans with no exposure. There were no differences in the rates or types of hospitalizations. (Gray, et al., 1999c) Several health outcomes were compared between 653 Army Gulf War veterans with potential nerve agent exposure and 610 Army Gulf War veterans with no exposure. (McCauley, et al., 2002b; Shapiro, et al., 2002) There were no differences between the two groups, regarding: 19 medical conditions diagnosed by a physician, rates of hospitalization since 1991, rates of current unemployment, or rates of service-connected disability. (McCauley, et al., 2002b) In addition, there were no differences in the rates or patterns of 25 symptoms. (Shapiro, et al., 2002) 98,835 veterans who were enrolled in the VA or DoD Gulf War registries were divided into a group with potential exposure to nerve agents and a group without exposure. Veterans with potential exposure were 10% more likely to be enrolled in the registries, compared to veterans with no exposure. The authors interpreted that this increase was likely to be due to the notification letters or to media coverage of Khamisiyah events. (Smith, et al., 2002b) Overall, these five studies demonstrated no differences in the health of Gulf War veterans who had potential exposure to nerve agents due to Khamisiyah, compared to Gulf war veterans who did not have exposure.

Symptoms and General Health Status-Individual Studies:

1. Gray, GC, Reed, RJ, Kaiser, KS, Smith, TC, and Gastanaga, VM. Self-reported symptoms and medical conditions among 11,868 Gulf War era veterans: The Seabee Health Study. *American Journal of Epidemiology* 2002b June 1; 155(11):1033-1044. **(DoD-1E)**

In May 1997 to May 1999, a mail survey was performed of all regular and Reserve Navy personnel who served on active duty in seven Naval Mobile Construction Battalions (NMCB, also known as Seabees) during the Gulf War period (August 1990 to July 1991). (Gray, et al., 2002b) The primary objective of this study was to compare the rates of self-reported symptoms among veterans who deployed to the Gulf War (Gulf War Seabees), veterans who deployed to another foreign country (Seabees deployed elsewhere), and veterans who did not leave the U.S. (non-deployed Seabees). Some of the earliest and most persistent reports of illnesses among Gulf War veterans came from members of one Reserve Seabee unit from the southeastern U.S. (24th Seabees). (IOM, 1995; Presidential Advisory Committee, 1996b; Haley, et al., 1997a; Gray, et al., 1999a) The secondary objective of this study was to study all Gulf War-era Seabees, including active-duty, Reserve, and separated veterans, to determine if increased symptom reporting was more prevalent in 24th Seabees, compared to other Seabee units.

11,868 of 17,559 potential subjects completed the survey (69% response rate), including 3,831 Gulf War Seabees, 4,933 Seabees deployed elsewhere, and 3,104 non-deployed Seabees. (Gray, et al., 2002b) The questionnaire requested data on past medical history, current symptoms, current health status, lifestyle habits, and environmental exposures. Gulf War veterans were significantly more likely to report one or more hospitalizations since 1990, and to report digestive diseases or depression since 1990, that caused them to lose one or more weeks of work. Gulf War veterans were significantly more likely to report each of 33 symptoms during the previous 12 months. Gulf War veterans were also significantly more likely to report 18 of 23 physician-diagnosed illnesses since 1991, than were the other two groups of veterans.

Gulf War veterans were at significantly higher risk for four of the 23 physician-diagnosed illnesses: chronic fatigue syndrome, posttraumatic stress disorder, multiple chemical sensitivity, and irritable bowel disease. Because several studies have tried and failed to identify a unique "Gulf War syndrome," the authors

developed their own working case definition of "Gulf War illnesses" (GWI) by aggregating these four diagnoses. Gulf War veterans who reported 12 or more of the 33 symptoms in the previous 12 months were also classified as cases of GWI. 845 Gulf War veterans (22%) met the working case definition of GWI. In a multivariable model, and in comparison with other Gulf War veterans, the 845 veterans who met the GWI case definition were significantly more likely to be female gender, Reserve status, or members of two regular active-duty Seabee units (NMCB 40 or NMCB 133). After Reserve status was controlled in this model, personnel assigned to the 24th Seabees did not report more symptoms than members of other Seabee units. Several previous studies of Gulf War veterans have shown that female gender and Reserve status were associated with increased symptom reporting.

In the multivariable model, 12 out of a possible 34 self-reported environmental exposures were weakly associated with the GWI case definition, such as "fumes from munitions" or "seeing anyone getting killed." This finding of multiple, weak associations with environmental exposures has been reported in several studies in Iowa, Pennsylvania, Portland, Oregon, Boston, and Great Britain. (Iowa, 1997; Fukuda, et al., 1998; Nisenbaum, et al., 2000; Spencer, et al., 2001; Wolfe, et al., 2002; Cherry, et al., 2001b) The authors concluded: "The exposure associations seem too weak and disparate to support a cohesive explanation of postwar morbidity. Instead, the aggregate stressors of war seem a more plausible etiology." (Gray, et al., 2002b) The authors cautioned that this study was limited, because "recall bias is a very real problem among Gulf War Seabees. It is likely that some Gulf War Seabees may have been influenced by news stories, previous survey participation, or the mailings sent to more than 300,000 Gulf War veterans by the Defense Department's Office of the Special Assistant for Gulf War Illnesses."

2. McCauley, LA, Lasarev, M, Sticker, D, Rischitelli, DG, and Spencer, PS. Illness experience of Gulf War veterans possibly exposed to chemical warfare agents. *American Journal of Preventive Medicine* 2002b October; 23(3):200-206. **(DoD-63)**

Scientists at the Oregon Health Sciences University conducted a telephone survey to investigate neurological symptoms and medical diagnoses in Gulf War veterans who may have had low-level nerve agent exposure, as a result of the demolitions of munitions at Khamisiyah, Iraq in March 1991. (McCauley, et al., 2002b) All participants had been on active-duty in the Army or Army National Guard during the period of January to March 1991. At the time of the interviews in 1998-99, all participants were residents of North Carolina, Georgia, Oregon, Washington, and California. These locations were selected because the majority (88%) of veterans who had deployed near Khamisiyah were located in North Carolina or Georgia; and the scientific team was located in or near the other three states. 653 participants were located within 50 km of Khamisiyah in early March 1991, and they had received notification letters from DoD in early 1997 about potential low-level exposure to nerve agents. 610 participants were located farther than 50 km from Khamisiyah during March 1991, and were therefore unlikely to have been exposed to nerve agents. 516 participants had not deployed to the Gulf War. The objectives of this particular analysis were to examine the relationship between low-level exposure to organophosphate nerve agents and subsequent health effects, including medical diagnoses, hospitalizations, and disability. (McCauley, et al., 2002b)

There were significant demographic differences among the three groups of veterans. The veterans near Khamisiyah were nearly all male, active-duty troops, who were living in North Carolina and Georgia. Because of these differences, all analyses were adjusted for region of residence, gender, age, and ethnicity. The rates of 19 medical conditions diagnosed by a physician were compared among the three groups of veterans. There were no differences in the rates of any of the 19 conditions among the 653 veterans near Khamisiyah, compared to the 610 veterans farther away. Six conditions were significantly elevated in the group of all 1,263 Gulf War veterans, compared to the 516 non-deployed veterans. These were: PTSD (odds ratio=14.9); hospitalization for depression (OR=5.1); heart disease (OR=2.5); high blood pressure (OR=1.7); periodontal disease (OR=1.8); and slipped disk or pinched nerve (OR=1.5). Many studies of Gulf War veterans have consistently demonstrated increased rates in the diagnoses of PTSD and depression, compared to controls. There were no differences in the rates of peripheral neuropathy, which is

noteworthy because a previous study had hypothesized that low-level exposure to nerve agents and/or the use of pyridostigmine bromide had caused organophosphate-induced peripheral neuropathy in Gulf War veterans. (Haley, et al, 1997c)

There were no differences in current rates of use of prescription medication for chronic health problems among the three groups of veterans. (McCauley, et al., 2002b) There were no differences in the rates of hospitalization since the Gulf War (37% of veterans near Khamisiyah; 32% of veterans farther away from Khamisiyah, and 31% of non-deployed veterans). There were no differences in the rates of current unemployment (3.1% in both groups of Gulf War veterans and 3.5% in non-deployed veterans). Service-connected disability did not differ among the three groups (29% of veterans near Khamisiyah; 22% of veterans farther away from Khamisiyah; and 26% of non-deployed veterans). This study had three limitations. First, the study population was limited to individuals whose current telephone numbers could be successfully located, so this sample may not be completely representative of the entire population of 697,000 Gulf War veterans and 814,000 non-deployed veterans. Second, all the analyses were adjusted for regional location; however, the differences between the Gulf War and non-deployed groups may have been influenced by some unrecognized factor associated with regional location. Third, the categories of within 50 km or farther than 50 km of Khamisiyah may have led to some misclassification of exposure. However, DoD has reported that no troops experienced symptoms at any location, even in the units closest to Khamisiyah.

The authors concluded: "Our findings suggest that veterans who were possibly exposed to low levels of chemical warfare agents do not differ from other deployed veterans on any health indicator, including self-reported medical diagnoses, hospitalization, or disability. . . While the long-term sequelae of low-dose exposure to chemical warfare agents remains an area of scientific debate, the results of our study indicate that the exposed Khamisiyah group does not currently appear to be at increased risk for the development of chronic disease." The results of this study are consistent with two other studies that evaluated the effects of potential nerve agent exposure due to Khamisiyah. One study of hospitalization rates and one study of mortality rates demonstrated no adverse effects due to Khamisiyah. (Gray, et al., 1999c; Kang and Bullman, 2002)

3. Shapiro, SE, Lasarev, MR, and McCauley, L. Factor analysis of Gulf War illness: what does it add to our understanding of possible health effects of deployment? *American Journal of Epidemiology* 2002 September 15: 156(6):578-585. **(DoD-63)**

The primary objectives of this particular analysis were to determine if a unique pattern of symptoms was present in veterans located within 50 km of Khamisiyah; and if so, to determine if the pattern differed from that of veterans located farther away from Khamisiyah, or from that of non-deployed veterans. (Shapiro, et al., 2002) Factor analysis was the statistical technique used to detect patterns of correlation among symptoms. The secondary objective of this study was to examine how the statistical technique of factor analysis behaves when the data are dichotomous (as opposed to interval data). At the time of the interviews in October 1998-April 1999, veterans were questioned about 25 symptoms during the past month. The rates of symptoms in the total group of 1,263 Gulf War veterans were compared to the rates of symptoms in the 516 non-deployed veterans. (McCauley, et al., 2001) Gulf War veterans reported significantly higher rates of 24 of the 25 symptoms (all except recurrent fainting). Also, the 653 veterans within 50 km Khamisiyah were compared to 610 veterans who were farther away. There were no significant differences in the rates of any symptoms.

A correlation matrix with the 25 symptom variables was constructed, including all 1,779 veterans. (Shapiro, et al., 2002) Six symptoms were not highly correlated with the others, and were therefore excluded from further analyses. An exploratory factor analysis using the remaining 19 symptoms was performed for each group of veterans. Three patterns of symptoms were identified among the 653 veterans near Khamisiyah. The first pattern, labeled "cognitive-psychological," included six symptoms: unusual irritability/anger; mood swings; changes in memory; persistent fatigue, tiredness, or weakness; difficulty concentrating; and depression. The second pattern, labeled "dysesthesia," included two symptoms, numbness or lack of feeling, and tingling,

burning sensation of pins and needles. The third pattern, labeled "vestibular dysfunction," included two symptoms, dizzy spells, and loss of balance or coordination.

Three extremely similar patterns of symptoms were identified among the 653 veterans near Khamisiyah, among the 610 veterans farther away from Khamisiyah, and among the 516 non-deployed veterans. While the patterns of symptoms among the three groups were not identical, there was 90% or greater overlap in the symptoms within each pattern. The authors concluded: "While we were able to identify clusters of symptoms that appeared to form plausible syndromes, they were not unique to any deployment group, even among veterans who had the greatest acknowledged likelihood of having been exposed to chemical warfare agents." These results were consistent with six previous controlled studies that used factor analysis; that is, patterns of symptoms could be identified, but the patterns in Gulf War veterans and non-deployed veterans were similar. (Fukuda, et al., 1998; Knoke, et al., 2000; Kang, et al., 2002; Doebbeling, et al., 2000; Ismail, et al., 1999; Cherry, et al., 2001a)

The authors carried out a simulation study for each of the three deployment groups to investigate how factor analysis methods performed using dichotomous data. (Shapiro, et al., 2002) Simulation experiments were set up, using randomly generated data. Results from experiments that used randomly made-up data were similar to the results obtained in the analyses that used the actual interview data. The authors stated: "We are forced to reconsider the existence of syndromes found in earlier studies, especially those discovered through factor analysis of dichotomous variables. . . Factor analysis is often used as a last resort when other analyses fail to yield significant results. . . In the absence of more robust decision rules for these kinds of data, the resulting factors [patterns of symptoms] may be a rich mixture of randomness, which could lead investigators down uninformative paths." They concluded that the complexities of research related to Gulf War veterans "make it unlikely that any single analytical tool, such as factor analysis, will be the sole source of answers in this continuing controversy."

4. Kang, HK, Mahan, CM, Lee, KY, Murphy, FM, Simmens, SJ, Young, HA, and Levine, PH. Evidence for a deployment-related Gulf War syndrome by factor analysis. *Archives of Environmental Health* 2002 January/February; 57(1):61-68. **(VA-2A and VA-2B)**

In 1995-98, VA performed a population-based mail survey, entitled the "National Health Survey of Gulf War Era Veterans and Their Families." (Kang, et al., 2000) The objective of this particular analysis was to use factor analysis to determine if patterns of reported symptoms were similar in Gulf War veterans, compared to patterns of reported symptoms in non-deployed veterans. (Kang, et al., 2002) Complete data were available on 47 physical and psychological symptoms reported by 10,423 Gulf War veterans (69% response) and 8,960 non-deployed veterans (60% response). Factor analysis is a statistical technique that is used to detect patterns of correlation in variables, in this case, symptoms. The authors explained: "A factor represents a group of variables that were intercorrelated with each other-but were relatively uncorrelated with other variables." Therefore, factor analysis is strictly a statistical method, which does not consider whether correlated symptoms have clinical relevance to each other. The authors cautioned: "there is no absolute method for determining the number of meaningful factors;" and the "approach to determining the number of factors introduces a subjective component."

Both groups of veterans reported five similar factors (patterns of symptoms), which were labeled "fatigue/depression, musculoskeletal/ rheumatologic, gastrointestinal, pulmonary, and upper respiratory." A significantly higher proportion of Gulf War veterans (2.4%) reported a sixth pattern, labeled "neurological," compared to non-deployed veterans (0.5%). Four symptoms were included in the "neurological" factor, but not in the other five factors: blurred vision, loss of balance/dizziness, tremors/ shaking, and speech difficulty. 191 of the 277 (69%) Gulf War veterans who reported these four symptoms also met the diagnostic criteria for PTSD on the PTSD Checklist, indicating considerable overlap. Previous studies have shown that Gulf War veterans diagnosed with PTSD reported significantly higher rates of physical symptoms in nearly every organ system, compared to other Gulf War veterans. (Wolfe, et al., 1998; Proctor, et al., 1998; Wolfe, et al., 1999b; Wagner, et al., 2000; Engel, et al., 2000; Natelson, et al., 2001) Consistent with previous studies, these 277 veterans reported significantly

higher rates of physical symptoms in several organ systems, compared to other Gulf War veterans, such as seizures/blackouts, tachycardia, and diarrhea.

Although Gulf War veterans reported the "neurological" pattern more frequently, the control population also reported it. Therefore, this pattern cannot be interpreted to represent a "unique Gulf War syndrome." In fact, a commentary by the editor disagreed with the authors' interpretation of the statistical results, as follows: "I would not conclude that 6 factors should be used for the interpretation of the data. I believe that the data suggest, at most, 4 factors, and maybe only 3 factors." (Kilburn, 2002) The "neurological" factor was the last of the 6 factors and was the least robust, statistically. The authors noted that this study was limited because the symptoms were self-reported, and therefore subject to recall bias; and that a pattern of correlated symptoms "by itself, does not constitute a disease syndrome." (Kang, et al., 2002) They concluded that the "neurological" pattern required "validation through clinical examinations in which standardized objective testing can be performed on the suspected cases and on controls." In 2000, the authors obtained funding to perform comprehensive neurological and neurophysiological evaluations of veterans who reported symptoms of blurred vision, tremors, speech difficulty, and ataxia/dizziness (DoD-104). The purpose of the follow-up study was to compare Gulf War veterans who reported the four symptoms with three groups: non-deployed veterans who reported the four symptoms; Gulf War veterans diagnosed with PTSD; and Gulf War veterans who reported none of the four symptoms. The medical evaluations have been completed, and the results will be published in 2003.

Seven large, controlled studies have used factor analysis, and each study has shown that Gulf War veterans do not suffer from a unique, previously unrecognized "Gulf War syndrome." Thousands of Gulf War veterans and non-deployed veterans have been evaluated in these studies, involving the US Air Force; the US Navy; the U.S. Army; all three services in the US, in two independent studies; and all three services in Great Britain, in two independent studies. (Fukuda, et al., 1998; Knoke, et al., 2000; Shapiro, et al., 2002; Doebbeling, et al., 2000; Kang, et al., 2002; Ismail, et al., 1999; Cherry, et al., 2001a) In all seven studies, the patterns of symptoms reported by Gulf War veterans were similar to the patterns reported by non-deployed veterans. In general, Gulf War veterans reported higher rates of the patterns of symptoms than non-deployed veterans, for example, in a 2002 study. (Kang, et al., 2002) However, in some studies, non-deployed veterans reported higher rates of some of the patterns of symptoms. (Knoke, et al., 2000; Cherry, et al., 2001a)

5. McCauley, LA, Joos, SK, Barkhuizen, A, Shuell, T, Tyree, WA, and Bourdette, DN. Chronic fatigue in a population-based study of Gulf War veterans. *Archives of Environmental Health* 2002a July-August; 57(4):340-348. **(VA-6)**

The Portland Environmental Hazards Research Center performed a population-based case-control study, which was designed to compare Gulf War veterans, who reported unexplained symptoms that could not be diagnosed, with healthy Gulf War veterans. (McCauley, et al., 1999a; McCauley, et al., 1999b; Storzbach, et al., 2000; Bourdette, et al., 2001; Spencer, et al., 2001) Cases and controls were selected from respondents to a questionnaire, which was mailed in November 1995 to June 1997 to a random sample of 2,022 Gulf War veterans who lived in Oregon or Washington. Questions focused on chronic fatigue, psychological and cognitive symptoms, and musculoskeletal symptoms. A total of 443 potential cases of unexplained illnesses and healthy controls were recruited for clinical evaluations within 3 months of returning the mail questionnaire. The evaluations included a physical exam with an emphasis on neurological and musculoskeletal systems, a detailed health history, and psychological and neurobehavioral tests.

The objective of this particular analysis was to examine the clinical characteristics of 44 Gulf War veterans with chronic fatigue syndrome (CFS), compared to 113 healthy Gulf War veterans. (McCauley, et al., 2002a) The 1994 CDC criteria for CFS requires a substantial reduction in previous levels of occupational, educational, social, or personal activities, as well as four or more of eight symptoms, such as, headaches, changes in memory, sore throat, or painful joints. Potential cases were excluded from the study, if they had diagnoses that explained the symptoms of fatigue, diagnoses that exclude the diagnosis of CFS, or if they

denied fatigue symptoms at the time of clinical evaluation. 130 Gulf War veterans who had chronic symptoms of fatigue participated in medical exams, after which, 27 were excluded from further study. Among the 103 cases with unexplained fatigue who remained, 44 cases met the 1994 CDC criteria for CFS. The most common diagnoses, among the potential cases with medical exclusions, were hepatitis B or C, cancer, diabetes, and HIV infection. The authors observed "This study highlights the importance of conducting a comprehensive clinical evaluation of patients with the nonspecific and very common complaint of fatigue." These results were consistent with a study of CFS in Gulf War veterans in New Jersey, which demonstrated that a thorough evaluation of veterans with chronic fatigue yielded many medical diagnoses. (Pollet, et al., 1998; Lange, et al., 1999; Natelson, et al., 2001)

Compared to 113 healthy Gulf War veterans, the 44 veterans with CFS were significantly more likely to be younger, female, and in the Army vs. other service branches. (McCauley, et al., 2002a) Veterans with CFS were also five times more likely to have enrolled in the VA Gulf War Registry than healthy veterans. Surprisingly, none of the 44 cases had received CFS as a diagnosis in their VA Registry exams. The most common symptoms reported by the veterans with CFS were: memory or concentration problems, unrefreshing sleep, prolonged fatigue after exercise, joint pain, and new types of headaches. The 44 veterans with CFS were similar to the 113 healthy controls on almost all physical exam findings and laboratory results. Veterans with CFS were more likely to be unemployed than the healthy veterans (27% vs. 14%). (McCauley, et al., 2002a) 41% the 44 cases with CFS also met the criteria for fibromyalgia. (Bourdette, et al., 2001)

The relationships between unexplained symptoms and several self-reported exposures were previously reported. (Spencer, et al., 2001) The authors concluded "The risk factors associated with unexplained fatigue were no different from those associated with cognitive symptoms or unexplained musculoskeletal complaints. Our results suggest that these unexplained symptoms are most highly associated with combat conditions, heat stress, and having sought medical attention during the Gulf War." (McCauley, et al., 2002a) The authors also pointed out that CFS "symptoms are treatable with various therapeutic strategies, most notably, cognitive behavioral therapy and regular aerobic exercise. Gulf War veterans with unexplained fatigue should be encouraged to seek treatment to reduce its impact on their overall quality of life." This conclusion is relevant to a jointly funded VA/DoD trial of these two therapies in Gulf War veterans with CFS-like symptoms, which was completed in 2001, and which will be published in 2003.

6. Unwin, C, Hotopf, M, Hull, L, Ismail, K, David, A, and Wessely, S. Women in the Persian Gulf: lack of gender differences in long-term health effects of service in United Kingdom armed forces in the 1991 Persian Gulf War. *Military Medicine* 2002 May 167(5):406-413. **(DoD-39)**

In 1997-98, a survey was mailed to three randomly-selected samples of British veterans, including members of all three branches of service. 3,529 subjects were Gulf War veterans, 2,052 were veterans of the 1992-97 Bosnia conflict, and 2,614 veterans did not deploy outside of Great Britain. (Unwin, et al., 1999) The primary objective of this particular analysis was to compare the health outcomes of British service women who served in the Gulf War with women who served in Bosnia and women who were in the service, but who did not leave Great Britain (era veterans). The secondary objective was to compare the health outcomes of British service women to British service men. (Unwin, et al., 2002) The main outcome measures were 50 self-reported symptoms; 39 self-reported medical conditions; scores on the health perception and physical functioning subscales of the Medical Outcome Survey Short Form 36; a fatigue scale; the General Health Questionnaire (GHQ-a measure of psychological distress); and symptoms of PTSD (labeled post-traumatic stress reaction by the authors). Potential confounders were controlled through the use of logistic regression, including age, smoking, alcohol use, education, rank, and whether still serving vs. discharged from the service.

This survey included 226 female Gulf War veterans, 227 female Bosnia veterans, and 192 female era veterans (65% participation among women veterans). Female Gulf War veterans reported nearly all of the 50 symptoms more frequently than the comparison groups. After controlling for demographic variables and psychological distress on the GHQ, female Gulf

War veterans reported significantly higher rates of 28 of the 50 symptoms and eight of the 39 medical conditions. All but one of the major health outcomes were significantly associated with the Gulf War cohort, including mean score on the GHQ, mean fatigue score, PTSR, and health perception score on the SF-36. The only exception was physical functioning score on the SF-36. No clear pattern was found between various self-reported military exposures and the health outcomes measured. However, the total numbers of military exposures were significantly associated with worse health outcomes (PTSR, GHQ score, and fatigue) in female Gulf War veterans.

Female and male Gulf war veterans were compared, and there were no significant differences in the reported rates of 32 of 50 symptoms. Women reported significantly higher rates than men for six symptoms, and men reported significantly higher rates than women for 12 symptoms. There were no significant differences between female and male Gulf War veterans on all but one of the major health outcomes, including mean score on the GHQ, mean fatigue score, PTSR, and physical functioning score on the SF-36. The only exception was that men reported significantly worse scores on the health perception subscale of the SF-36. The authors concluded that female Gulf War veterans reported more symptoms than female Bosnia and era veterans, similar to their male counterparts. They concluded: "women are neither more nor less vulnerable to the physical and psychological stressors of active service;" and they found nothing to suggest that "any special considerations be made on health grounds for service women in future deployments."

7. Higgins, EM, Ismail, K, Kant, K, Harman, K, Mellerio, J, du Vivier, AW, and Wessely, S. Skin disease in Gulf War veterans. *Quarterly Journal of Medicine* 2002 October; 95(10):671-676. **(DoD-39)**

In Stage I of this study, a survey was mailed in 1997-98 to three randomly-selected samples of British veterans, including members of all three branches of service. 3,529 subjects were Gulf War veterans, 2,052 were veterans of the 1992-97 Bosnia conflict, and 2,614 veterans did not deploy outside of Great Britain. (Unwin, et al., 1999) Stage II of this study was a nested case-control study, which included medical assessments during January 1999 to September 2000. (Higgins, et al., 2002) Four randomly-selected groups of veterans who participated in Stage I were invited to undergo a one-day medical exam at King's College Hospital in London. This study was the fourth of four publications based on Stage II medical exams. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Higgins, et al., 2002) The objectives of this particular analysis were to compare the nature and prevalence of skin disease in Gulf War veterans with Bosnia and era veterans, and to assess whether skin disease was associated with disability. (Higgins, et al., 2002)

The four groups in Stage II were selected based on their reported level of physical disability during Stage I: 111 Gulf War veterans who reported disability; 98 Gulf War veterans who did not report disability; 54 veterans of the Bosnia conflict who reported disability; and 79 veterans who did not deploy outside the UK who reported disability (era veterans). (Higgins, et al., 2002) The latter two groups were combined into one group of disabled non-Gulf War veterans. Because there is no specific case definition of Gulf War illnesses, a generic measure of illness was used to define physical disability, the Physical Functioning (PF) subscale of the Medical Outcome Study Short Form-36. The PF score at the lowest tenth percentile during Stage I was selected as the cut-off for the ill groups during Stage II, because this score would identify the most disabled veterans.

Gulf War veterans have reported skin rashes at higher rates than non-deployed veterans in several surveys; however, this is the first controlled study of clinician diagnoses of dermatological conditions. (Higgins, et al., 2002) Only one previous publication has described the types of skin diseases diagnosed in 111 consecutive patients in the DoD Gulf War Registry, who were evaluated at Walter Reed Army Medical Center. (Krivda, et al., 1996) Skin conditions have been important health concerns during deployments throughout history, particularly during combat. The authors pointed out that "Contributory factors are climatic (heat and UV exposure), the occlusive effect of protective clothing, cramped living conditions, and the stress of deployment." (Higgins, et al, 2002) There were no significant differences in the rates of the presence of at least one skin condition in the three groups: 48% of disabled Gulf War veterans; 37% of healthy Gulf War

veterans; and 43% of disabled Bosnia and era veterans. Among 19 types of skin conditions, only seborrheic dermatitis was significantly more prevalent in Gulf War veterans than in the Bosnia and era veterans (7.2% of disabled Gulf War veterans vs. 9.2% of healthy Gulf War veterans vs. 2.3% of disabled Bosnia and era veterans). The reason for the increased rate of seborrheic dermatitis in Gulf War veterans was unknown.

Among the 19 skin conditions, only "miscellaneous benign conditions" were significantly more prevalent in disabled Gulf War veterans than in healthy Gulf War veterans (12.6% vs. 4.1%). There were no differences in the rates of this group of benign conditions in disabled Gulf War veterans, compared to disabled Bosnia and era veterans (12.6% vs. 10.5%). This diverse group of benign skin conditions included congenital nevi, urticaria, lipoma, dermatofibroma, and vitiligo. Logistic regression was then used to adjust for age, sex, rank, smoking and alcohol use, which are recognized risk factors for skin disease. There was only one significant difference in the adjusted rates of the various skin conditions: "miscellaneous benign conditions" were four times more frequent in disabled Gulf War veterans than in healthy Gulf War veterans. The authors concluded: "Skin disease does not appear to be contributing to ill health in Gulf War veterans, with the exception of an unexplained two-fold increase in seborrheic dermatitis."

8. Hull, L, David, AS, Hyams, KC, Unwin, C, Wessely, SC, and Hotopf, M. Self-reported health of Persian Gulf War veterans: a comparison of help-seeking and randomly ascertained cases. *Military Medicine* 2002 September; 167(9):747-752. **(DoD-39)**

In 1997-98, a survey was mailed to three randomly-selected samples of British veterans, including members of all three branches of service. 3,529 subjects were Gulf War veterans, 2,052 were veterans of the 1992-97 Bosnia conflict, and 2,614 veterans did not deploy outside of Great Britain. (Unwin, et al., 1999) In 1993, the UK Ministry of Defence established a Gulf War registry exam program, the Medical Assessment Program (MAP), to assess the health of veterans who believed that the Gulf War had affected their health. As of June 2001, more than 3000 veterans had been evaluated in the MAP, and their most prevalent conditions were psychiatric disorders (most commonly, PTSD), and musculoskeletal, respiratory, and gastrointestinal diseases. (Lee, et al., 2002) The objective of this particular analysis was to compare the characteristics of veterans who participated in the MAP with veterans who did not, particularly in regard to their rates of ill health and health attributions. (Hull, et al., 2002) Among the 3,529 Gulf War veterans who participated in the 1997-98 survey, 173 (5%) veterans had participated in the MAP before June 30, 2000; and 3,356 (95%) veterans had not.

The mailed survey included a checklist of 50 symptoms; a checklist of 39 medical disorders; a fatigue questionnaire; the General Health Questionnaire (GHQ-12), a measure of psychiatric morbidity; two subscales of the Medical Outcomes Study Short Form-36 (SF-36), health perception and physical functioning; and symptoms that approximated PTSD (labeled post traumatic stress reaction by the authors). Compared to the other 3,356 veterans, the 173 veterans who participated in the MAP were significantly more likely to be older, female, unemployed, to have less education, and to have been medically discharged from the service. The 173 veterans in the MAP had significantly lower scores on the SF-36 physical functioning subscale and health perception subscale.

Logistic regression was used to control for age, gender, rank, education, and physical functioning on the SF-36. After adjustment, the 173 veterans in the MAP reported significantly higher numbers of symptoms (mean of 20.5 vs. 10.3 symptoms), and higher numbers of medical conditions (mean of 4.5 vs. 2.2 conditions). The 173 veterans in the MAP were significantly more likely to fulfill case criteria for fatigue (odds ratio=2.8); psychiatric morbidity on the GHQ-12 (odds ratio=1.9); and PTSR (odds ratio=2.9). These 173 veterans were also significantly more likely: to think that they "had Gulf War Syndrome" (odds ratio=8.6); to have "experienced a change in functioning since the Gulf War" (odds ratio=6.3); and to think that any of their "symptoms have been caused by serving in the Gulf" (odds ratio=6.9). These findings were consistent with a previous analysis of health attributions of the entire cohort of 3,529 British Gulf War veterans. (Chalder, et al., 2001)

The authors concluded: "The belief that one had Gulf War syndrome and attributing health problems to Gulf War service were the most

powerful predictors of MAP attendance, even when controlling for the level of physical functioning. The findings suggest that health beliefs rather than symptoms are more important predictors of attendance at an assessment program and that Gulf War veterans who attended the MAP have different characteristics than those who did not. This suggests that MAP patients are unrepresentative of the wider deployment to the Persian Gulf." (Hull, et al., 2002)

9. Smith, TC, Smith, B, Ryan, MA, Gray, GC, Hooper, TI, Heller, JM, Dalager, NA, Kang, HK, and Gackstetter, GD. Ten years and 100,000 participants later: occupational and other factors influencing participation in US Gulf War Health Registries. *Journal of Occupational and Environmental Medicine* 2002b August; 44(8):758-768. **(DoD-94)**

VA and DoD initiated health registries in 1992 and 1994, respectively, to provide systematic clinical evaluations of Gulf War veterans who had health concerns that were war-related. There was extensive, global outreach by both VA and DoD, which encouraged veterans with health concerns or questions to enroll for evaluations, whether or not they were ill. The objective of this study was to identify demographic and military factors and occupational and environmental exposures that were associated with registry participation. (Smith, et al., 2002b) The authors stated that "Identification of these predictors for registry participation may help the military better understand the specific demographic and military service characteristics and wartime exposures that could result in increased self-reported symptoms, as well as increased health care-seeking behavior after deployment." The study population included 66,227 patients enrolled in the VA Gulf War Registry alone, and 29,721 patients enrolled in the DoD registry alone (the Comprehensive Clinical Evaluation Program or CCEP), who had been examined by September 1999. It also included 2,887 patients who were evaluated in both registries (total of 98,835). This long observation period, since 1992, is likely to include nearly all veterans who had substantial enough concerns to warrant a medical evaluation. This was the first publication of an analysis of combined Registry data. Later in 2002, VA and DoD published a more detailed analysis in a 106-page monograph. (VA and DoD, 2002) This monograph is accessible at: www.va.gov/environagents/

While simultaneously adjusting for several factors, logistic regression modeling was used to determine risk factors that were associated with participation in either registry. (Smith, et al., 2002b) Enrollment was significantly associated with female gender (OR=1.33); age 31 years or older in 1990 (OR=2.04); enlisted rank (OR=2.04); Reserve/National Guard status vs. active-duty (OR=1.62); and hospitalization in a military hospital in the 12 months before the war (OR=1.19). Hospitalization in the 12 months before a war has been consistently associated with post-war hospitalization, both after the Gulf War and after the Bosnia conflict. (Gray, et al., 1996; Gray, et al., 1999c; Brundage, et al., 2002) Deployment to the Gulf War for more than 198 days (the highest quartile of number of days) was significantly associated with registry enrollment (OR=1.24); as was deployment to the Gulf War during the period of February to April 1991, which included the period of the air and ground war (OR=1.32). Among ten major categories of military occupational specialties, the category that was most strongly associated with registry enrollment was craft workers, which includes carpenters, construction equipment operators, metalworkers, machinists, plumbers, welders, and electricians (OR=1.27). This finding was consistent with previous studies that demonstrated increased symptom reporting among Navy construction battalions called Seabees, particularly in Reserve units. (Haley, 1997a; Gray, et al., 1999a; Gray et al., 2002b)

Navy troops were least likely to enroll in the registries. (Smith et al., 2002b) In comparison to the Navy, the odds ratios for enrollment were 1.56 for the Air Force, 2.64 for the Marines, and 4.57 for the Army. Modeling was performed to estimate potential exposures of military units to particulates from the oil well fire smoke, from February to July 1991. (Smith, et al., 2002a) Registry enrollment was associated with potential exposure to oil well fire smoke (OR=1.79). The authors stated that the "dramatic visual evidence of gross air pollution emanating from the oil well fires" might have increased concerns that these exposures could eventually lead to poor health. Modeling was also performed to estimate potential exposures of military units to nerve agents from the demolitions of munitions at Khamisiyah, Iraq in early March 1991. (Gray, et al., 1999c) Registry

enrollment was associated with potential exposure to nerve agents due to Khamisiyah (OR=1.10). Other studies of troops with potential exposure due to Khamisiyah have not demonstrated increased rates of objective medical conditions. (Gray, et al., 1999c; Kang, et al., 2001; Kang and Bullman, 2002; McCauley, et al., 2002b; Shapiro, et al., 2002) The authors interpreted their findings related to Khamisiyah, as follows: "The more likely explanation would be that this increase in participation is the result of DoD and VA notification letters along with possible media influence to persuade veterans who were potentially exposed to the plumes to participate in one of the registries." (Smith, et al., 2002b)

The authors cautioned that the establishment of the registries encouraged "health-care seeking behavior; that access to care is increased for those eligible; that the existing system of entitlements encourages health care utilization and evaluation of eligibility for service-connected benefits; and that the prevailing public perception of Gulf War health risks based on media coverage of war-related events raises the anxiety level of those potentially exposed." They recommended: "Better health risk communication efforts aimed at the media and the general public, as well as active-duty and veteran populations, post-deployment debriefing programs, and/or greater access to postwar counseling may mitigate some of the consequences attributed to war-related experiences."

10. Richardson, RD, Engel, CC, Hunt, SC, McKnight, K, and McFall, M. Are veterans seeking Veterans Affairs' primary care as healthy as those seeking Department of Defense primary care? A look at Gulf War veterans' symptoms and functional status. *Psychosomatic Medicine* 2002 July-August; 64(4): 676-683. **(VA-58)**

The primary objective of this study was to compare Gulf War veterans seeking primary care at two different settings, at the Seattle VA Medical Center and Walter Reed Army Medical Center, on measures of physical symptoms, psychiatric distress, and functional status. (Richardson, et al., 2002) The secondary objective was to evaluate the association of veterans' employment status with physical symptoms, psychiatric distress, and functional status. Participants included 406 consecutive patients at the primary care clinics in Seattle (253 veterans) and in Washington, DC (153 active-duty or reservists), during the period of March 1998 to September 1999. Compared to VA patients, DoD patients were more likely to be older, female, black, more educated, Army vs. other branches, reservists rather than active-duty before the Gulf War, currently employed, have an income more than $25,000 per year, and current non-smokers. Six percent of DoD patients were unemployed (nearly all of them reservists), compared to 29% of VA patients. The Desert Storm Trauma Questionnaire included 19 questions about potentially traumatic experiences, such as being stationed close to enemy lines or seeing others killed or wounded. VA patients reported significantly higher numbers of such experiences, compared to DoD patients (mean of 6.9 vs. 4.7).

A modified version of the somatoform assessment module of the Patient Health Questionnaire (PHQ) was developed, which included 20 questions about physical symptoms of specific concern to Gulf War veterans, during the past 30 days. VA patients reported significantly more symptoms than DoD patients (mean of 6.1 vs. 5.2). The Brief Symptom Inventory (BSI) was used to measure nine psychiatric conditions during the past seven days, such as anxiety and depression, as well as a summary measure of psychiatric distress called the Global Severity Index. Compared to DoD patients, VA patients scored significantly higher (worse) on each of the nine subscales, as well as on the GSI. The PTSD Checklist-Military (PCL-M) was used to screen for symptoms of PTSD in the past 30 days. Compared to DoD patients, VA patients scored significantly higher (worse) on the PTSD Checklist. The Medical Outcomes Study Short Form-36 (SF-36) was used to assess health-related quality of life. The Mental Component Summary (MCS) of the SF-36, a composite measure of mental health functioning, was significantly lower (worse) among VA patients compared to DoD patients. The Physical Component Summary (PCS), a composite measure of physical functioning, was not significantly different between the two groups of patients.

Analysis of covariance was performed to determine whether site differences (VA vs. DoD) and employment status (employed vs. unemployed) existed, after controlling for the effects of demographic variables and combat

exposure. Three separate analyses were performed, adjusting for age, gender, ethnicity, education, service branch (Army vs. other), duty status before the war (Reserve/National Guard vs. active-duty), current smoking, and number of traumatic combat experiences during the war. First, an analysis was performed that included all 406 subjects, which demonstrated that anxiety symptoms on the BSI and PTSD symptoms on the PCL-M were significantly associated with site (VA vs. DoD). Also, depression symptoms on the BSI and PTSD symptoms on the PCL-M were significantly associated with employment status. Second, an analysis was performed that included 234 employed subjects only (117 VA patients and 117 DoD patients). Anxiety symptoms and the Global Severity Index on the BSI, as well as PTSD symptoms on the PCL-M, were significantly associated with site (scores on all three scales were significantly worse in VA patients, compared to DoD patients). Third, an analysis was performed with 165 VA patients only (117 employed and 48 unemployed). Severity of physical symptoms on the PHQ, PTSD symptoms on the PCL-M, and PCS score on the SF-36 were significantly associated with employment status (scores on all three scales were worse in unemployed patients).

In summary, Gulf War veterans who sought primary care at a DoD primary care clinic were more likely to describe themselves as employed, physically healthier, and less emotionally distressed, compared to Gulf War veterans who sought primary care at a VA clinic. The authors commented: "Research findings based exclusively on one sample or the other may not generalize to the population of Gulf War veterans at large. In addition to the findings on site differences, employment status among Gulf War veterans was consistently and independently predictive of health functioning." The authors provided three possible explanations for these findings, as follows: "One explanation may be that veterans who have left the military have done so in part because poorer health has reduced their ability to function on the job. . . A second potential explanation is that employment, either in the military or civilian sector, helps protect against distress and enhances health-related functioning. . . A third explanation may be that site differences are the result of different selection factors related to patient referral criteria or referral patterns. . . In the VA setting, demonstrating a connection between one's health status and military service may be integral to determining eligibility for disability and benefits."

11. Voelker, MD, Saag, KG, Schwartz, DA, Chrischilles, E, Clarke,WR, Woolson, RF, and Doebbeling, BN. Health-related Quality of Life in Gulf War Era Military Personnel. *American Journal of Epidemiology* 2002 May 15; 155(10): 899-907. **(HHS-1** and **DoD-58**)

In 1995-96, a survey was performed of a randomly-selected sample of military personnel, whose home state of residence at enlistment was Iowa, using a telephone interview. Study subjects were drawn from four groups: Gulf War active-duty, Gulf War National Guard/Reserve, non-deployed active-duty, and non-deployed National Guard/Reserve. A total of 3,695 subjects completed the survey (76% response rate). (Iowa, 1997; Doebbeling, et al., 2000) The objectives of this particular analysis were to compare the health-related quality of life (HRQL) of Gulf War veterans with non-deployed veterans, and to identify potential risk factors for poorer HRQL, before and during deployment. (Voelker, et al., 2002) Non-deployed veterans self-reported their overall health as excellent at a significantly higher rate than Gulf War veterans (31% vs. 21%), as opposed to very good, good, fair, or poor.

The Medical Outcome Study Short Form 36 (SF-36) was used to assess HRQL. The SF-36 is a widely used, general health questionnaire that has demonstrated sensitivity to health differences in the general population and in patients with chronic diseases. Several factors explain up to 40% of the variance in HRQL scores in the population, including current medical illness, illness duration and severity, sociodemographic factors, psychological factors, and treatment characteristics. There are eight subscales and two summary scales-the Physical Component Score (PCS), and the Mental Component Score (MCS). The PCS is derived from the physical functioning, role-physical, bodily pain, and general health subscales. The MCS is derived from the mental, role-emotional, social functioning, and vitality subscales. The PCS and MCS are scored from 0 to 100, with a mean of 50 in the general population. A difference of one point in the PCS score is roughly equal to the average decline in one year for people aged 65 years or more.

The mean scores on each of the eight subscales and the two summary scores were significantly lower for Gulf War veterans, compared to the non-deployed veterans. Non-deployed veterans reported the same or slightly higher (better) mean scores than the general US population. In contrast, scores of Gulf War veterans were lower than the scores in the general US population for the PCS and five of the eight subscales. Multivariate modeling suggested several independent risk factors for lower scores on the PCS and MCS, including service in the Army vs. other branches, marital status, level of military preparedness, cigarette smoking, prior history of mental health care, and several specific pre-war medical conditions (including asthma, arthritis/rheumatism, posttraumatic stress disorder, and depression). After adjustment for these potential confounders, there were minimal changes in the scores. The mean PCS and MCS scores remained about two points lower in Gulf War veterans vs. non-deployed veterans.

The authors noted that some of these risk factors were potentially modifiable, such as cigarette smoking and level of military preparedness, which could be considered in force health protection efforts. The risk factors might be "useful in designing preventive and therapeutic interventions aimed at helping both Gulf War veterans and future military personnel successfully adapt to life after war." The SF-36 findings in this Iowa study were quite consistent with the findings of SF-36 studies of Gulf War veterans in Pennsylvania, Boston, Portland, Cincinnati, and the UK**.** (Fukuda, et al., 1998; Proctor, et al., 1998; Proctor, et al., 2001a; Bourdette, et al., 2001; Baker, et al., 2001; Unwin, et al., 1999; Chalder, et al., 2001; Unwin, et al., 2002; Hull, et al., 2002)

12. Wolfe, J, Proctor, SP, Erickson, DJ, and Hu, H. Risk factors for multisymptom illness in US Army veterans of the Gulf War. *Journal of Occupational and Environmental Medicine* 2002 March; 44(3):271-281. **(DoD-52)**

The Boston Environmental Hazards Research Center has been following 2,949 Army veterans who processed through Fort Devens, Massachusetts, at the time of their return from the Gulf War in 1991. (Wolfe, et al., 1996; Wolfe, et al., 1999b**)** These veterans have been evaluated at four time points, starting within five days of their return to the U.S., and again at 18 to 24 months later (Time 2), at four years (Time 3), and at six to seven years (Time 4). The study population includes about 72% Reserve/National Guard, and about 28% active-duty, and it includes 84 units with a wide range of military occupational specialties from several regions of the U.S. The objective of this particular analysis was to determine if self-reported environmental exposures and psychological distress at Time 4 were associated with "chronic multisymptom illness," according to a CDC definition. (Wolfe, et al., 2002)

In March 1997 to March 1998, a detailed questionnaire was mailed to 2,903 members of the original cohort of 2,929 veterans, for whom contact data were available. (Wolfe, et al., 2002) A total of 1,290 veterans responded to the survey, of whom 945 provided complete data (32.5% of 2,903). This low response rate was mainly due to difficulty in locating individuals, because of the mobility of this population, some of whom changed residences annually. The number of individuals who actually refused to participate was low. The survey included questions on general symptoms, psychological symptoms, medical conditions, health functioning, and several potential environmental exposures. The primary indicator of general psychological symptoms was the Global Severity Index (GSI) of the Brief Symptom Inventory (BSI). The GSI represents the most sensitive single BSI indictor of a subject's distress level, combining information on a number of psychological symptoms and their intensity. 388 veterans (41%) met criteria for psychological distress, according to the GSI.

In 1998, the Centers for Disease Control and Prevention (CDC) developed a working case definition of a "chronic multisymptom illness" (CMI) in Gulf War veterans. (Fukuda, et al., 1998) CDC defined CMI as one or more symptoms, from at least 2 of 3 categories of symptoms (fatigue, mood and cognition symptoms, and musculoskeletal symptoms). These symptoms had to begin during or after the Gulf War and had to persist for at least 6 months up to the present. In the Fort Devens study, the case definition was modified, so that symptoms only had to occur during the past month. (Wolfe, et al., 2002) Mild CMI cases were defined as symptoms that were reported as occurring "sometimes." Severe CMI cases were defined as symptoms that occurred "a lot." 30% of the 945 veterans met the definition for mild cases, and 30% met the definition for severe

cases. Lower educational attainment, higher exposure to combat stressors, and psychological distress on the GSI were significantly associated with both mild and severe cases of CMI. It is noteworthy that psychological distress on the GSI was reported by 10% of the non-cases, 47% of the mild cases, and 77% of the severe cases.

Logistic regression analyses were performed to evaluate the unique associations between specific exposures and CMI, while simultaneously controlling for demographic variables and other risk factors. There were significant associations between CMI and female gender, lower educational attainment, and psychological distress on the GSI. The 945 individuals were then stratified into two groups: 388 (41%) who met criteria for psychological distress on the GSI, and 557 who did not meet the criteria. In this stratified analysis, four exposures were associated with CMI. Veterans also consistently reported these four exposures when they were surveyed at two time points (good test-retest reliability). Two environmental exposures were significantly associated with CMI in the 388 individuals with psychological distress: having a heater in their sleeping area at least once, and having received an anthrax vaccination. Two environmental exposures were significantly associated with CMI in the 557 individuals without psychological distress: having been seen in the clinic during the Gulf War; and having taken 22 or more pyridostigmine bromide pills. The authors concluded: "These findings support the suggestion that Gulf War veterans' illnesses may not be associated with one exposure or Gulf War event, but rather with one or more different factors."

13. 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. **(DoD-70)**

The objective of this study was to determine if "post-combat syndromes have existed after modern wars and what relation they bear to each other." (Jones, et al., 2002) The authors stated: "It is now clear that service in the Gulf War is associated with an increased rate of reported symptoms and worsening of subjective health, even if most research has not confirmed the existence of a specific new syndrome. The question we address is whether this phenomenon is unique to the Gulf War or has been seen after previous conflicts." A previous evaluation of the secondary medical literature had concluded: "Poorly understood war syndromes have been associated with armed conflicts at least since the U.S. Civil War. Although these syndromes have been characterized by similar symptoms (fatigue, shortness of breath, headache, sleep disturbance, forgetfulness, and impaired concentration), no single recurring illness that is unrelated to psychological stress is apparent." (Hyams, et al., 1996) The current study utilized British war pension files as the primary data source because they contained detailed medical and military reports. (Jones, et al., 2002) This method is a more direct approach than use of the secondary medical literature.

Records of 1,856 British veterans were randomly selected from war pension files awarded from 1872 through the post-World War II period, including 400 veterans of the Boer War, 640 veterans of World War I, and 367 veterans of World War II. In addition, medical records for 400 Gulf War veterans were abstracted from the Medical Assessment Program (the British equivalent of the two U.S. Gulf War registries). Medical notes were detailed in the pension records, covering the veterans' histories from enlistment until death, and often including death certificates. Veterans selected for this study were diagnosed with the following conditions: disordered action of the heart; rheumatism (in the absence of organic signs such as inflammation and joint swelling); neurasthenia; history of exposure to mustard gas without permanent organic injury; effort syndrome; psychoneurosis; and non-ulcer dyspepsia. The long-term nature of the notes allowed the authors to exclude cases, if a veteran was found to be suffering from an organic disorder or a major mental illness. The records of each veteran were abstracted, including a list of 94 symptoms, comments of examining physicians, and cause of death. After abstraction was complete, this list of 94 symptoms was reduced to the 25 most common, due to the overlapping information that would be inevitable in such a large set of symptoms.

The 25 symptoms were subjected to cluster analysis, which yielded three clusters of correlated symptoms. These were: a debility syndrome, without psychological or cognitive symptoms (including fatigue, difficulty completing tasks, shortness of breath, and

weakness); a somatic syndrome focused on the heart (including rapid heartbeat, shortness of breath, fatigue, and dizziness); and a neuropsychiatric syndrome with a range of associated somatic symptoms (including fatigue, headaches, depression, anxiety, and difficulty sleeping). The era in which the war occurred was overwhelmingly the best predictor of the particular cluster of symptoms that a given veteran would report. The debility syndrome was predominantly reported by veterans of the Boer War and World War I; the somatic syndrome was predominantly reported by veterans of World War I, but it was also sometimes reported after the Boer War and World War II; and the neuropsychiatric syndrome was predominantly reported by veterans of World War II and the Gulf War. An analysis of death certificates showed that veterans with these three syndromes did not develop a particular organic illness or have increased mortality.

Illnesses in the 400 Gulf War veterans did not stand apart from the other conflicts. Although most cases fell into the neuropsychiatric cluster (54%), Gulf War veterans were found in all three clusters (37% debility and 10% somatic). The authors suggested that "the three syndromes are unrelated to any particular exposure as they occurred during several wars, albeit with different frequencies." Based on an analysis of the causes to which the 1,856 veterans had attributed their symptoms, such as climate or toxic exposures, the authors concluded: "what has changed is not the symptoms themselves but the way in which they have been reported by veterans and interpreted by doctors." They recommended: "If each new post-combat syndrome is not interpreted as a unique or novel illness but as part of an understandable pattern of normal responses to the physical and psychological stress of war, then it may be managed in a more effective manner."

B. Brain and Nervous System Function

Overview:

Five studies published in 2002 focused on brain and nervous system function. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Barrett, et al., 2002; Orcutt, et al., 2002) These publications included results of studies conducted at three Federally-funded research centers in Iowa City, Boston, and in London, U.K. Four of these studies included hundreds to thousands of individuals. (Ismail, et al., 2002; David, et al., 2002; Barrett, et al., 2002; Orcutt, et al., 2002) Three studies relied upon psychiatric, neuropsychological, or neurological evaluations, rather than relying solely on self-administered surveys. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002) Four of these studies were population-based, which means that the results of these studies may have implications for the overall population of 697,000 Gulf War veterans. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Barrett, et al., 2002)

The objectives of the first, second, and third studies were linked, and were based on an investigation of three groups of British veterans: disabled Gulf War veterans, healthy Gulf War veterans, and disabled veterans who did not deploy to the Gulf War. The objectives of the first study were: to determine the relationship between reported physical disability and psychiatric disorders in Gulf War veterans, using structured psychiatric interviews; and to determine if Gulf War veterans who reported physical disability were more likely to have psychiatric disorders, than the two comparison groups of veterans. (Ismail, et al., 2002) The objectives of the second study were to determine: whether the pattern of neuropsychological deficits, if any, differed across symptomatic veterans from different deployments; and whether such deficits could be specifically attributed to Gulf War deployment vs. any overseas deployment. (David, et al., 2002) The objectives of the third study were to determine if the neuromuscular symptoms reported by some Gulf War veterans were related to objective abnormalities of peripheral nerves, skeletal muscles, or neuromuscular junctions; and to compare the rates of neurological abnormalities among Gulf War veterans, Bosnia veterans and non-deployed veterans. (Sharief, et al., 2002)

The objective of the fourth study was to examine the relationship between posttraumatic stress disorder (PTSD) and perceived physical health and health-related quality of life in a representative sample of 3,682 Gulf War and non-deployed veterans from the state of Iowa. (Barrett, et al., 2002)

The objectives of the fifth study were to examine the relationship between exposure to combat during the Gulf War and exposure to traumatic

life events in the two years after the war among 2,313 members of the Fort Devens, MA cohort; and to examine if PTSD symptoms were potential mediators between combat exposure and the risk of subsequent exposure to traumatic events. (Orcutt, et al., 2002)

Many studies have evaluated the rates of symptoms of PTSD in Gulf War veterans and non-deployed veterans, including national studies in the U.S., U.K., and Canada, and in Iowa, Portland, New Jersey, New Orleans, and Boston. Gulf War veterans have consistently reported increased symptoms of PTSD, compared to control populations. (Iowa, 1997; Barrett, et al., 2002; Pierce, 1997; Gray, et al., 1999a; Gray, et al., 2002b; Dlugosz, et al., 1999; Kang, et al., 2000; Goss Gilroy, 1998; Unwin, et al., 1999; Reid, et al., 2001; Unwin, et al., 2002; Storzbach, et al., 2000; Ford, et al., 2001; McCauley, et al., 2002b; Pollet, et al., 1998; Lange, et al., 1999; Natelson, et al., 2001; Lange, et al., 2001; Benotsch, et al., 2000; Wolfe, et al., 1999a; Wolfe, et al., 1999b; Wagner, et al., 2000; Proctor, et al., 2001a; Proctor, et al., 2001b; White, et al., 2001)

In several studies, diagnoses of PTSD were made by clinicians through structured diagnostic interviews, not solely through self-administered surveys. These have included a national U.S. study and studies in New Jersey, Boston, and in the U.K. (Dlugosz, et al., 1999; Pollet, et al., 1998; Lange, et al., 1999; Natelson, et al., 2001; Lange, et al., 2001; Wolfe, et al., 1999b; Proctor, et al., 2001a; Proctor, et al., 2001b; White, et al., 2001; Ismail, et al., 2002; David, et al., 2002)

Gulf War veterans have consistently reported increased symptoms of major depression compared to control populations, in Iowa, Pennsylvania, Portland, New Jersey, Boston, and in the U.K. (Iowa, 1997; Fukuda, et al., 1998; Ford, et al., 2001; McCauley, et al., 2002b; Pollet, et al., 1998; Lange, et al., 1999; Lange, et al., 2001; Wolfe, et al., 1999b; Proctor, et al., 2001a; Proctor, et al., 2001b; White, et al., 2001; Ismail, et al., 2002; David, et al., 2002) In several studies, diagnoses of major depression were made by clinicians through structured diagnostic interviews, not solely through self-administered surveys. These have included studies in Pennsylvania, New Jersey, Boston, and in the U.K. (Fukuda, et al., 1998; Pollet, et al., 1998; Lange, et al., 1999; Lange, et al., 2001; Wolfe, et al., 1999b; Proctor, et al., 2001a; Proctor, et al., 2001b; White, et al., 2001; Ismail, et al., 2002; David, et al., 2002)

Gulf War veterans have consistently reported increased symptoms of anxiety disorders compared to control populations, in New Jersey, Boston, and in the U.K., including general anxiety disorder, panic disorder, and phobias. These diagnoses of anxiety disorders were made by clinicians through structured diagnostic interviews, not solely through self-administered surveys. (Pollet, et al., 1998; Lange, et al., 1999; Lange, et al., 2001; Wolfe, et al., 1999b; Ismail, et al., 2002)

Several different populations of ill Gulf War veterans have consistently reported more combat stressors than healthy Gulf War veterans, such as deaths of unit members. These have included veterans with PTSD (King et al., 2000; Sharkansky, et al., 2000; Orcutt, et al., 2002; Benotsch, et al., 2000; Engel, et al., 2000; Barrett, et al., 2002; Unwin, et al., 2002); veterans with major depression (Sharkansky, et al., 2000); veterans with chronic fatigue syndrome (Fiedler, et al., 2000); and veterans with unexplained symptoms that could not be diagnosed after a thorough medical evaluation (Storzbach, et al., 2000; Spencer, et al., 2001; Ford, et al., 2001).

Several populations of Gulf War veterans and non-deployed veterans have demonstrated consistent results on neuropsychological testing, in New Orleans, Boston, New Jersey, Portland, and in London, U.K. Self-reports of memory and concentration problems have been more frequent among Gulf War veterans than among control subjects in several studies. However, on objective testing, performance was the same on most neuropsychological tests in Gulf War veterans and controls. In a small proportion of tests, such as attention or response speed, Gulf War veterans performed significantly more poorly than controls. After adjustment for PTSD, depression, or other psychological distress, the differences on the tests between the two groups diminished or disappeared. (Vasterling, et al., 1997; Vasterling, et al., 1998; White, et al., 2001; Lange, et al., 2001; Anger, et al., 1999; Binder, et al., 1999; Storzbach, et al., 2000; Storzbach, et al., 2001; David, et al., 2002)

In summary, Gulf War veterans have consistently been diagnosed with significantly higher rates of PTSD, major depression, and

anxiety disorders than non-deployed veterans. These higher rates have been demonstrated in several different populations of Gulf War veterans, through structured psychiatric interviews, as well as through self-administered questionnaires. Long-term follow-up evaluations of physical and psychological symptoms are continuing in five studies that include about 18,000 Gulf War veterans and non-deployed veterans, in Boston, New Orleans, New Jersey, Iowa, and the United Kingdom. In addition, the health of about 20,000 Gulf War veterans and non-deployed veterans will be re-evaluated as follow-up to the VA National Survey. This research will provide a better understanding of the mind/body connection and how stress may have placed Gulf War veterans at increased risk for adverse health outcomes, ultimately leading to improved treatment and prevention strategies in the future.

Brain and Nervous System Function-Individual Studies:

1. Ismail, K, Kent, K, Brugha, T, Hotopf, M, Hull, L, Palmer, I, Reid, S, Unwin, C, David, AS, and Wessely, S. The mental health of UK Gulf War veterans: phase 2 of a two phase cohort study. *British Medical Journal* 2002 September 14; 325(7364):576-581. **(DoD-39)**

The primary objective of this British study was to test the strength of the association between reported physical disability and psychiatric disorders in Gulf War veterans, using structured psychiatric interviews. The secondary objective was to test whether Gulf War veterans who reported physical disability were more likely to have psychiatric disorders, than two comparison groups of veterans. (Ismail, et al., 2002) In Stage I of this study, a survey was mailed in 1997-98 to three randomly-selected samples of British veterans, including members of all three branches of service. (Unwin, et al., 1999) 3,529 subjects were Gulf War veterans, 2,052 were veterans of the 1992-97 Bosnia conflict, and 2,614 veterans did not deploy outside of Great Britain. Stage II of this study was a nested case-control study, which included medical assessments during January 1999 to September 2000. (Ismail, et al., 2002) Four randomly-selected groups of veterans who participated in Stage I were invited to attend a one-day medical exam at King's College Hospital in London. This study was the first of four publications based on Stage II medical exams. (Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Higgins, et al., 2002)

The four groups in Stage II were selected based on their reported level of physical disability during Stage I: 111 Gulf War veterans who reported disability; 98 Gulf War veterans who did not report disability; 54 veterans of the Bosnia conflict who reported disability; and 79 veterans who did not deploy outside the UK who reported disability (era veterans). (Ismail, et al., 2002) The latter two groups were combined into one group of non-Gulf War controls. The overall response rate was 57%, the highest rate being among the ill Gulf War group (67%). In the absence of a clear definition of Gulf War-related ill health, a generic measure of illness was used to define physical disability, the Physical Functioning subscale of the Medical Outcome Study Short Form-36 (SF-36). The score on the PF that was at the lowest tenth percentile during Stage I was selected as the cut-off for the ill groups during Stage II, because this score would identify the most disabled veterans. The psychiatric interview used the World Health Organization's Schedule of Clinical Assessment in Neuropsychiatry. The presence and severity of symptoms in the past four weeks were used to determine the presence or absence of psychiatric disorders, including mood, anxiety, PTSD, somatoform, sleep, and alcohol related disorders.

The rates of common psychiatric disorders were not increased in healthy Gulf War veterans, compared to the rates in the general adult population. Ill Gulf War veterans were two to ten times more likely to be diagnosed with most psychiatric disorders, than healthy Gulf War veterans were. These disorders included major depression, generalized anxiety disorder, panic disorder, phobias, somatoform disorders, and sleep disorders. The only two exceptions were PTSD (rates of 3% in ill Gulf War veterans, compared to 1% in healthy Gulf War veterans; not significant); and alcohol related disorders, which were more frequent in healthy Gulf War veterans (10%) than in ill Gulf War veterans (7%). In comparison with healthy veterans, ill Gulf War veterans were likely to be older, to be lower rank, and to have been discharged from military service. Logistic regression was performed to adjust for confounding of age, sex, military rank, and marital status. After adjustment, ill Gulf War veterans continued to demonstrate significantly higher rates of depression, anxiety, somatoform, and sleep

disorders, compared to healthy Gulf War veterans. In contrast, there were smaller differences between the rates of most disorders in the ill Gulf War veterans, and the rates in ill Bosnia and era War veterans. The main exception was somatoform disorders, which were diagnosed three times more frequently in ill Gulf War veterans, compared to ill Bosnia and era veterans, even after adjustment.

The proportions of veterans who were diagnosed with any psychiatric disorder (depression, anxiety, PTSD, and alcohol related disorders) were: 24% of ill Gulf War veterans, 12% of healthy Gulf War veterans, and 19% of ill non-Gulf War veterans. The adjusted risk of any psychiatric disorder was 2.4 times higher in ill Gulf War veterans than in healthy Gulf War veterans. These results were consistent with several previous Gulf War studies that used structured psychiatric interviews in New Jersey and Boston. (Pollet, et al., 1998; Lange, et al., 1999; Natelson, et al., 2001; Lange, et al., 2001; Wolfe, et al., 1999b; Proctor, et al., 2001a; Proctor, et al., 2001b; White, et al., 2001) From Stage I to Stage II, a substantial proportion of the disabled veterans improved (40% of ill Gulf War veterans; 33% of ill Bosnia veterans, and 50% of ill non-deployed veterans). During this period, only 11% of healthy Gulf War veterans became disabled. This is a limitation of this study, because it could have caused an underestimation of current psychiatric disorders in disabled Gulf War veterans. In addition, by using the Physical Functioning subscale of the SF-36, veterans with physical symptoms may have been over-identified, and veterans with psychological symptoms may have been under-identified.

2. David, AS, Farrin, L, Hull, L, Unwin, C, Wessely, S, and Wykes, T. Cognitive functioning and disturbances of mood in UK veterans of the Persian Gulf War: a controlled study. *Psychological Medicine* 2002 November; 32(8):1357-1370. **(DoD-39)**

The objectives of this British study were to determine: whether the pattern of neuropsychological deficits, if any, differed across symptomatic veterans from different deployments; whether such deficits could be specifically attributed to Gulf War deployment vs. any overseas deployment; and which deficits were associated with general ill health. (David, et al., 2002) This particular analysis was the second of four publications in 2002 based on Stage II medical assessments; and it included the same participants who were described previously. (Ismail, et al., 2002; Higgins, et al., 2002) Veterans took part in a full-day medical exam, including a 2.5-hour neuropsychological assessment. During Stage II, the Medical Outcome Study Short Form-36 (SF-36) was administered a second time. (David, et al., 2002) The score on the Physical Functioning subscale that was at the lowest tenth percentile during Stage II was selected as the cut-off for the ill groups, because this would identify the most disabled veterans. Based on the Stage II classification, there were 76 ill Gulf War veterans, 131 well Gulf War veterans, 36 ill Bosnia veterans, 18 well Bosnia veterans, 39 ill non-deployed veterans, and 39 well non-deployed veterans.

There were 23 neuropsychological measures, which included assessments of current IQ, estimated premorbid IQ, memory, attention, visual perception, and motor dexterity. In addition, four questionnaires were used: the Cognitive Failures Questionnaire (CFQ), Beck Depression Inventory (BDI), State-Trait Anger Expression Inventory (STAXI), and Mississippi Combat Related PTSD Scale (PTSD). The CFQ is a self-reported measure of everyday cognitive lapses or failures, which assesses perception of cognitive performance. Two separate multivariable analyses were performed to compare the 6 veteran groups on the 23 measures: on the basis of current health status (ill or well); and on the basis of deployment (Gulf War, Bosnia, or non-deployed). The analyses were adjusted in two steps: first, on the confounding factors of age, education, and premorbid IQ; and second, on age, education, premorbid IQ, plus the depression score on the BDI.

When the veteran groups were compared based on health status rather than deployment (ill vs. well), ill veterans reported significantly higher scores on the BDI and PTSD, compared to healthy veterans. PTSD scores remained significantly higher in the ill veterans, even after adjustment for depression. This suggested that PTSD symptoms were distinct from depressive symptoms, to some extent, and could have contributed to a perceived loss of physical and mental functioning. Ill veterans demonstrated poorer performance than healthy veterans on only one of the 23 neuropsychological tests, after adjustment for confounding-the Digit Symbol

test, a measure of attention. This difference on the Digit Symbol test disappeared after adjusting for multiple statistical comparisons. When the veteran groups were compared based on deployment status rather than health (Gulf War, Bosnia, or non-deployed), there were no differences on the four self-report questionnaires, after adjustment for confounding. After adjustment, Gulf War veterans demonstrated poorer performance than Bosnia or non-deployed veterans on only one of the 23 neuropsychological tests-the Purdue Pegboard assembly score, a measure of motor function. This difference on the Purdue Pegboard score disappeared after adjusting for multiple statistical comparisons.

The authors concluded: "There is no evidence of major neuropsychological impairment in Gulf War veterans. Those weak effects which were detected were patchy in terms of the cognitive systems implicated. Furthermore, they were just as likely to be attributable to any active deployment and hence not likely to be related to specific Gulf-related exposures." The authors pointed out that this study confirmed the findings of previous studies that emotional and psychological disorders were common in Gulf War veterans; and this could, "in itself, explain the subjective cognitive problems reported by veterans." (White, et al., 2001, Lange, et al., 2001; Anger, et al., 1999; Binder, et al., 1999; Storzbach, et al., 2000; Storzbach, et al., 2001; Vasterling, et al., 1997; Vasterling, et al., 1998) They concluded that the increased prevalence of depression "disorders in Gulf veterans is an obvious cause for concern, a target for therapeutic intervention and for research into possible preventative action."

3. Sharief, MK, Priddin, J, Delamont, RS, Unwin, C, Rose, MR, David, A, and Wessely, S. Neurophysiologic analysis of neuromuscular symptoms in UK Gulf War veterans: a controlled study. *Neurology* 2002 November 26; 59(10):1518-1525. **(Funded by the UK Ministry of Defense)**

The objectives of this British study were to determine if the neuromuscular symptoms reported by some Gulf War veterans were related to objective abnormalities of peripheral nerves, skeletal muscles, or neuromuscular junctions; and to compare the rates of neurological abnormalities among Gulf War veterans, Bosnia veterans and non-deployed veterans. (Sharief, et al, 2002) This particular analysis was the third of four publications in 2002 based on Stage II medical assessments, which were described previously. (Ismail, et al., 2002; David, et al., 2002; Higgins, et al., 2002) However, the participants in this study underwent a different selection process than the individuals in the first three studies. Symptomatic veterans were selected on the basis of five or more neuromuscular symptoms reported at Stage I, including fatigue, joint stiffness, muscle weakness, myalgia at rest or after exercise, sensory symptoms (for example, numbness of the fingers or toes), and autonomic symptoms (for example, disturbance of bladder, bowel, or sexual function). (Sharief, et al, 2002) Healthy veterans were selected on the basis of zero or one of the above symptoms at Stage I. Comprehensive evaluations were performed, including neurological exams; nerve conduction studies; quantitative sensory thresholds (thermal and vibration); autonomic function tests (cardiovascular reflexes and sweat testing); and concentric needle and single-fiber electromyography (EMG).

110 veterans participated in this study (77% participation), including 49 ill Gulf War veterans, 26 healthy Gulf War veterans, 13 ill Bosnia veterans, and 22 ill non-deployed veterans. Notably, substantial proportions of the 84 veterans, who were ill at Stage I, reported improvements in symptoms at Stage II (39% of ill Gulf War veterans, 8% of ill Bosnia veterans, and 32% of ill non-deployed veterans). None of the 26 veterans, who were healthy at Stage I, reported an increase in neuromuscular symptoms at Stage II. Neurological exams of all participants were "generally unremarkable; and "there was specifically no clinical evidence for peripheral neuropathy or fatigable muscle weakness." However, on neurological exam and nerve conduction studies, eight individuals were diagnosed with mild median nerve compression (carpal tunnel syndrome); and three individuals were diagnosed with mild ulnar neuropathy. These included, respectively: two ill Gulf War veterans, two healthy Gulf War veterans, one ill Bosnia veteran, and three ill non-deployed veterans; and one ill Gulf War veteran and two ill non-deployed veterans. There were no other abnormalities on neurological exam or nerve conduction studies.

There were no significant differences among the four groups of veterans on quantitative sensory

testing or autonomic function tests. Detailed EMG testing was performed to rule out chronic denervation, myopathic changes, or abnormalities of neuromuscular transmission. Again, there were no significant differences among the four groups of veterans. The authors concluded: "there were no objective abnormalities of autonomic nervous system, neuromuscular transmission, or skeletal muscles in symptomatic veterans." They disagreed with the hypothesis that low-level organophosphate nerve agent exposure or pyridostigmine bromide could have caused nerve damage, as follows: "Results of the single-fiber EMG presented here are of particular interest, as they would argue against potential toxic causes of Gulf War-related symptoms. We did not observe electrophysiologic abnormalities such as disorders of neuromuscular transmission or neuropathy to support toxicity from organophosphates or pyridostigmine."

The authors concluded: "By including these representative groups and through the use of robust and highly sensitive neurophysiologic tests, we provide convincing evidence that the symptoms reported by Gulf War veterans were not associated with objective generalized neurologic or neuromuscular dysfunction. However, some neurogenic symptoms that were reported by Gulf War veterans and other servicemen studied here could be attributed to focal compressive neuropathies such as carpal tunnel syndrome or ulnar neuropathy. These are common neurologic syndromes that are known to occur following repetitive activities of the upper limbs, and are not specifically related to Gulf War deployment." These results are consistent with two controlled studies of neurological function in Gulf War veterans, performed by CDC and by scientists in Portland, Oregon. (Fukuda, et al., 1998; Nisenbaum, et al., 2000; McCauley, et al., 1999a; Bourdette, et al., 2001; Spencer, et al., 2001; McCauley, et al., 2002a) These studies demonstrated a lack of abnormalities on neurological exams and nerve conduction studies in ill and healthy Gulf War veterans. The Oregon scientists reached similar conclusions as the British scientists, as follows: "Most unexplained illness in Gulf War veterans cannot be explained by neurotoxic effects of exposures to chemicals that inhibit cholinesterase activity." (Spencer, et al., 2001)

4. Barrett, DH, Doebbeling, CC, Schwartz, DA, Voelker, MD, Falter, KH, Woolson, RF, and Doebbeling, BN. Post-traumatic stress disorder and self-reported physical health status among U.S. military personnel serving during the Gulf War period: A population-based study. *Psychosomatics* 2002 May-June; 43(3):195-205. **(HHS-1 and DoD-58)**

In 1995-96, a telephone survey was performed of a randomly-selected sample of military personnel, whose home state of residence at enlistment was Iowa. Study subjects were in four groups: Gulf War active-duty, Gulf War National Guard and Reserve, non-deployed active-duty, and non-deployed National Guard and Reserve. A total of 3,682 subjects participated (76% response rate). (Iowa, 1997; Doebbeling, et al., 2000; Voelker, et al., 2002) The objective of this analysis was to examine the relation between PTSD and perceived physical health and health-related quality of life in a representative sample of Gulf War and non-deployed veterans. (Barrett, et al., 2002)

The prevalence of PTSD was assessed by use of the PTSD Checklist-Military Version (PCL-M), a screening instrument that has been validated with structured psychiatric interviews. A cutoff score of 50 or more was used to categorize PTSD. The interview included 37 questions about physical health symptoms during the previous year, related to seven organ systems; and 57 questions about medical conditions during the previous year, related to 12 ICD-9 categories. The Medical Outcomes Study Short Form-36 (SF-36) was used to assess functional status and health-related quality of life. Multivariable logistic regression analysis was used to determine the association between PTSD status and demographic, military, and smoking variables. Linear regression was used to compare the mean number of physical symptoms and medical conditions and the mean SF-36 scores by PTSD status, while controlling for age, sex, race, rank, service branch, and smoking status.

The prevalence of PTSD in this population was estimated to be 1.09% (37 Gulf War veterans and 16 non-deployed veterans), as measured by the PCL-M. The rate of PTSD was increased two-fold in Gulf War veterans. Controlling for deployment, the rate of PTSD was increased more than four-fold in Army veterans, compared to other branches. Among the 53 veterans with PTSD, only 42% rated their current general health status as good to excellent, compared to

94% of persons without PTSD, who rated their health as good to excellent. In addition, veterans with PTSD reported a significantly higher number of physical symptoms, compared to veterans without PTSD (mean of 19.8 symptoms vs. 3.6 symptoms). More than 90% of veterans with PTSD reported at least one symptom from each of five symptom categories (constitutional, neurological, gastrointestinal, skin, and musculoskeletal). Veterans with PTSD reported significantly higher numbers of medical conditions, compared to veterans without PTSD (mean number of 10.2 conditions vs. 1.7 conditions). Veterans with PTSD reported significantly increased numbers of medical conditions in ten of twelve ICD-9 categories. Veterans with PTSD reported significantly lower levels of functioning and quality of life on each of the eight subscales of the SF-36.

These results confirm the relationship between PTSD and increased reporting of physical symptoms in nearly all organ systems, which was shown previously in Gulf War veterans. (Wolfe, et al., 1998; Proctor, et al., 1998; Wolfe, et al., 1999b; Wagner, et al., 2000; Engel, 2000; Natelson, et al., 2001) The rates of PTSD were increased four-fold in current smokers, compared to non-smokers. The authors noted: "Smoking and other adverse health behaviors, including alcohol and drug use, may explain some of the increased physical symptoms reported by veterans with PTSD." They suggested that the possible interaction between PTSD, depression, cigarette smoking, and the prevalence of physical health symptoms merited further study. In 1999-2001, a subset of more than 600 veterans in the Iowa cohort study participated in a comprehensive medical evaluation, including structured psychiatric interviews, physical exams, and laboratory tests; and the results have been submitted for publication.

5. Orcutt, HK, Erickson, DJ, and Wolfe, J. A prospective analysis of trauma exposure: the mediating role of PTSD symptomatology. *Journal of Traumatic Stress* 2002 June; 15(3):259-266. **(VA-7)**

The Boston Environmental Hazards Research Center has been following 2,949 Army veterans who processed through Fort Devens, Massachusetts, at the time of their return from the Gulf War in 1991. These veterans have been evaluated at four time points, starting within five days of their return to the U.S., and again at 18 to 24 months later (Time 2), at four years (Time 3), and at six to seven years (Time 4). At Time 2, 2,313 subjects participated, which was 78% of the original cohort. (Wolfe, et al., 1996; Wolfe, et al., 1999b; Sharkansky, et al., 2000; Erickson, et al., 2001) The primary objective of this particular analysis was to examine the relationship between exposure to combat during the Gulf War and exposure to traumatic life events in the two years after the war. (Orcutt, et al., 2002) The secondary objective was to examine if PTSD symptoms were potential mediators of the relationship between combat exposure and the risk of subsequent exposure to traumatic events.

In a previous study of this population, increased PTSD symptoms at Time 1 were predicted by reported combat exposures at Time 1. Increased PTSD symptoms at Time 2 were predicted by reported combat exposures at Time 1, PTSD symptoms at Time 1, and traumatic life events in the intervening two years. (Sharkansky, et al., 2000) The hypothesis of this study was that higher combat exposure during the Gulf War would predict greater exposure to traumatic events reported at Time 2. (Orcutt, et al., 2002) The experience of PTSD could contribute to a vulnerability to future traumatic events through deficiencies in self-protective behaviors or increases in risk-taking behavior.

The Laufer Combat Scale was used at Time 1 to assess combat exposure, including 33 items, such as being on alert for SCUD attack or for chemical attack. The 33 items were summed to create a total Gulf War combat exposure score. PTSD symptoms were evaluated at Time 1 using the Mississippi Scale for Combat-Related PTSD, and a summary score was calculated. Traumatic life events at Time 2 were measured as a count of four life events that could have occurred since Time 1. These life events, and the proportion of veterans who reported each one, were: 1) very serious accident, illness, or medical procedure involving yourself (14%); 2) loss of your home or property due to fire, flood or other natural or man-made disaster (2%); (3) an assault on yourself (3%); and 4) an event where you saw someone you didn't know badly hurt or violently killed (12%). After controlling for the effects of age, sex, marital status, and education, reported combat exposure at Time 1 was significantly associated with traumatic life events at Time 2. Combat exposure at Time 1 was significantly associated with PTSD symptoms at Time 1.

PTSD symptoms at Time 1 were significantly associated with traumatic life events at Time 2. After controlling for the effects of PTSD at Time 1, the direct effect of combat exposure on later traumatic events was reduced by 48%. These results suggested that PTSD symptoms partially mediated the link between combat exposure and later traumatic events. However, a significant direct effect of combat exposure on later traumatic events remained, that was not accounted for by PTSD symptoms. The authors concluded that Gulf War veterans who were exposed to combat were at increased risk of exposure to traumatic events in the two years after the war, and that this increased risk was partially mediated by the individual's level of PTSD symptoms. They suggested that if an individual developed combat-related PTSD, "therapeutic intervention to minimize symptoms may also reduce an individual's risk of future trauma. Treatment of PTSD symptoms may therefore exert a significant role in breaking a cycle of multiple traumatizations."

C. Diagnosis

Ladich, ER, Lewin-Smith, MR, Specht, CS, Moroz, AL, Kalasinsky, VF, and Mullick, FG. A histopathological study of head and neck specimens from a cohort of Persian Gulf War military veterans. *Military Medicine* 2002 October; 167(10):864-867. **(Funded by DoD and VA)**

One study published in 2002 focused on the diagnosis of anatomical abnormalities. (Ladich, et al., 2002) The objective of the study was to describe the types and frequencies of pathological findings in head and neck specimens from Gulf War veterans, which were studied at the Armed Forces Institute of Pathology (AFIP). Between 1992 and June 30, 2000, AFIP received 361 head and neck specimens from 264 veterans, contributed by VA and DoD medical facilities nationally. These patients were 90% male, with a mean age of 35 years. This study included biopsy, surgical pathology, cytopathology, and autopsy specimens from the head and neck, excluding thyroid, parathyroid, skin, and lymph node specimens. Fifty-one percent of the specimens were from the nose and respiratory system, 23% were from the digestive system, and 21% were from tonsils and adenoids. Seventeen percent of the specimens showed no pathological abnormalities. Inflammatory changes were present in 48% of the specimens, most frequently, chronic sinusitis, allergic rhinitis, and lymphoid hyperplasia of the tonsils (tonsillitis). The authors commented, "Chronic rhinosinusitis occurs in nearly 15% of the general U.S. population."

Infectious organisms were found in only two individuals in whom *Aspergillus* was cultured, which is a fungal infection that is common in the U.S. The authors said: "Most of the specimens in this study were obtained months to years after deployment, and possible etiologic environmental exposures may have occurred in the U.S. as well as during deployment." These results were consistent with an earlier AFIP study that focused on infectious diseases. (Specht, et al., 2000) The earlier AFIP study evaluated specimens from 2,852 Gulf War veterans from 1992 to December 1997, and it found no cases of infectious diseases that are endemic to the Middle East. Five percent of the individuals were diagnosed with benign tumors, most frequently from the mouth and throat. (Ladich, et al., 2002) Five individuals were diagnosed with squamous cell carcinomas of the larynx or tonsil. Squamous cell carcinomas of the head and neck are generally associated with heavy smoking and alcohol use. One diffuse large B cell lymphoma of the nasopharynx was diagnosed in a HIV-positive patient. In HIV patients, lymphoma is a relatively frequent malignancy. The authors said: "The relatively few malignancies seen overall may reflect the relatively young age of this cohort."

The major conclusions were: "Most of the pathological diagnoses rendered in this study are diseases commonly encountered in surgical pathology practice in the U.S. . . No diagnostic conditions listed as endemic to the Persian Gulf region were seen in the pathology specimens in this cohort. Overall, these findings support clinical studies of Gulf War veterans in which the majority of study participants have diagnosed conditions common in the U.S. adult population."

D. Immune Function

Everson, MP, Shi, K, Aldridge, P, Bartolucci, AA, and Blackburn, WD. Immunological responses are not abnormal in symptomatic Gulf War veterans. *Annals of the New York Academy*

of Sciences 2002 June; 966:327-342. **(Funded by DoD-42 and VA-56)**

One study published in 2002 focused on immune function among Gulf War veterans. (Everson, et al., 2002) The objective of the study was to systematically evaluate components of the acquired immune system in ill Gulf War veterans, healthy Gulf War veterans, and ill non-deployed veterans. To date, there has been no evidence of increased rates of recurrent or opportunistic infections in Gulf War veterans. Therefore, the authors hypothesized that if immunological abnormalities were related to symptoms in Gulf War veterans, these would be detected in the acquired immune system, rather than the innate immune system. Sensitive *in vitro* immunological assays were used to detect functional abnormalities in antigen-presenting cells, including dendritic cells and monocytes; T cells; Th1 and Th2 cells; and B cells that function in acquired immunity.

Ill and healthy Gulf War veterans were selected from the VA Gulf War Registry at the Birmingham VA Medical Center. Fifty-two symptomatic Gulf War veterans participated, who were selected because they had symptoms that their treating physicians could not ascribe to a particular diagnosis. Eligibility criteria required medically unexplained symptoms related to at least two organ systems. On average, the 52 ill veterans reported symptoms attributable to 4.9 organ systems, most frequently, the neurological, musculoskeletal, gastrointestinal, and pulmonary systems. Thirty-one asymptomatic Gulf War veterans participated in this study. A second control group included twenty-one ill non-deployed veterans, who were identified from disability claims filed with the Alabama Veterans Benefits Administration, and who were confirmed with medical records of the Birmingham VA Medical Center. Subjects were contacted for blood draws and collection of demographic and health information. At the time of this study, ill veterans continued to report symptoms, and healthy veterans continued to remain asymptomatic. Gulf War veterans were significantly older than non-deployed veterans (mean age of 46 vs. 40 years); and Gulf War veterans were significantly more likely to have served in the National Guard/Reserve vs. on active-duty, compared to non-deployed veterans (69% vs. 0%). When regression analyses were performed, there was no direct statistical effect of age on the lab data.

This study was designed to evaluate the functional integrity of cells involved in acquired immunity, including cytokine levels and several types of white blood cells. Overall, no abnormalities were detected that would indicate that any of the three study groups were immunodeficient or immunocompromised. Tests of acquired immunity function demonstrated no significant abnormalities in the ill Gulf War veterans. Gulf War veterans did not have an impaired capacity to mount an immune response to an antigen (anthrax vaccine), to which they would have been exposed during the Gulf War. If their immune systems had been suppressed by deployment, the predicted effect would have been that they would have a decreased recall response when tested several years later.

The overall conclusions were: "Results of sensitive *in vitro* cellular and humoral immune responses used to detect functional abnormalities in antigen-presenting cells, T cells, and B cells revealed no consistent differences between study groups and indicated that *in vitro* immunological responses are not abnormal in Gulf War veterans. These data should reassure U.S. service members who are Gulf War veterans that there are no significant immunological abnormalities due to their service in the Gulf War." These results were consistent with three previous studies, which did not demonstrate unusual immune function abnormalities in Gulf War veterans. (Grady, et al., 1998; Klaustermeyer, et al., 1998; Zhang, et al., 1999)

E. Prevention

Overview:

Six articles published in 2002 focused on general topics in prevention of illness, and four articles focused on potential health effects of the anthrax vaccine, a preventive measure.

The objective of the first general study was to describe the Defense Medical Surveillance System, which serves as the central repository of medical surveillance data for the U.S. armed forces. (Rubertone and Brundage, 2002)

The objective of the second general study was to describe the Recruit Assessment Program, a

DoD program designed to routinely collect demographic, medical, psychosocial, occupational, and health risk factor data from all US military personnel at the time of recruitment. (Hyams, et al., 2002)

The objectives of the third and fourth general studies were linked. The objective of the third study was to investigate one-year Navy attrition in relation to factors assessed by the Sailors' Health Inventory Program (SHIP) questionnaire, a medical and psychosocial history completed by all Navy recruits. (Booth-Kewley, et al., 2002) The objective of the fourth study was to examine the predictive accuracy and practical usefulness of items from the Sailors' Health Inventory Program (SHIP) questionnaire for identifying Navy personnel at risk for attrition during basic training. (Larson, et al., 2002)

The objective of the fifth general study was to describe the goals and methods of the Millennium Cohort Study, which are to "determine if risk factors related to military service, such as occupational specialty, deployment history, service type, and other exposures are associated with the development of chronic disease." (Gray, et al., 2002a)

The objectives of the sixth general study were to "describe the psychological screening program for U.S. military personnel in different operations; present key findings from the psychological screening program; and highlight some of the lessons learned when implementing a psychological screening program." (Wright, et al., 2002)

Four articles published in 2002 focused on potential health effects of the anthrax vaccine. The objective of the first study was to monitor anthrax vaccine safety by comparing the rates of hospitalizations among anthrax-immunized and non-immunized U.S. military personnel on active duty in 1998. (Sato, et al., 2002)

The objective of the second vaccine study was to assess the safety of the anthrax vaccine given to nearly 400,000 military personnel in 1998 and 1999, through the evaluation of reports of adverse events submitted to the Vaccine Adverse Event Reporting System (VAERS). (Sever, et al., 2002)

The objective of the third vaccine study was to compare the rates of ambulatory medical care among deployed persons who received the anthrax vaccine, with the rates in deployed persons who were not vaccinated. (Rehme, et al., 2002)

The objectives of the fourth vaccine study were to determine if anthrax vaccination would result in a measurable decrease in pregnancy rates, and to measure its effects on fetal loss and adverse birth outcomes. (Wiesen, et al., 2002)

Prevention-Individual Studies:

1. Prevention-General Topics

1. Rubertone, MV, and Brundage, JF. The Defense Medical Surveillance System and the Department of Defense serum repository: Glimpses of the future of public health surveillance. *American Journal of Public Health* 2002 December; 92(12):1900-1904. **(Funded by DoD)**

The objective of this study was to describe the Defense Medical Surveillance System, which serves as the central repository of medical surveillance data for the U.S. armed forces. (Rubertone and Brundage, 2002) Deployment medical surveillance has become a priority for the DoD, partly in response to the experience of investigating the illnesses in Gulf War veterans. Due to lack of uniformity, accuracy, and accessibility of records containing demographic, deployment location, potential exposures, and medical diagnoses of individual soldiers, associations between exposures and illnesses in Gulf war veterans have been difficult to evaluate. In addition, as national security issues have fundamentally changed, a comprehensive, fully integrated military medical surveillance system has become essential to effective military operations. The maximization of the health, fitness, and medical preparedness of forces being deployed and the minimization or disease and injury risks during deployments have become cornerstones of a post-cold war military medical support strategy.

The Defense Medical Surveillance System (DMSS) began as an Army data center in 1986 to support its HIV screening, clinical care, and epidemiological research program. In 1993, this data system transitioned into the Army Medical Surveillance System and expanded its scope to include all illnesses and injuries of public health or military operational importance. In 1997, this

system became the DMSS, a fully integrated, easily accessed relational database. The DMSS now serves as the central repository of data from many sources, including more than 100 field sites. Longitudinal records have been established and continuously updated for more than seven million individuals who have served in the armed forces since 1990. Information on demographic and military characteristics is maintained in this database, as well as deployment and medical experiences of all service members throughout their military careers. Records are maintained in person, place, and time frames of references, which permits almost immediate assessment of morbidity experiences of service members who were in specific locations, who shared characteristics, or who had similar experiences on specific days.

The DoD serum repository is also integrated into this system. Since 1990, sera collected before and after major deployments have been sent to this repository. Serum identification numbers and repository locations are linked to dates of specimen collection and personal identification of donors, which provides a powerful seroepidemiological capability to the military surveillance program. More than 27 million specimens related to 7.5 million individuals have been stored. About 4.5 million individuals have two or more stored specimens. Practical applications of the DMSS include conducting investigations of potential disease outbreaks, monitoring adverse effects associated with vaccinations, evaluating emerging infectious disease threats, surveillance of specific deployments, and evaluating policies aimed at prevention of illness. Since 1998, DMSS has responded to an annual average of 350 requests for tailored data sets, data summaries, and epidemiological analyses. These applications provide a model of the capabilities and benefits of a future comprehensive surveillance system for general public health use.

2. Hyams, KC, Barrett, DH, Duque, D, Engel, CC, Friedl, K, Gray, G, Hogan, B, Kaforski, G, Murphy, F, North, R, Riddle, J, Ryan, MA, Trump, DH, and Wells, J. The Recruit Assessment Program: a program to collect comprehensive baseline health data from US military personnel. *Military Medicine* January 2002; 167(1):44-47. **(DoD-98)**

Since the Gulf War, several scientific review panels have recommended that DoD maintain more complete and accessible medical records and collect more health surveillance data. One specific recommendation has been for DoD to document health status before hazardous deployments. A major problem in evaluating clinical and epidemiological data from Gulf War veterans has been the lack of baseline data, which are necessary to evaluate whether health problems were caused or exacerbated by wartime experiences. DoD has been evaluating the feasibility of establishing a program to collect baseline data, in a pilot program called the Recruit Assessment Program (RAP). The objective of this study was to describe the RAP, a DoD program designed to routinely collect demographic, medical, psychosocial, occupational, and health risk factor data from all US military personnel at the time of recruitment. (Hyams, et al., 2002) The RAP survey will become part of the service member's permanent medical record.

The electronic format of the RAP data could be used to automate the enrollment of new recruits into administrative and health care databases. For many years, baseline health information has been obtained from recruits and recorded on standard forms; however, the data were not computerized, often were not readily accessible, and were limited in scope. During initial military training, baseline data would aid in identifying recruits who could benefit from health promotion efforts, such as smoking cessation. The RAP could assist in routine health case by aiding in diagnosis and clinical preventive medicine. Data on preexisting health status is important for clinical purposes to document changes in a patient's condition. The RAP would be useful in monitoring trends in health behaviors and in the development of population-based preventive health measures. It would be especially valuable in the evaluation of military and veteran populations during and after hazardous overseas assignments by providing baseline medical and psychological data. Baseline data would also be useful for DoD and VA to provide documentation of previous health status when determining service-connected disability.

Since the mid-1990s, the Navy has used a shorter health questionnaire, called the Sailors Health Inventory Project (SHIP) at the Great Lakes Naval Recruit Training Command (Project DoD-

110). The SHIP demonstrated the feasibility of providing health questionnaires to recruits. The RAP questionnaire has to be simple and easy to understand, to obtain accurate responses when self-administered. The survey has to be short enough that it could fit into the busy basic training schedule. The current version of the survey takes about 45 minutes to complete. As much as possible, design of the RAP relied on validated survey instruments. Pilot testing of the RAP began in mid-2001 at the Marine Corps Recruit Depot in San Diego, and about 30,000 Marines have completed the survey, as of early 2003. A second site was added later at the Army Recruit Center at Fort Jackson, South Carolina.

The RAP will provide extensive data from large numbers of service personnel that can be analyzed to identify risk factors for medical and psychiatric illnesses. There are plans to use RAP data in the Millennium Cohort Study, which will track the health of 140,000 service personnel from 2001 to 2022 (Project DoD-143/VA-78). The major goal of the RAP pilot program is to determine the feasibility of fully instituting the RAP among all military branches. If successful, the RAP will have to be able to process almost 5,000 active-duty, reserve, and National Guard personnel who enter military service each week.

3. 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. **(Funded by DoD-110 and Office of Naval Research)**

First-term attrition, defined as failing to complete the contracted first enlistment term, is one of the most serious and costly personnel problems faced by the U.S. military. For example, in the mid-1990s, 16% of Navy recruits left the service within the first six months, and a total of 36% left before the end of their first term. If the three services could improve screening methods of applicants, attrition rates would be likely to decline. Few studies have examined medical or psychological factors as possible predictors of military discharge. The objective of part one of this two-part study was to investigate one-year Navy attrition in relation to factors assessed by the Sailors' Health Inventory Program (SHIP) questionnaire, a medical and psychosocial history completed by all Navy recruits. (Booth-Kewley, et al., 2002) Starting in 1997, the SHIP questionnaire has been given to Navy recruits during basic training at Great Lakes Recruit Training Command.

The attrition vs. retention status at the one-year mark was determined for 66,690 individuals who completed the SHIP in 1997 to 1999. At one year, 23,372 individuals (35%) had been discharged, and 43,318 individuals (65%) were still in the Navy. The population was 84% male, with a mean age of 19.9 years. 87% had a high school diploma or some college, vs. 13% who did not have a high school diploma. The SHIP includes a short demographic section and 191 health and psychosocial questions, which generally have yes/no answers. This analysis focused on four demographic variables (age, gender, ethnicity, and education), and 35 medical or psychosocial questions, which were endorsed by at least 5% of the discharged group. The study evaluated factors associated with total attrition, and factors associated with the three reasons for discharge-medical, behavioral, and administrative. These account for 16%, 57%, and 26% of discharged individuals, respectively. The administrative category includes discharges for erroneous entry (e.g. failure to meet educational standards), hardship (e.g. parenthood), and other reasons.

The ten strongest predictors of overall attrition were, in order: less than a high school education (odds ratio of 1.87), shortness of breath, ever suspended or expelled from school, history of depression/excessive worry, fainting or dizziness (in the past 12 months, not caused by exercise, heat, or standing up quickly), recurrent back pain, history of broken bones, ever arrested for a crime, female gender, and pain or pressure in the chest (odds ratio of 1.42). Similar variables were predictors across the three categories of discharges (medical, behavioral, and administrative). For example, less education, shortness of breath, history of broken bones, depression/excessive worry, and ever suspended or expelled emerged among the ten best predictors for all categories. The finding that the same predictors were associated with all three categories of attrition was consistent with the results of a study of 32,114 Air Force recruits. (Talcott, et al., 1999)

Individuals who lacked a high school diploma were almost twice as likely to be discharged, especially for behavioral reasons. (Booth-Kewley, et al., 2002) The authors noted that this finding highlights "the challenges associated

with the military's recent policy to allow more non-high school graduates to enlist." Female gender was predictive for medical and administrative discharges, but not behavioral discharges. Shortness of breath was one of the strongest predictors for all three discharge categories. The authors stated: "This result may have occurred because shortness of breath can be a symptom of both asthma and anxiety disorders. It is possible that both of these conditions link shortness of breath to attrition." The overall conclusion was: "Although the full array of characteristics that should be assessed is not clear at this time, our study indicates the potential importance of depression and anxiety, juvenile misconduct, various physical and psychosomatic complaints, and failure to graduate from high school."

4. 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. **(Funded by DoD-110 and Office of Naval Research)**

Among the demographic data gathered about military recruits, educational attainment and Armed Forces Qualification Test (AFQT) mental ability scores have traditionally served as the benchmarks for recruit quality and as tools to manage attrition. However, the high attrition rates in the 1990s suggested the need to determine additional predictors of success in the military. The objective of part two of this two-part study was to examine the predictive accuracy and practical usefulness of items from the Sailors' Health Inventory Program (SHIP) questionnaire for identifying Navy personnel at risk for attrition during basic training. (Larson, et al., 2002) The 66,690 individuals included 52,142 basic training graduates (78%) and 14,548 who were discharged during basic training (22%). A major goal was to determine the best subset of the 191 SHIP questions for predicting basic training attrition. (Note: these SHIP questions did not include age, gender, ethnicity, or education.) Logistic regression modeling was used to identify 40 questions that were significantly associated with attrition.

The nine strongest predictors of overall attrition were, in order: asthma symptoms in the last 12 months (adjusted odds ratio of 3.06); asthma; serious suicide thoughts or suicide attempts; ever suspended or expelled from school; bone, joint, or other deformity; current smoking; depression/excessive worry; anemia; undergone breathing treatments; and migraine headaches (odds ratio of 1.52). Some of these variables were frequently present in cases of attrition. For example, 11.8% of basic training graduates had been suspended or expelled, vs. 26.4% of those who did not graduate. 21.7% of basic training graduates were current smokers, vs. 38.4% of those who did not graduate. The authors commented: "Although a number of medical conditions such as bone, joint, and ear/nose/throat problems can be linked to early personnel loss, the best predictors are psychological and behavioral in nature. In particular, a history of depression, anxiety, and misconduct was shown to represent the greatest risk for basic training attrition." These results were consistent with previous research on attrition during Air Force basic training.

A composite score was calculated for each individual by summing the responses for the 40 variables (one point for yes and zero points for no; range of zero to forty points). The correlation between this overall composite score and attrition was 0.32. This composite score had a significantly higher correlation with attrition, than did level of education (correlation of 0.11), or score on the AFQT (correlation of 0.10). This indicated that educational level and AFQT scores, although invaluable as broad quality indicators, could be improved upon as attrition management tools.

These results could be used to develop screening programs to identify individuals at risk for attrition, potentially to discourage their enlistment or to identify them for placement in remedial programs after enlistment. The authors suggested that the composite score would be the most efficient tool because it provided the highest correlation with attrition. The SHIP could be used to assign at-risk recruits to attrition prevention programs that are already in place for populations such as recruits without high school diplomas. These results could also be used to identify specific areas in which interventions may be needed. For example, the increased risk of attrition among smokers indicated a need to design programs to reduce attrition in smokers. The authors concluded: "Overall, however, our results primarily indicate that remedial programs should continue to address psychological problems in recruits, including depression and anxiety."

5. 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* 2002a June; 167(6):483-488. **(DoD-143/VA-78)**

The primary objective of this prospective study is to "determine if risk factors related to military service, such as occupational specialty, deployment history, service type, and other exposures are associated with the development of chronic disease." (Gray, et al., 2002a) Secondary objectives include "examining characteristics of military service associated with common clinician-diagnosed diseases and with scores on several standardized self-report health inventories for physical and psychological functional status." The Millennium Cohort Study was established partly in response to a recommendation made by the Institute of Medicine, which was that DoD should begin to collect population-based data to evaluate the health of service personnel throughout their careers and after separation from service. (IOM, 1999) This collaborative effort between investigators from the Army, Navy, Air Force, and the VA began in late 1999.

The 2001 cohort consists of a random sample selected from all regular active duty, National Guard, and Reserve personnel of the Army, Navy, Air Force and Marine Corps. It is stratified into 30,000 study participants who have been deployed after August 1997 to southwest Asia, Bosnia, and Kosovo, and 70,000 participants who have never been deployed to these areas. This represents approximately 3.7% of the 2.7 million persons in uniform. In 2004, and again in 2007, additional samples of 20,000 US active duty, National Guard and Reserve military personnel will be added to the study. Ultimately, the researchers hope to enroll over 140,000 individuals into the study, including those deployed to Afghanistan and younger troops. The initial survey instrument is both paper and web-based. It includes questions to collect basic demographic information, as well as information on smoking, alcohol use, occupational classification, self-reported symptoms, and medical conditions. It also assesses physical and functional status, using the Medical Outcomes Short Form-36 (SF-36); psychosocial status, using the Patient Health Questionnaire; and PTSD, using the Patient Checklist for PTSD.

Data sets will be linked to the core survey data, including demographic and deployment data, immunization data, DoD and VA outpatient visits, DoD and VA hospitalizations, DoD birth registry data, VA disability data, and mortality data. Targeted outcomes include common chronic diseases, such as heart disease, cancer, and diabetes, as well as more subtle abnormalities, such as changes on the SF-36. The study questionnaire will be sent to participants every three years, through 2022. To maximize participation and prevent loss to follow-up, the research staff will use repeat mailings and incentives. Veteran Service Organizations are involved to support, endorse, and publicize the study.

In August 2001, 245,000 letters of invitation to participate in the study were mailed out. About half of the respondents filled out the paper-based questionnaire, while the other half completed the questionnaire online. As of late 2002, there was an enrollment of over 70,000 individuals in the study. The authors commented that this study "has the potential to uncover unanticipated exposure-disease associations in a relatively young, healthy, screened population that might otherwise remain unrecognized." The findings of the study "will assist researchers and military leaders in understanding the health impact of future military deployments more completely than in the past. In turn, this better understanding may affect deployment polices as well as prevention and treatment programs, possible influencing veterans' benefits for the future."

6. Wright, KM, Huffman, AH, Adler, AB, and Castro, CA. Psychological screening program overview. *Military Medicine* 2002 October; 167(10):853-861. **(DoD-144)**

The objectives of this study were to "describe the psychological screening program for U.S. military personnel in different operations; present key findings from the psychological screening program; and highlight some of the lessons learned when implementing a psychological screening program." (Wright, et al., 2002) The psychological screening component of the Joint Medical Surveillance Program was mandated by the Assistant Secretary of Defense for Health Affairs in 1996.

Since then, soldiers have been regularly screened across the deployment cycle: in garrison, predeployment, at redeployment just before return, and at post-deployment several months later. A detailed description of the psychological screening program is provided, including the screening procedures as well as the method used to determine whether further intervention is warranted. There is a summary of key findings from the screenings conducted of military personnel deployed to Bosnia, military personnel in garrison, and peacekeepers deployed to Albania and Kosovo. As of January 1999, more than 65,000 personnel deployed to Bosnia completed the screening, as well as several thousand personnel deployed to Kosovo.

The psychological screening program was first instituted among military personnel returning from Bosnia. Three clinical scales comprised the initial psychological screening instrument, including validated scales assessing PTSD, depression, and alcohol use. Several additional measures have been added since then, including the Hostility Scale of the Brief Symptom Inventory and the Quality of Marriage Index, as well as questions assessing peacekeeping experiences, history of traumatic experiences, the Physical Health Questionnaire, and lost work time because of illness. The basic procedure has remained constant for administering the psychological screening and providing brief secondary interviews by mental health providers, as appropriate. First, the primary psychological screen and the clinical and personal history are completed by the soldier. If the cutoff score for one or more scales for PTSD, depression, or alcohol use is exceeded, then the soldier is interviewed by a mental health provider. If the interviewer determines that the screening correctly detected a significant mental health problem, it is classified as mild, moderate or severe, and an appropriate referral is provided to the soldier.

Overall, findings of past psychological screenings conducted from February 1996 until June 2000 indicated significant differences across samples in primary screen and referral rates, with primary screen rates ranging from 16.0% to 25.6%, and referral rates ranging from 2.4% to 11.3%. Apparently, some mental health interviewers set high thresholds for referrals, while other staff had lower screening thresholds. These approaches varied, depending on the officer assigned to conduct the screening, and, therefore, the referral rates are difficult to interpret across deployments. The key demographic findings from the program were that officers and non-commissioned officers were less likely to exceed criteria on any of the scales or to receive a referral than were junior enlisted personnel. In addition, active duty soldiers had the highest rates of exceeding the criteria on the primary screen, compared with National Guard and Reserve soldiers. In garrison, female soldiers had significantly higher rates of exceeding criteria on the primary screen than did male soldiers; however, the rates in females and males were the same in the deployed environment. In general, female soldiers exceeded criteria on the PTSD and depression scales at higher rates than male soldiers, but male soldiers had significantly higher rates of exceeding criteria on the alcohol screen.

Related to the link between physical and psychological health, personnel who exceeded criteria on the primary screen were at almost double the risk of reporting physical problems. Also, among personnel who exceeded the primary screen criteria, over half reported a history of alcohol problems and roughly a quarter reported marital, financial, or legal problems. There also was a significant relationship between deployment length and exceeding the primary screen criteria. This became especially noticeable after three or four months of deployment to Bosnia. This pattern has also been found for other deployments, indicating that for peacekeeping missions, mental health monitoring should be conducted when the deployment lasts longer than three months. The authors identified a data gap related to longitudinal follow-up of individual soldiers, and they commented: “A longitudinal study of soldiers throughout the different phases of the deployment cycle has the advantage of validating the effectiveness of the screening instruments in identifying those soldiers requiring referral. In addition, longitudinal follow-up will determine whether soldiers identified for referral actually seek treatment.”

2. Prevention-Anthrax Vaccine

1. Sato, PA, Reed, RJ, Smith, TC, and Wang, L. Monitoring anthrax vaccine safety in US military service members on active duty: surveillance of 1998 hospitalizations in temporal association with anthrax immunization. *Vaccine* 2002 May 22; 20(17-18):2369-2374. **(DoD-99)**

The Secretary of Defense ordered a mandatory program for anthrax immunization of all US military personnel in December 1997. From March 1998 to December 31, 1998, 159,386 service members had received 433,999 anthrax vaccine doses. However, some members refused anthrax vaccination due to their concerns about possible long-term effects, despite potential disciplinary action. The objective of this study was to monitor anthrax vaccine safety by comparing the rates and types of hospitalizations among anthrax-immunized and non-immunized U.S. military personnel on active duty in 1998. (Sato, et al., 2002) Anthrax immunization status, demographic data, and deployment data were obtained from the Defense Manpower Data Center. Data were collected on date of immunization, dose lot number, age, gender, changes in military assignment, dates of accession to and discharge from military service, and deployments. 11.3% of active-duty service members received at least one dose of the anthrax vaccine during 1998.

Hospitalization data were obtained from a DoD database that contains inpatient data records for all hospitalizations at U.S. military medical treatment facilities (MTF). A hospitalization event was defined as being discharged from an MTF with a diagnosis classified under one of 14 ICD-9 categories. An immunized subject experienced a hospitalization event if it occurred within 42 days following the anthrax vaccine dose. Non-immunized service members experienced an event if they were hospitalized at any time between 1 January and 31 December 1998. A Cox proportional hazards model was developed to compare risk for hospitalization between immunized and non-immunized service members, while controlling for age, gender, race, marital status, and hospitalization during the year of 1997.

For anthrax immunized service members, there were 719 unique hospitalizations within the 14 ICD-9 diagnostic categories during 28,619 person-years of observation (2.5%). Among the non-immunized, there were 47,391 hospitalizations during 1,248,332 person-years (3.8%). Across all 14 ICD-9 diagnostic categories, anthrax-immunized service members had lower rates of hospitalization. Rates of seven of the diagnostic categories were significantly lower in immunized individuals (cancer, infections, and disorders of blood, endocrine, circulatory, musculoskeletal, and respiratory systems). The major conclusions were: "Anthrax immunization was not associated with an increase in hospitalization within 42 days following immunization. Immunized service members were at equal or lesser risk for hospitalization than non-immunized service members during the period of observation."

One limitation of this study was the potential for a "healthy deployment effect," since those who were immunized against anthrax were likely to be among the forward deployed or stationed to a high threat area. Because of the selection of healthier military personnel for deployment, this might explain some of the decreased risk of hospitalizations among those vaccinated. The authors attempted to address this by controlling for hospitalizations in the previous year. This study only included the first year of the data, and person-years of observation will increase rapidly as the study proceeds. In the future, the study will develop sufficient statistical power to examine potential associations between the anthrax vaccine and specific diagnoses alleged to be associated with the use of vaccines, such as Guillain-Barre syndrome.

2. Sever, JL, Brenner, AI, Gale, AD, Lyle, JM, Moulton, LH, and West, DJ. Safety of anthrax vaccine: a review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology and Drug Safety* 2002 April/May; 11(3):189-202. **(Funded by DoD and HHS Health Resources and Services Administration)**

The objective of this study was to assess the safety of the anthrax vaccine (AV) given to nearly 400,000 military personnel in 1998 and 1999, through the evaluation of reports of adverse events submitted to the Vaccine Adverse Event Reporting System (VAERS). (Sever, et al., 2002) VAERS is a passive surveillance program that started in 1990 and that is cooperatively managed by the Food and Drug Administration and the Centers for Disease Control and Prevention. Evaluation of VAERS case reports can be used to identify adverse events (AE) that physicians or patients believe are important enough to report; and to identify a pattern that shows some medically important event might be occurring at a higher than expected frequency. DoD issued a directive in April 1998 that requires military physicians to report to VAERS any event following the use of

AV that results in hospitalization or loss of work time of 24 hours or more. In June 1998, the Army Surgeon General requested that an independent civilian panel be created to perform ongoing medical assessment of VAERS reports related to AV. DoD appointed this panel of expert civilian physicians and scientists, the Anthrax Vaccine Expert Committee (AVEC), to medically evaluate the causal relationship between AV and each VAERS report; and to identify unexpected patterns in the rates of serious medical events.

This report summarizes the findings from the first 602 VAERS reports related to the AV that were filed in 1998 and 1999. During these two years, DoD administered 1,349,327 AV doses. AVEC adopted the VAERS definition of "serious adverse event," which includes death, life-threatening illness, hospitalization, prolongation of an existing hospitalization, or permanent disability. AVEC also adopted a World Health Organization scale of likelihood of the relationship between a vaccine and an adverse event (very likely/certain; probable; possible; unlikely; unrelated; and unclassifiable). 22% of the 602 reports noted a local injection-site AE alone. 56% of the 602 reports cited a systemic AE alone. 22% of the reports noted both local and systemic AE. The most common systemic AE, by far, were flu-like symptoms, malaise, rash, arthralgia, and headache, each of which was reported in more than 10% of the VAERS reports. 92% of the local reactions were assessed as very likely/certain to be caused by AV. 9% of the systemic AE were assessed as very likely/certain to be caused by AV.

There were 34 serious AE (6%), which included 20 cases that required hospitalization. There were 13 other medically important events (2%). Seven of the 34 serious AE were judged as certainly or probably caused by AV, including six local reactions that required hospitalizations, and one case of bronchiolitis obliterans organizing pneumonia. Five of the 13 other medically important events were judged as possibly due to AV (2 cases of aggravation of spondyloarthropathy, 1 case of anaphylactoid reaction, and 2 cases of arthritis). AVEC concluded, "While these events were clearly very significant to the individuals involved, their aggregate numbers do not yet suggest an unexpectedly high occurrence of any AV-attributable serious AE." There has been concern among active-duty military personnel, as well as Gulf War veterans, that AV might cause a chronic non-specific illness. AVEC developed a working case definition that included at least three of the following symptoms: malaise/fatigue, paresthesia, memory loss, sleep disorder, and altered mentation. Five VAERS reports described cases that fit this definition; however, in no case was AV judged to be a certain or probable cause of the symptoms.

The authors concluded that, at this time, the evaluation of VAERS reports does not suggest a high frequency or unusual pattern of serious or other medically important AE. They stated: "None of the other patterns found in this review of VAERS reports (i.e., a tendency for vaccinees reporting an AE to more often be female, older, or in the Air Force) suggest that AV is unsuitable for members of certain subpopulations." AVEC is continuing its ongoing review of VAERS reports, with special attention to serious AE.

3. Rehme, PA, Williams, R, and Grabenstein, J. Ambulatory medical visits among anthrax-vaccinated and unvaccinated personnel after return from Southwest Asia. *Military Medicine* 2002 March; 167(3):205-210. **(Funded by DoD)**

The objective of this study was to compare the rates of ambulatory medical care among deployed persons who received the anthrax vaccine, with the rates in deployed persons who were not vaccinated. (Rehme, et al., 2002) The study included 4,045 exposed persons and 1,133 unexposed persons, all of whom were Air Force personnel who were deployed to southwest Asia (SWA). Inclusion criteria for both groups required a medical treatment facility visit in southwest Asia, between January 1 and September 10, 1998, as recorded in an Air Force ambulatory care database. In 1998, only personnel who planned to stay in SWA for at least 30 days were administered the anthrax vaccine. Vaccinated personnel had at least one anthrax vaccination administered in SWA, which was recorded in the Defense Eligibility Enrollment Registry System (DEERS). Unvaccinated personnel had no anthrax vaccines recorded in DEERS.

A 6-month follow-up period after the first recorded anthrax vaccination was used to capture any vaccine-related medical problems. All outpatient visits after returning to the U.S. were included, that occurred within the 6-month

follow-up period after the SWA outpatient visit ("post-SWA" visits or diagnoses). The Defense Medical Surveillance System was used to identify outpatient visits and their respective ICD-9 diagnostic codes, during the 6-month follow-up period. 2,077 individuals received one or more post-SWA diagnoses, among the 4,045 vaccinated subjects (51.3%). 607 individuals received one or more post-SWA diagnoses, among the 1,133 unvaccinated subjects (53.6%). The relative risk for one or more post-SWA diagnoses within 6 months after the SWA deployment was 0.96. The mean number of unique diagnoses was calculated for each individual. There were a total of 4,184 unique diagnoses among the 2,077 vaccinated persons, who had a diagnosis, with a mean number of 2.01. There were a total of 1,302 diagnoses among the 607 unvaccinated persons, who had a diagnosis, with a mean number of 2.14.

The relative risk was calculated for each of 17 ICD-9 diagnostic categories. Vaccinated persons did not demonstrate a significantly increased risk of any of the 17 diagnostic categories. The data were examined for specific disorders, which have been anecdotally linked to anthrax vaccine, to identify associations that might have been obscured by the broad diagnostic categories. These included 15 disorders, such as autoimmune disorders, thyroid disorders, arrhythmias, anemia, and hearing loss. The only association that was found was that hearing loss was significantly increased in the unvaccinated group. The overall conclusion was: " Personnel immunized against anthrax do not have a greater risk of being diagnosed with a disorder at an Air Force medical treatment facility than similar unvaccinated personnel. This is true at the aggregate level for each of the 17 specific categories of disease and for specific disease entities such as autoimmune disorders that have been the focus of concern among the public."

4. Wiesen, AR, and Littell, CT. Relationship between prepregnancy anthrax vaccination and pregnancy and birth outcomes among US Army women. *Journal of the American Medical Association* 2002 March 27; 287(12):1556-1560. **(Funded by DoD)**

The anthrax vaccine is administered to large numbers of women in their early reproductive years, and questions related to reproductive effects have been common concerns. The primary objective of this study was to assess whether or not anthrax vaccination would result in a measurable decrease in pregnancy rates. The secondary objectives were to measure effects of the vaccine on fetal loss and adverse birth outcomes. (Wiesen, et al., 2002) Study subjects included women aged 17 to 44 who were on active-duty in the U.S. Army and who were stationed at Ft Stewart, Georgia or Hunter Army Airfield, Georgia, between January 1999 through March 2000. 4,092 women were identified through local databases, of whom, 3,136 (77%) had received at least one anthrax vaccination. The primary outcome measure was pregnancy, and the secondary outcomes were rates of live birth, low birth weight, and congenital anomalies. Pregnancy status was determined by serum or urine human chorionic gonadotropin hormone detection, or if a woman was hospitalized and discharged with an ICD-9 diagnosis of live birth. There were a total of 513 pregnancies among the 4,092 women who were identified as being eligible for inclusion.

Anthrax vaccination status was considered positive if the women received at least one anthrax immunization before the date of her positive pregnancy test result, and there were 385 pregnancies in the exposed group. ICD-9 codes were used to determine the number of live births among the 513 pregnancies, as well as adverse outcomes such as low birth weight and congenital structural abnormalities. However, no information was available on adverse reproductive outcomes among some of the women who left Ft. Stewart. There were 488 pregnancies with a known outcome, and 25 pregnancies lost to follow-up. There were 385 pregnancies following at least 1 anthrax vaccination during 28,815 person-months of follow-up, resulting in an annual pregnancy rate of 159.5 person-years. There were 130 pregnancies in the unvaccinated group during 9,734 person-months of follow-up, resulting in an annual pregnancy rate of 160.0 person-years. The pregnancy rate ratio was 0.94. Thus, there was no difference in pregnancy rates between the two groups. A power analysis indicated that with a sample size this large, there would be a 90% chance to detect a decline in the pregnancy rate of 25% in the vaccinated group.

There were 353 live births among the 488 women with complete follow-up. Among these 488 women, the odds ratio for live birth and anthrax vaccine was 0.9 (not significant). For the birth outcomes analyses, there was complete

ICD-9 coding for 327 births. 11 of the births (3.3%) were low birth weight (less than 2500 grams). The odds ratio for anthrax vaccination and low birth weight was at 1.3 (not significant). There were 15 structural abnormalities of medical and/or cosmetic significance. The odds ratio for anthrax vaccination and congenital anomalies was 0.7 (not significant). This study was limited because it did not have adequate statistical power to rule out a small effect of vaccination on adverse birth outcomes, given their low incidence. The overall conclusion was: "These results do not support the hypothesis of a decrease in pregnancy rates nor an increase in fetal loss rates or adverse fetal outcome among those receiving anthrax vaccination prior to pregnancy."

F. Environmental Toxicology (Includes Oil Well Fire Smoke)

Overview:

Two studies published in 2002 focused on environmental toxicology, specifically, the health effects of the oil well fire smoke. The objective of the first study was to explore the relationships between modeled exposures to contaminants released as a result of the Kuwaiti oil fires and rates of hospitalization due to any cause; hospitalization rates due to a diagnosis in one of 15 major categories; and hospitalization rates due to one of nine diagnoses that could be related to smoke exposure. (Smith, et al., 2002a) The objectives of the second study were to explore the relationships between symptoms of respiratory illness reported by Gulf War veterans and modeled exposures to contaminants released as a result of the Kuwait oil fires, as well as to self-reported smoke exposures. (Lange, et al., 2002)

Environmental Toxicology (Oil Well Fire Smoke)-Individual Studies:

1. Smith, TC, Heller, JM, Hooper, TI, Gackstetter, GD, and Gray, CG. Are Gulf War veterans experiencing illness due to exposure to smoke from Kuwaiti oil well fires? Examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 2002a May 15; 155(10):908-917. **(DoD-1B)**

The objective of this environmental epidemiology study was to explore the relationships between modeled exposures to contaminants released as a result of the Kuwaiti oil fires and rates of hospitalization due to any cause; hospitalization rates due to a diagnosis in one of 15 major ICD-9 categories; and hospitalization rates due to one of nine specific diagnoses that could be related to smoke exposure. (Smith, et al., 2002a) The study population of 405,142 individuals consisted of regular, active duty US military personnel who were deployed to the Gulf War theater of operations for 1 or more days between August 8, 1990 and July 31, 1991, who were still in the theater of operations during the time of the Kuwaiti oil wells fires, and who did not remain in the Gulf region after the war. Hospitalization data was collected for each service member from all DoD treatment facilities for the period October 1, 1988 to July 31, 1999. This provided an opportunity to capture medical conditions before the Gulf War as well as 8 years of follow-up after the end of the Gulf War.

Estimates of individual dose were determined using DoD databases containing information regarding service history, troop location and troop movement, linked together with smoke-plume modeling data. Each study subject was classified into 1 of 7 exposure categories, which included total suspended particulate matter air concentration, as well as duration of exposure. Risk ratios were calculated for hospitalization rates, while adjusting for demographic, exposure and deployment variables (age, sex, race, branch of service, military rank, occupational category, and pre-war hospitalization). Cox's proportional hazards modeling was used to compare hospitalization rates of veterans, by exposure category, while at the same time accounting for attrition from the military during the 8-year follow-up period.

The adjusted risk of any-cause hospitalization was significantly lower for three of the exposed groups, compared to the non-exposed group. There was no evidence of a trend of increasing risk of hospitalization for veterans exposed to oil well fire smoke with increasing dose. For the nine specific diagnoses possibly related to oil well fire smoke, such as asthma or bronchitis, the 7 exposure categories were collapsed into two: exposed and non-exposed. None of the nine specific diagnoses were associated with exposure. The results of this study showed that Gulf War veterans exposed to air contaminants from the burning of Kuwaiti oil wells did not experience higher rates of hospitalization,

compared to non-exposed Gulf War veterans, during the 8 years after the war ended. These findings supported the conclusion of a 1998 RAND Corporation review, that adverse health effects would not be expected in Gulf War veterans due to exposure to the Kuwaiti oil well fires. (Spektor, 1998).

Strengths of this study included the use of meteorological data, sophisticated air dispersion modeling, and knowledge of troop movements and locations that permitted an estimation of individual dose. (Smith, et al., 2002a) Also, this study used objective health outcome data instead of self-reported symptoms. Finally, the large sample sizes allowed for robust estimates of risk that made it likely that even small differences between the exposure groups would be detected. The limitations of this study included: the choice of hospitalizations as a health outcome that could miss less severe health outcomes; the lack of control of potential confounders, such as tobacco use or exposure to fine desert dust; and the outcome data were only available for those who remained in the military.

2. Lange, JL, Schwartz, DA, Doebbeling, BN, Heller, JM, and Thorne, PS. Exposures to the Kuwait oil fires and their association with asthma and bronchitis among Gulf War veterans. *Environmental Health Perspectives* 2002 November; 110(11):1141-1146. **(HHS-1 & DoD-58)**

The objectives of this environmental epidemiology study were to explore the relationships between symptoms of respiratory illness reported by Gulf War veterans and modeled exposures to contaminants released as a result of the Kuwait oil fires, as well as to self-reported smoke exposures. (Lange, et al., 2002) The study population included 1,560 individuals identified through a DoD database who met three criteria: 1) any military service between August 2, 1990 and July 31, 1991; 2) Iowa listed as the home state of record; and 3) military service within the Gulf War theater. Of 8,089 persons identified, 2,241 subjects were selected at random for study participation. Telephone interviews were performed in 1996, and the response rate was 78.3%. Structured telephone interviews were used to collect information on demographics, health information, and exposures to contaminants from the oil fires. Health outcomes were assessed with questions about symptoms of asthma and bronchitis using questions from the American Thoracic Society Questionnaire. Symptoms of two conditions that have no biologically plausible relationship to oil fire exposure, major depression and injury, were used as negative control outcomes.

Self-reported exposure status was assessed with questions on the estimated number of days subjects were exposed to smoke from the oil fires. Individual exposures to the oil well fire smoke were also estimated by integrating military unit locations and smoke concentration locations using a geographic information system. The daily concentration of oil fire smoke at all locations was estimated. Exposure was categorized as the number of days over a low threshold of smoke concentration (50^{th} percentile of all data points) and the number of days over a high threshold (95^{th} percentile of all data points). The prevalence of self-reported symptoms was 8.3% for asthma, 4.7% bronchitis, 24.7% for injury, and 8.6% for major depression. In regard to self-reported exposure to the oil fire smoke, 27.3% subjects reported no exposure, 16.9% reported 1 to 5 days of exposure, 30.0% reported 6 to 30 days, and 25.7% reported greater than 31 days. In the modeled exposure measure, the 25^{th} and 75^{th} percentiles of exposures were 8 and 28 days exceeding the low threshold concentration, respectively, and 0 and 8 days for the high threshold exposures.

There was a moderate correlation between the self-reported exposures and the low and high threshold modeled measures of exposure to oil well fire smoke. Multivariate logistic regression indicated no association between the modeled measures of exposure to oil fire smoke and symptoms of bronchitis or asthma. In contrast, regression analysis did find statistically significant associations between self-reporting of respiratory symptoms and self-reporting of smoke exposures. In addition, the risk of these self-reported health outcomes increased with increased magnitude of self-reported exposure. However, the risk also increased for injury and major depression, which were the two negative control outcomes, with greater levels of self-reported smoke exposures.

A major limitation to this study included recall bias associated with self-reporting of exposures and health outcomes. Recall bias was a likely possibility, because of the associations between self-reported exposures and the prevalence of major depression, a link that has little biological

plausibility. A second limitation was that the modeled exposures were subject to measurement error, given that there were many different sources from which estimated exposures were derived. The authors concluded that the lack of association between modeled exposures and respiratory illness symptoms, together with the association between self-reported exposures and depression, did not support the theory that exposures to the oil well smoke were associated with respiratory symptoms in Gulf War veterans.

G. Depleted Uranium

Overview:

Two studies published in 2002 focused on the health effects of depleted uranium. The objective of the first study was to describe the initial results of a uranium bioassay program for active and retired Canadian Forces personnel. (Ough, et al., 2002) The objective of the second study was to investigate potential mechanisms of carcinogenicity of depleted uranium (DU) fragments implanted in the soft tissue of rats. (Hahn, et al., 2002)

Depleted Uranium-Individual Studies:

1. Ough, EA, Lewis, BJ, Andrews, WS, Bennett, LG, Hancock, RG, and Scott, K. An examination of uranium levels in Canadian forces personnel who served in the Gulf War and Kosovo. *Health Physics* 2002 April; 82(4):527-632. **(Funded by Canadian Department of National Defence)**

The objective of this study was to describe the initial results of a uranium bioassay program for active and retired Canadian Forces personnel. (Ough, et al., 2002) During the Gulf War, Canadian Forces were generally far away from the combat areas. The one exception was the Canadian unit stationed at Camp Doha in Kuwait, where an ammunition fire occurred in July 1991, which led to a release of depleted uranium (DU). Due to concerns of some Canadian veterans, the Canadian Minister of National Defence announced a voluntary uranium testing program in February 2000. Total uranium concentrations in 24-hour urine samples were analyzed separately by two independent commercial labs (two samples from each individual). One lab used the technique of inductively coupled plasma mass spectrometry (ICP-MS), and the other lab used instrumental neutron activation analysis (INAA).

103 veterans submitted urine samples, who were concerned about their potential exposures. 79 served in the Gulf War, 39 served in Kosovo, 15 served in both areas, and 4 were not stationed in either area. The mean urinary uranium concentration was 4.5 nanograms per liter of urine by the ICP-MS method (range of 0.5 to 49.5). The mean was 17 nanograms per liter by the INAA method (range of 1 to 81). There was a much higher limit of detection for the INAA method, so the reported concentrations were all in the vicinity of the detection limit. This is the reason that the mean levels were different for the two methods. The authors commented: "At the very low levels of uranium present in the urine samples analyzed, the ICP-MS data are potentially meaningful, while the INAA data are less sensitive as a result of the higher detection limit for this technique."

The ICP-MS results for the uranium concentrations in these 103 veterans were consistent with studies of levels in the general population, who did not have occupational uranium exposure. These results were also consistent with the levels found in U.S. troops who did not have retained metal fragments, who have been evaluated at the Baltimore VA Medical Center. (Hooper, et al., 1999; McDiarmid, et al., 2000; McDiarmid, et al., 2001a; McDiarmid, et al., 2001b) The overall conclusions were: "The concentrations of total uranium in the urine of Canadian veterans were well within the range determined for non-occupationally exposed individuals. . . The high urinary uranium concentrations observed in known DU-exposed American veterans (e.g., those with retained DU fragments) have yet to be observed in urine samples provided by Canadian veterans." (Ough, et al., 2002)

Analysis of uranium isotopes was carried out in hair samples of 19 of these Canadian veterans, to determine if natural or depleted uranium was present. (Ough, et al., 2002) (The concentrations in the urine were too low to perform isotopic analysis.) In each of the 19 veterans, the isotopic analyses of the hair samples were consistent with the presence of natural uranium. These results agreed with a study of 14 U.S. veterans who had been exposed to friendly fire, and who were evaluated in the Baltimore program. (Hodge, et al., 2001) In the

U.S. study, urinalysis of samples from ten veterans, who had retained metal fragments, demonstrated that a large proportion of the urinary uranium was DU. In contrast, there was no evidence of DU in the urine samples of four other U.S. veterans without retained fragments.

2. Hahn, FF, Guilmette, RA, and Hoover, MD. Implanted depleted uranium fragments cause soft tissue sarcomas in muscles of rats. *Environmental Health Perspectives* 2002 January; 110(1):51-59. **(DoD-7B)**

The objective of this long-term bioassay study was to investigate potential mechanisms of carcinogenicity of depleted uranium (DU) fragments implanted in the soft tissue of rats. (Hahn, et al., 2002) This is a relevant issue because a small number of Gulf War veterans have fragments of DU embedded in their tissues as a result of friendly fire incidents. During the Gulf War, DoD used some munitions that contain DU alloyed with 0.75% titanium. Six groups of 50 male Wistar rats were implanted with either DU, tantalum, Thorotrast, or they underwent sham surgery; and they were observed for their life spans. Tantalum was used as a negative foreign body control (no radioactivity) and was implanted as four squares in the thigh muscle of each rat. Thorotrast, a 25% colloidal thorium dioxide radiographic contrast media, was used a positive control for radioactive materials and was injected twice into the thigh muscle of each rat. Finally, DU was implanted into the thigh muscle of each rat either as 4 pellets or 4 fragments.

The rats were weighed every month and radiographs of implant sites were taken at time of implantation and at death. At death, complete autopsies were performed. There were histological examinations of the implant site, the draining lymph nodes, implant site neoplasms, potential neoplasms, kidneys, bladder, prostate and other organs. Differences in the tumor incidences among the various exposure groups were compared using the Fischer's exact test. There were no differences in the survival rates of the rats across groups of exposure. The incidence of tumors was significantly increased in the rats with the largest DU implants, compared to the sham or tantalum controls. In addition, there was a correlation between fragment size of DU and increased tumor incidence. The rats injected with Thorotrast had a significantly increased incidence of tumors, compared to the DU-treated rats. There appeared to be a dose-response relationship with the alpha radioactivity and incidence of tumors. For the DU implants, the larger the surface area, the higher the alpha particle radioactivity. The Thorotrast injections had the highest alpha particle radioactivity, regardless of surface area. All the tumors detected were located adjacent to the implants. There were no tumors in any other tissues. The lack of an increased incidence of tumors, other than at the site of the implants, indicates that uranium is not an effective systemic carcinogen.

A connective tissue capsule formed around the metal implants, but not around the Thorotrast. The radiographs from the tantalum-treated rats revealed sharp, smooth fragments with well-defined edges at all times. This was in contrast to the DU radiographs, which changed markedly over time. The appearance of the DU fragments changed from a smooth, sharp surface with well-defined edges to one with a corroded surface and rounded, jagged edges with no corners. Histological analysis of tissues revealed: 1) extensive tissue destruction with fibrosis, inflammation, degeneration and mineralization of the capsule surrounding the DU fragments; 2) inflammation, but no degeneration or mineralization, of the capsules surrounding the tantalum fragments; and 3) accumulation of macrophages between muscle fibers, but no fibrosis or inflammation, surrounding the Thorotrast injection sites.

These results demonstrate an increased incidence of soft tissue tumors associated with DU implants. However, the mechanism for DU-induced carcinogenesis remains unclear. Foreign body carcinogenesis was not likely to be totally responsible for the development of an increased number of tumors occurring in the DU treated rats, compared to the non-radioactive tantalum group. There is the possibility that the increased tumor incidence was due to a radiation-induced carcinogenesis, because of the dose-response seen with increasing alpha radioactivity. Also, the damage and repair mechanism could be responsible for the increased incidence of tumors in the tissue surrounding the DU implants, since compounds that produce tissue destruction with subsequent collagen formation invariably induce soft tissue sarcomas. The researchers cautioned that these results could not be directly extrapolated to humans, because rats are more sensitive to both foreign body carcinogenesis and

radiation carcinogenesis than humans are. In 2001, the authors were funded to continue their investigation of the possible carcinogenicity of DU in rats (DoD-127).

H. Chemical Weapons

Overview:

Six studies published in 2002 focused on the health effects of sarin in laboratory animals (rats and guinea pigs). (Mioduszewski, et al., 2002; Hulet, et al., 2002; Abdel-Rahman, et al., 2002; Henderson, et al., 2002; Conn, et al., 2002; Kalra, et al., 2002) The results of these laboratory experiments cannot be directly extrapolated to predict the possible long-term effects of low-level exposures of sarin in humans, for two reasons. First, some of these studies utilized very high doses of sarin, sometimes by the route of injection, which caused seizures and/or death within minutes. Second, none of these studies followed the effects of sarin exposure in the animals for longer than 30 days, so the possible longer-term health effects, if any, were unknown.

The objective of the first study was to develop a model for predicting dose-response effects of lethal vapor concentrations of sarin, as a function of duration, for a range of five minutes to six hours of exposure. (Mioduszewski, et al., 2002)

The objective of the second study was to determine a dose of injected sarin that could be given over a two-week period of daily exposures without causing severe, easily identifiable cholinergic symptoms such as tremors, seizures, or death. (Hulet, et al. 2002)

The objective of the third study was to investigate early neuropathological changes in the rat brain following a single exposure to different doses of injected sarin. (Abdel-Rahman, et al., 2002)

The fourth, fifth, and sixth studies were related to a single set of experiments. (Henderson, et al, 2002; Conn, et al., 2002; Kalra, et al., 2002) The objective of the fourth study was to determine whether single or repeated inhalation exposures to sub-clinical doses of sarin could result in subtle, adverse health effects in rats, that persisted as long as 30 days after the exposures ended. (Henderson, et al., 2002) The objective of the fifth study was to determine if single or repeated inhalation exposures to sub-clinical doses of sarin could impair regulation of body temperature and locomotor activity in rats, particularly under conditions of heat stress. (Conn, et al., 2002) The objective of the sixth study was to determine the effects of inhalation exposures to sub-clinical doses of sarin on immune function in the rat and to determine the possible mechanisms for such effects. (Kalra, et al., 2002)

Chemical Weapons-Individual Studies:

1. Mioduszewski, R, Manthei, J, Way, R, Burnett, D, Gaviola, B, Muse, W, Thomson, S, Sommerville, D, and Crosier, R. Interaction of exposure concentration and duration in determining acute toxic effects of sarin vapor in rats. *Toxicological Sciences* 2002 April; 66(2):176-184. **(Funded by DoD)**

The objective of this study was to develop a model for predicting dose-response effects of sarin vapor concentrations as a function of duration, for a range of five minutes to six hours of exposure. (Mioduszewski, et al., 2002) Specifically, it was hypothesized that the probability of a toxic effect (lethality) could be adequately modeled by Haber's rule, which states that the probability of a toxic effect from exposure to a chemical is linearly related to the product of concentration and exposure duration (C times T). Alternatively, a second hypothesis was tested: that the probability of a toxic effect can be more adequately modeled by a variation of Haber's Law (toxic load model). This model includes an additional term, which is used to describe the modification of dose by certain characteristics of a particular gas/aerosol or exposure scenario. If the latter model better quantified the health risks of sarin exposure, the implication would be that the traditional method of quantifying dosage (C times T) could lead to either overestimates or underestimates of risk due to sarin exposure.

Groups of male and female Sprague-Dawley rats were exposed to varying concentrations of sarin for a single duration (5 to 360 minutes) in a whole-body exposure chamber. The concentrations of sarin ranged from 2.3 to 54.4 mg per cubic meter of air. At each concentration, the onset of clinical signs (miosis, salivation, tremors, convulsion, lethality) was recorded, and changes in red blood cell acetylcholinesterase (AChE) and plasma

butyrylcholinesterase (BuChE) activity were measured. The LC_{50} was determined (the concentration at which 50% of the animals died), and the corresponding dose-response slope for each exposure duration was calculated by the Bliss Probit method. The experimental results indicated that Haber's rule was not the appropriate model to predict the dose-response effects of sarin. Instead, as the exposure times lengthened, the concentrations of sarin required to cause lethality increased disproportionately. The researchers concluded that these findings demonstrated the need to expand beyond dependence on Haber's rule.

Blood AChE and plasma BuChE activities were inhibited as a result of exposure to various combinations of sarin vapor concentrations and exposure duration. Except for AChE in female rats, there were statistically significant correlations between cholinesterase activities and (C times T). However, the fits were poor for (C times T) versus male AChE, female AChE, male BuChE and female BuChE, and could not be used for predictive purposes. The authors interpreted this to mean that RBC and plasma cholinesterase activities might be sensitive measures of exposure to sarin; however, they might not necessarily be good indicators of toxicity. This was indicated by the poor correlation between the degree of cholinesterase inhibition and the severity of clinical signs in the lethal range.

Mean pupil size was measured in surviving rats after 5, 60, 240 and 360-minute exposures. All combinations of sarin vapor concentration and exposure duration resulted in complete miosis (pupil constriction) at one hour post-exposure. This was followed by a transient pupil dilation at 24 and 48-hours post-exposure, which lasted for several days. By day 7 post-exposure, pupil diameters decreased in size, but were still larger than pre-exposure size. The researchers proposed that sarin exposure upset the balance between the sympathetic and parasympathetic control over pupil size.

2. Hulet, SW, McDonough, JH, and Shih, TM. The dose-response effects of repeated subacute sarin exposure on guinea pigs. *Pharmacology, Biochemistry, and Behavior* 2002 July; 72(4):835-845. **(Funded by National Research Council)**

The objective of this study was to determine a dose of injected sarin that could be given over a two-week period of daily exposures without causing severe, easily identifiable cholinergic symptoms such as tremors, seizures, or death. (Hulet, et al. 2002) The authors' longer-term goal was to develop an animal model to determine if subtle neurobehavioral and/or physical deficits were associated with repetitive exposures to sarin. While the immediate effects associated with high exposures to sarin are well known, there is a paucity of information on potential chronic effects associated with exposures well below those eliciting an immediate response. The authors chose the guinea pig because it is a more valid animal model than the rat or the mouse. Rats and mice have high blood concentrations of the enzyme, carboxyesterase, which specifically binds to nerve agents such as sarin, requiring much higher doses to elicit the same response in guinea pigs or nonhuman primates.

Guinea pigs were injected subcutaneously with 0.5 X LD_{50} sarin, 0.4 X LD_{50} sarin, or saline, for 5 days per week for a period of 2 weeks. (The subcutaneous LD_{50} for sarin is 42 micrograms per kilogram body weight.) On each of these days, red blood cell AChE activity, EEG, and body weight were monitored. In addition, the animals were evaluated with a functional observational battery to determine such neurobehavioral functions as righting response, movement, sensory deficits, and physical deficits. At the 0.5 X LD_{50} sarin dose level, 2 of the 13 animals died before the end of the 10-day experimental period, however, none of the animals showed signs of seizures. After the second dose, the RBC AChE activity level dropped to 10% of baseline (but never below 9%), and noticeable symptoms of sarin toxicity became apparent (chewing, hyperactivity and muscle tremor). The guinea pigs exposed to 0.5 X LD_{50} sarin demonstrated a significant decrease in weight gain, impairment of drop reflexes, and alteration in angle of gait, which is considered a "cardinal sign" of anti-cholinesterase toxicity. However, there were no significant differences in the functional battery score between this group and the other groups, with the exception of a few aspects of the testing such as approach and touch response. Histological examination of brain and heart tissue from the 11 animals that survived treatment showed no pathological damage induced by exposure to sarin.

At the 0.4 X LD_{50} sarin dose level, none of the animals died during the 10-day experiment. The red blood cell AChE activity dropped to 35% of baseline after the second dose and then to 11% (never below 10%) after the 10^{th} day of sarin injections. There were no apparent signs of acute toxicity from exposure to sarin in the animals. In addition, there were no significant differences from the saline group in weight gain, gait angle, or in any of the functional battery test scores. The lack of cholinergic symptoms at the dosage of 0.4 X $LD_{50,}$ despite the eventual drop in the AChE activity level to 11% of baseline, parallels the findings of other researchers, who demonstrated no correlation between the onset of symptoms and AChE activity levels, when the nerve agent was administered at lower doses over several days.

The researchers concluded that the 0.4 X LD_{50} sarin dose given to guinea pigs was an acceptable model to study the long-term effects of repeated exposures to sarin. In addition, they hypothesized that the reason that the RBC AChE activity level held steady around 10% of baseline at both dose levels was due in part to *de novo* synthesis of RBC AChE, as well as an increasing rate of spontaneous reactivation of RBC AChE associated with repeated exposures to nerve agents.

3. Abdel-Rahman, A, Shetty, AK, and Abou-Donia, MB. Acute exposure to sarin increases blood brain barrier permeability and induces neuropathological changes in the rat brain: dose response relationships. *Neuroscience* 2002; 113(3):721-741. **(DoD-72)**

The objective of this study was to investigate early neuropathological changes in the rat brain following a single exposure to different doses of injected sarin. (Abdel-Rahman, et al., 2002) Adult, male Sprague-Dawley rats were injected intramuscularly with a single dose of sarin of 1 X $LD_{50,}$ 0.5 X $LD_{50,}$ 0.1 X $LD_{50,}$ 0.01 X $LD_{50,}$ or saline. Twenty-four hours later, the animals were sacrificed, and the following analyses were performed: plasma butyrylcholinesterase (BChE) activity; brain acetylcholinesterase (AChE) activity; blood-brain barrier permeability changes in the brain, using two methods; and histopathological changes in the brain, using three methods.

All the animals injected with sarin at the dose of 1 X LD_{50} developed excessive salivation, severe tremors, and convulsions within 10 minutes, and exhibited prolonged convulsions lasting approximately three hours. Twenty percent of the animals died within three hours. There was significant inhibition of plasma BChE activity (decreased to 30-41% of control activity). Brain AChE was decreased to 31-44% of control activity in the cerebrum, brainstem, midbrain, and the cerebellum. There was increased blood-brain barrier permeability (BBB) in the cerebrum, brainstem, midbrain, and cerebellum. Histopathology revealed a diffuse neuronal cell death in the cerebral cortex and hippocampus, and degeneration of Purkinje neurons in the cerebellum.

Only 20% of the animals injected with sarin at the dose of 0.5 X LD_{50} developed mild clinical signs within one hour. At the dose of 0.5 X LD_{50}, there were only a few brain alterations, including decreased plasma BChE activity, an increased BBB permeability in the midbrain and brainstem, and degeneration of Purkinje neurons in the cerebellum. The animals injected with the two lower doses of sarin did not develop cholinergic signs. Also, the animals injected with the two lower doses did not demonstrate any of the brain alterations. The authors concluded that animals treated at the three lower doses of sarin "exhibited neither the seizures nor the above-mentioned combination of neuropathological changes." They also concluded: "early brain damage after acute exposure to sarin is clearly dose-dependent and brain pathology is clearly apparent with only 1 X LD_{50} exposure." These results were consistent with previous studies that have shown that exposure to low or very low concentrations of sarin did not cause a variety of early adverse effects.

4. Henderson, RF, Barr, EB, Blackwell, WB, Clark, CR, Conn, CA, Kalra, R, March, TH, Sopori, ML, Tesfaigzi, Y, Menache, MG, and Mash, DC. Response of rats to low levels of sarin. *Toxicology and Applied Pharmacology* 2002 October 15; 184(2):67-76. **(DoD-53**)

The objective of this study was to determine whether single or repeated inhalation exposures to sub-clinical doses of sarin could result in subtle, adverse health effects in rats, that persisted as long as 30 days after the exposures ended. (Henderson, et al., 2002) Because some Gulf War veterans may have been exposed to extremely low levels of sarin that did not cause

immediate symptoms, there has been increased interest in investigating the potential long-term health effects of sub-clinical exposures to sarin. In addition, many Gulf War veterans were exposed to considerable heat stress; therefore, this study evaluated the combined effects of sarin exposure and heat stress. This is the first of three studies related to a single set of experiments. (Conn, et al., 2002; Kalra, et al., 2002)

Male Fischer 344 rats were exposed by inhalation to vehicle only, 0.2mg/m^3 sarin, or 0.4 mg/m^3 sarin, for 1 hour per day for either 1, 5 or 10 days. (Henderson, et al., 2002) The higher concentration was selected because it was approximately 10% of the LC_{50} through inhalation in rats. Half of the animals were housed at normal ambient temperature (25^o C), while the other half were housed at an elevated temperature (32^o C) to induce moderate heat stress. This raised their core body temperatures from about 37.0 degrees to 38.0 degrees Celsius. Pulmonary function was assessed during sarin exposure; body weight was assessed prior to the experiments, and again at time of sacrifice. The animals were sacrificed at either 1 or 30 days after the last sarin exposure. Brain histopathology, and brain and red blood cell cholinesterase (AChE) activity were assessed.

Body weight, pulmonary function, body temperature, and activity level during the 30-day follow-up period were not affected by 1, 5 or 10 days of sarin exposure. Heat stress, regardless of sarin exposure, reduced weight gain during the 30-day follow-up period. Microscopic analysis of brain tissue indicated no lesions in any of the regions examined, for any of the test conditions. In addition, there was no evidence of sarin-mediated apoptosis (evidence of cell death) in the brains of rats, with or without heat stress. AChE activity levels were decreased to 93% and 89% of baseline at the low and high dose sarin levels, respectively, after a 1-day exposure. AChE levels were 70% and 40% of baseline after 5 and 10 days of exposure, respectively. AChE levels demonstrated a linear cumulative effect of sarin on AChE activity up to 5 days of exposure, at which point the processes involved in maintaining AChE activity appeared to reach equilibrium.

Total brain AChE activity levels were not significantly decreased at either the low or high sarin dose at the 1, 5 or 10 day repeated exposures. However, histochemical staining did reveal regional reductions in AChE activity in the cerebral cortex, striatum, and olfactory bulb, due to sarin alone. In the rats exposed to both sarin and heat stress, there were reductions in AChE activity in the hippocampus. No reductions were seen in the brainstem or cerebellum. In summary, low-level sarin exposure did not lead to clinical symptoms (including tremors, excessive salivation or urination, or diarrhea), decrease in body weight or pulmonary function, or changes in activity during the 30-day follow-up period. The authors concluded that the sarin concentrations, to which the animals were exposed, provided a reliable animal model in which to assess subtle adverse effects due to low-level exposure.

5. Conn, CA, Dokladny, K, Menache, MG, Barr, EB, Kozak, W, Kozak, A, Wachulec, M, Rudolph, K, Kluger, MJ, and Henderson, RF. Effects of sarin on temperature and activity of rats as a model for Gulf War syndrome neuroregulatory functions. *Toxicology and Applied Pharmacology* 2002 October 15; 184(2):77-81. **(DoD-53)**

The objective of this study was to determine if single or repeated inhalation exposures to sub-clinical doses of sarin could impair regulation of body temperature and locomotor activity in rats, particularly under conditions of heat stress. (Conn, et al., 2002) Male Fischer 344 rats were randomly assigned to vehicle, 0.2 mg/m^3 sarin, or 0.4 mg/m^3 sarin. The rats were exposed to sarin through inhalation for 1 hour, for either 1, 5 or 10 days. Half of the rats from each exposure group were housed at 25 ^{o} C and half were housed at 32 ^{o} C. A preliminary experiment determined that exposure to 32 ^{o} C was sufficient to induce a mild chronic heat stress in the animals. This is the second of three studies related to a single set of experiments. (Henderson, et al., 2002; Kalra, et al., 2002)

Body temperature and activity were monitored via radiotelemetry for 2 days prior to sarin exposures through 28 days after exposure. (Conn, et al., 2002) Data were grouped into 4 time periods: 1) morning, 2) daytime or light period, 3) evening, and 4) night or dark period. The statistical analysis consisted of six repeated measures analysis to assess short-term and long-term effects, performed for median activity and median temperature. For each repeated measures analysis, the independent variables were number

of days of sarin exposure, sarin concentration, caging room temperature, and all possible interactions.

None of the rats exposed to sarin exhibited any observable signs of cholinergic toxicity, such as tremors; however, they did show reduced red blood cell acetylcholinesterase (AChE) activity. Animals without sarin exposure that were housed at 32 ^{o} C had significantly higher body temperatures during the dark periods than animals housed at 25 ^{o} C (rats are more active at night). There was no evidence of adverse effects due to sarin exposure, or interaction of sarin with heat stress, on body temperature or on locomotor activity in rats during the dark periods or the light periods.

The authors concluded that subclinical exposures to sarin have no effect on body temperature in a biologically meaningful manner after 1, 5, or 10 exposures, at either ambient temperatures (25 ^{o} C) or during chronic heat stress (32 ^{o} C). These data are consistent with the hypothesis that the sub-clinical levels of sarin, which were sufficient to reduce red blood cell cholinesterase activity, were below the threshold necessary to significantly alter body temperature regulation, even under periods of chronic heat stress. The authors concluded: "To the extent that thermoregulation is an indicator of neuroimmune function and locomotor activity can indicate fatigue, these data do not support the theory that subclinical exposure to nerve gas under conditions of heat stress may have resulted in symptoms" experienced by some Gulf War veterans.

6. Kalra, R, Singh, SP, Razani-Boroujerdi, S, Langley, RJ, Blackwell, WB, Henderson, RF, and Sopori, ML. Subclinical doses of the nerve gas sarin impair T cell responses through the autonomic nervous system. *Toxicology and Applied Pharmacology* 2002 October 15; 184(2): 82-87. **(DoD-53)**

The objective of this study was to determine the effects of inhalation exposures to sub-clinical doses of sarin on immune function in the rat and to determine the possible mechanisms for such effects. (Kalra, et al., 2002) This is the third of three studies related to a single set of experiments. (Henderson, et al., 2002; Conn, et al., 2002)

Male Fischer 344 rats were exposed to either 0.2mg/m^3 sarin, 0.4mg/m^3 sarin, vehicle only, sarin and chlorisondamine (CHL), or CHL only, through inhalation for 1 hour per day for either 1, 5 or 10 days. (Kalra, et al., 2002) CHL is a ganglionic blocker that inhibits the behavioral response to neuroactive substances for several months. To assess the effect of sub-clinical exposure to sarin on the formation of antibodies, the control and lower dose rats were injected with sheep red blood cells and euthanized 4 days later. To assess the effect of sub-clinical exposure to sarin on the proliferation of T cells to mitogens and antigens, spleen cells from each of the treatment groups were incubated with various concentrations of concanavalin A (Con A), as well anti-$\alpha\beta$-T cell receptor (TCR) monoclonal antibody. To assess the effect of sub-clinical exposure to sarin on the T-cell activation cascade, the intracellular ionized calcium level was measured. Finally, to assess whether sarin inhalation suppressed the immune system by elevating glucocorticoids, serum corticosterone levels (CORT) were measured.

Results indicated that the lower dose exposure to sarin caused a significant reduction in antibody formation, compared to the control group. In animals exposed to sarin for 5 days, there was a dose-dependent reduction in T-cell proliferation, as exhibited by the reduction in T-cells produced by the spleen after exposure to mitogens and antigens. In animals exposed to sarin, there was no increase in the level of intracellular ionized calcium during the T-cell activation cascade, compared to the control group. In the animals exposed to lower-dose sarin for 5 days, the CORT levels were significantly lower than those in the control group. This was unexpected since it was thought that the immunosuppressive effects from sarin exposure were the result of higher CORT levels. Finally, the inhibitory effects of exposure to low dose sarin on Con A and anti-TCR induced T-cell proliferation were attenuated by treatment with the ganglionic blocker, CHL. This suggested that the autonomic nervous system could play a role in sarin-induced immunosuppression.

The authors concluded that inhalation of sub-clinical doses of sarin (0.2mg/m^3 for at least 5 days) suppressed the T-dependent antibody and T cell proliferative responses in rats. They also concluded, that due to the low levels of CORT seen in the sarin-exposed animals as compared to the controls, sarin-induced immunosuppression

does not result from overproduction of CORT; therefore, it is not mediated by activation of the hypothalamic-pituitary-adrenal axis. Based on the results of the CORT assays and the lack of reduction in the T-cell proliferation in the sarin-exposed animals pretreated with CHL, they concluded that sarin-induced immunosuppression is probably mediated through the autonomic nervous system. The authors did not explain the possible clinical significance of these immune changes. The relevance of these experimental results in rats is difficult to interpret, considering that studies of immune system assays in Gulf War veterans have demonstrated normal functions. (Grady, et al., 1998; Klaustermeyer, et al., 1998; Zhang, et al., 1999; Everson, et al., 2002)

I. Pyridostigmine Bromide

Cook, MR, Graham, C, Sastre, A, and Gerkovich, MM. Physiological and performance effects of pyridostigmine bromide in healthy volunteers: a dose-response study. *Psychopharmacology* 2002 July; 162(2):186-192. **(DoD-64)**

One study published in 2002 focused on the health effects of pyridostigmine bromide (PB) in humans. The objective of this study was to evaluate the physiological and behavioral effects of PB in healthy, young volunteers, in particular, at the dosage of 30 mg three times a day, which DoD recommends for prophylaxis for nerve agent exposure. (Cook, et al., 2002) Specifically, the relationship was evaluated between the degree of acetylcholinesterase (AChE) inhibition induced by PB and alterations in cardiovascular function, complex cognitive task performance, and measures of physiological and sensorimotor function. A double-blind, cross-over, placebo-controlled design was used, in which each volunteer served as his or her own control. 36 healthy young men and 31 healthy young women participated, who were aged 18-35. 34 subjects received 30 mg PB every 8 hours for 5 days, and 33 subjects received 60 mg on the same schedule. The order of the PB week and the placebo week was counterbalanced. This is the second publication based on one set of experiments. (Cook, et al., 2001)

On day 5, blood acetylcholinesterase (AChE) activity was reduced to 67% of baseline in the 30 mg group, and to 53% in the 60 mg group. (Cook, et al., 2002) At three days after the last PB dose, blood AChE levels had returned to baseline levels. Overall, side effects occurred infrequently and they were generally mild, even at the 60 mg dose. Even at the same dose level, however, some subjects reported more side effects than others, when taking both placebo and PB. A multiple regression analysis was performed to determine the factors that were related to reported side effects during the PB week, using the following factors as possible predictors: reported side effects during the placebo week, percent activity of blood acetylcholinesterase (AChE), percent activity of plasma butyrylcholinesterase (BChE), dose of PB in milligrams per kilogram of body weight, and plasma concentration of PB. The only factor that significantly predicted side effects during the PB week was side effects during the placebo week.

Subjects performed a standardized neurobehavioral test battery of 13 performance tests, including reaction time, short-term memory, math processing, pattern memory, and switched attention. PB was associated with an overall improvement in reaction time on tests of memory and attention. PB did not lead to any other performance changes on the neurobehavioral tests. The authors concluded: "PB at either dose level had no detrimental effects of the ability to perform complex cognitive tasks, a finding in general agreement with previous research." The physiological tests consisted of seven measurements of the cardiovascular system, EEG activity, visual function, hand steadiness, and grip strength. There were no consistent effects of PB on the measures of EEG activity, visual function, hand steadiness, and grip strength. PB slowed the heart rate and it caused a significant decrease in the high-frequency component of heart rate variability, which was the most striking physiological response in the study. The degree of AChE inhibition compared to baseline was directly related to the dose of PB. The degree of AChE inhibition was also directly related to the decrease in the high-frequency component of heart rate variability.

These results were in good agreement with other controlled studies of the side effects of PB; however, they differed from some studies conducted under battlefield conditions. The authors commented: "The observation that side effects are experienced more frequently and are more severe in field studies compared to

laboratory studies implies that symptoms may be exacerbated by the unavoidable physiological and psychological stresses of war." The overall conclusions were: "Even at twice the typical military dose, PB does not appear to have detrimental physiological or cognitive effects when healthy, young volunteers are studied in a non-stressful laboratory environment. Under the present test conditions, we also did not observe any alterations that would implicate PB in Gulf War veterans' illnesses."

J. Interactions of Exposures (Pyridostigmine Bromide in Combination with Stress or Other Chemicals)

Overview:

Seven laboratory studies published in 2002 focused on the effects of pyridostigmine bromide (PB), in combination with stress or other chemicals.

Two studies focused on the effects of PB in combination with stress (forced swimming, forced running, or restraint). (Tian, et al., 2002; Song, et al., 2002) The objectives of the first study were to evaluate the effects of physical stress (forced swimming or forced running) on the short-term toxicity of pyridostigmine bromide (PB); and to determine if PB could cross the blood-brain barrier (BBB) and disrupt central nervous system function under conditions of physical stress. (Tian, et al. 2002)

The objective of the second study was to determine if stress modifies pyridostigmine (PB) neurotoxicity, by evaluating the effects of single and repeated restraint stress on PB-mediated cholinergic toxicity and inhibition of cholinergic activity in blood and brain tissues. (Song, et al., 2002)

Five studies focused on the effects of PB in combination with other chemicals (DEET, permethrin, sarin, or organophosphate pesticides). (Abou-Donia, et al., 2002; Chaney, et al., 2002; Wilson, et al., 2002; Usmani, et al., 2002; Vogel, et al., 2002)

The objective of the first study was to evaluate how exposure to sarin and pyridostigmine bromide (PB), alone or in combination, could affect sensorimotor performance as well as the central cholinergic system in rats. (Abou-Donia, et al., 2002)

The objective of the second study was to explore the immediate lethal interaction between pyridostigmine bromide (PB) and DEET when administered in combination at high doses, to determine the possible biological mechanism for this interaction. (Chaney, et al., 2002)

The objective of the third study was to determine if combined exposure to PB, sarin, and/or diisopropyl phosphofluoridate (DFP) is more neurotoxic to chickens than if given separately, by examining inhibition of two enzymes. (Wilson, et al., 2002)

The objectives of the fourth study were to quantify the metabolism of DEET by human microsomes; to identify the human P450 isoenzymes responsible for the metabolism of DEET; and to investigate the potential for inhibition or activation of DEET biotransformation, in combination with chlorpyrifos, permethrin or pyridostigmine bromide. (Usmani, et al., 2002)

The objective of the fifth study was to use accelerator mass spectrometry (AMS) to quantify radio-labeled diisopropylfluorophosphate (DFP) as a tracer at attomolar levels (10^{-18} molar), after co-exposures to two different classes of pesticides, alone or in combination. (Vogel, et al., 2002)

Stress alone has been shown to induce significant changes in blood-brain barrier (BBB) permeability in young rats and mice, but little or no changes in adults. Reports in rodents have shown effects of exogenous stressors like forced swim, restraint, or heat stress on the entry of radioactive tracers, dyes, or viruses into the central nervous system (CNS). These studies have been conducted primarily in young, immature animals. (Sharma, et al., 1991; Sinton, et al., 2000; Song, et al., 2002) The overall conclusion in a recent study was: "There is no evidence that exogenous stress increases BBB permeability in mature rodents." (Sinton, et al., 2000)

The one exception, regarding adult rodents, was a study by Friedman that suggested that pyridostigmine bromide (PB) could enter the brain of adult mice subjected to forced swimming stress. (Friedman, et al., 1996) Friedman demonstrated that the dose of PB required to produce 50% inhibition of brain

acetylcholinesterase (AChE) activity in stressed FVB/n mice was only 1% of the dose of PB required to produce 50% inhibition in non-stressed mice. However, there is some experimental evidence that the FVB/n mouse strain may have an unusually permeable BBB. (Telang, et al., 1999) Furthermore, the intensity of the reported effect in Friedman's study (more than 50% inhibition) could not be easily explained by the limited and localized changes in BBB permeability that had previously been reported to be induced by stress. (Sharma, et al., 1991, Telang, et al., 1999)

Several recent studies have evaluated whether stress can increase BBB permeability, and can therefore enhance penetration of PB into the brain. If PB does not cross the BBB, it is unlikely to cause long-term changes in brain function. These have included several species and strains of animals: guinea pigs (Lallement, et al., 1998); 3 different strains of mice (Telang, et al., 1999; Chaney, et al., 1999; Grauer, et al., 2000); and 3 strains of rats (Sinton, et al., 2000; Chaney, et al., 2000; Kant, et al., 2001; Tian, et al., 2002; Song, et al., 2002; Abou-Donia, et al., 2002). These studies have included several types of stressors: forced swimming stress (Telang, et al., 1999; Grauer, et al., 2000; Sinton, et al., 2000; Tian, et al., 2002); forced running stress (Tian, et al., 2002); heat stress (Lallement, et al., 1998; Sinton, et al., 2000); severe cold stress (Grauer, et al., 2000); restraint stress (Sinton, et al., 2000; Kant, et al., 2001; Song, et al., 2002); foot shock stress (Kant, et al., 2001); and chemical stress (coadministration of high doses of DEET or sarin) (Chaney, et al., 1999; Chaney, et al., 2000; Abou-Donia, et al., 2002).

All of these recent studies have reached the conclusion that stress does not increase BBB permeability to PB, and that PB does not penetrate the brain, even at sub-lethal doses. For example, the conclusion of a 2001 study was "The preponderance of the evidence by a number of laboratories now points to some unknown experimental artifact associated with the original positive report [Friedman, et al., 1996]." (Kant, et al., 2001) Another study by Sinton, Haley, and colleagues concluded "to the extent that cross-species comparisons are valid" between humans and rodents, "the effects of stress on BBB permeability to PB are unlikely to explain the chronic CNS symptoms reported by some Gulf War veterans." (Sinton, et al., 2000) The conclusion in this 2000 study was particularly noteworthy because one of the authors, Robert Haley, previously reported an association between a history of PB use and long-term CNS symptoms, based on a questionnaire administered to a small group of Gulf War veterans. (Haley, et al., 1997c)

In the most recent study, the authors reviewed these publications. (Song, et al., 2002) They concluded: "The results from our study as well as a number of other recent reports indicate that stress does not generally increase the anticholinesterase actions of PB in the central nervous system. (Lallement, et al., 1998; Telang, et al., 1999; Grauer, et al., 2000; Sinton, et al., 2000; Kant, et al., 2001; Tian, et al., 2002) While stress may in some way alter the toxicity of PB under some conditions, the overall data available to date do not support a link between stress and enhanced cholinesterase inhibition/cholinergic toxicity following PB exposure in the etiology of Gulf War illnesses." (Song, et al., 2002)

Interactions of Pyridostigmine Bromide in Combination with Stress or Other Chemicals-Individual Studies:

1. Tian, H, Song, X, Bressler, J, Pruett, S, and Pope, CN. Neither forced running nor forced swimming affect acute pyridostigmine toxicity or brain-regional cholinesterase inhibition in rats. *Toxicology* 2002 July 1; 176(1-2):39-50. **(DoD-107)**

The objective of this study was to evaluate the effects of physical stress on the short-term toxicity of pyridostigmine bromide (PB); and to determine if PB could cross the blood-brain barrier (BBB) and disrupt central nervous system function under conditions of physical stress. (Tian, et al. 2002) The acute maximum tolerated dose of PB (30 mg/kg) was given orally to 4 groups of male Sprague-Dawley rats. Physical stressors included 3 different conditions of forced running and 2 different conditions of forced swimming (varying times of activity and sequence of PB administration). The four treatment groups included: 1) saline, no stress; 2) PB, no stress; 3) saline, stress; and 4) PB, stress. The animals were sacrificed either at 1, 2 or 4 hours following PB treatment.

Functional signs of cholinergic toxicity from acute exposure to PB were measured just prior to sacrifice, which demonstrated autonomic

dysfunction. The presence of clinical signs, including salivation, urination, diarrhea, and tremors, confirmed that this dose of PB induced toxicity. However, there was no difference in these signs between the PB + stress group and the PB + no stress group. The effectiveness of forced running and forced swimming in inducing stress was objectively assessed by measuring plasma corticosterone levels at 0, 1 and 3 hours following the termination of the stressor. The plasma corticosterone results provided objective evidence that the exercise regimens (forced swimming and forced running) caused a stressful experience in the animals, with an increase of up to 30 times control levels. Blood cholinesterase levels (AChE) were significantly inhibited (decrease of 77 to 91%) in the two PB-treated groups as compared to the control group, 1 to 4 hours post PB exposure. However, neither forced running or forced swimming plus PB had any influence on blood AChE, beyond PB alone.

The effect of stress on the permeability of the blood-brain barrier (BBB) was assessed by the extent of horseradish peroxidase (HRP) accumulation in brain tissues following intracardiac administration at the termination of the exercise regimens. In addition, cholinesterase (AChE) activity was assessed in the cerebellum, cortex and hippocampus, as an additional measure of the effect of stress on BBB permeability. PB alone led to a slight inhibition (decrease of 21 to 28%) of AChE activity in the cerebellum, cortex and hippocampus. However, neither swimming stress nor running stress affected regional brain AChE activities. Finally, the results from the HRP assays indicated no increase in accumulation of HRP in the cortex, cerebellum or hippocampus following the exercise regimens combined with PB. This provided further evidence that physical stressors do not increase BBB permeability of PB in rats.

The authors concluded that, although the very high doses of PB "caused cholinergic toxicity, marked inhibition of blood AChE, and slight inhibition of brain-regional AChE, stress had very little influence on either the degree of toxicity or blood or brain-regional AChE inhibition." They noted that their results confirmed the results of other researchers, that physical stressors such as extreme heat or forced swimming did not increase the blood-brain permeability of PB in various animals such as guinea pigs, rats, and mice. (Lallement, et al., 1998; Telang, et al., 1999; Grauer, et al., 2000; Sinton, et al., 2000) Their findings contradicted those of Friedman, et al. (1996), whose work indicated that forced swimming increased the entry of PB into the brain of one strain of mice. The authors concluded that the weight of the published "data suggest that stress does not generally influence the central actions of PB."

2. Song, X, Tian, H, Bressler, J, Pruett, S, and Pope, C. Acute and repeated restraint stress have little effect on pyridostigmine toxicity or brain regional cholinesterase inhibition in rats. *Toxicological Sciences* 2002 September; 69(1):157-164. **(DoD-107)**

This objective of this study was to determine if stress modifies pyridostigmine (PB) neurotoxicity, by evaluating the effects of single and repeated restraint stress on PB-mediated cholinergic toxicity and inhibition of cholinergic activity in blood and brain tissues. (Song, et al., 2002) The maximum tolerated dose of oral PB was determined to be 30 mg/kg. This dose was given in three variations of the single restraint stress model. Male Sprague-Dawley rats were either: 1) placed in restraint tubes for 90 minutes, then immediately given PB; 2) given PB immediately before placing them into the restraint tubes for 60 minutes; or 3) placed in the restraint tubes for 3 hours, briefly removed, treated with PB, and replaced into the restraint tubes for an additional 60 minutes. At the end of each treatment, the rats were observed for signs of cholinergic toxicity and then were sacrificed one hour after PB dosing. For repeated restraint studies, model 2 was used on a daily basis for 14 consecutive days using 0, 3, or 10 mg oral pyridostigmine per kg per day.

Measurements of functional cholinergic toxicity (salivation, diarrhea, tremors, etc.) revealed slight toxicity after PB exposure. None of the stress models increased this PB-induced toxicity, compared to PB alone. Outcome measures included: corticosterone levels as an indicator of stress; cholinesterase activity in blood and brain tissues (AChE); and horseradish peroxidase (HRP) activity in brain tissues after systemic administration, as an indicator of blood-brain barrier permeability. Plasma corticosterone levels were found to be significantly increased following single restraint and repeated daily restraint, indicating that this was a valid model to induce stress in the animals. In general, 30 mg/kg PB resulted in significant decreases in AChE activity in blood (up to 95% decrease of

control levels), while having minimal effect on brain regional AChE activity (11 to 22% decrease of control levels). Lower doses of PB over 14 days had little effect on brain AChE activity. There appeared to be no additional effect of PB plus single restraint or daily repeated restraint on AChE activity in either blood or brain tissues, compared to PB alone. HRP activity was not increased by PB plus restraint stress in the frontal cortex, cerebellum, or hippocampus, compared to PB alone, which indicated no increase in blood-brain permeability.

The authors concluded: "The results suggest that acute and repeated restraint stress have little effect of PB neurotoxicity or apparent entry of PB into the brain." They added: "The results from our study as well as a number of other recent reports indicate that stress does not generally increase the anticholinesterase actions of PB in the central nervous system. (Lallement, et al., 1998; Telang, et al., 1999; Grauer, et al., 2000; Sinton, et al., 2000; Kant, et al., 2001; Tian, et al., 2002) While stress may in some way alter the toxicity of PB under some conditions, the overall data available to date do not support a link between stress and enhanced cholinesterase inhibition/cholinergic toxicity following PB exposure in the etiology of Gulf War illnesses."

3. Abou-Donia, MB, Dechkovskaia, AM, Goldstein, LB, Bullman, SL, and Khan, WA. Sensorimotor deficit and cholinergic changes following coexposure with pyridostigmine bromide and sarin in rats. *Toxicological Sciences* 2002 March; 66(1):148-158. **(DoD-72)**

The objective of this study was to evaluate how exposure to sarin and pyridostigmine bromide (PB), alone or in combination, could affect sensorimotor performance as well as the central cholinergic system in rats. (Abou-Donia, et al., 2002) The experimental design consisted of two treatment trials conducted in male Sprague-Dawley rats. The first trial involved administering a repeated oral dose of PB by gavage, and/or a single intramuscular injection of sarin (doses ranged from 0.1X LD_{50} to 1.0X LD_{50}). There were four treatment groups: oral water for 15 days, then injected saline on day 15; oral PB each day for 15 days, then injected saline on day 15; oral water for 15 days, then injected sarin on day 15; and oral PB each day for 15 days, then injected sarin on day 15. In the first trial, sensorimotor performance was assessed at 7 days and at 15 days after the last treatment of PB or sarin. The animals performed a battery of neurobehavioral tests that included beam walking, inclined plane, and forepaw grip strength. The animals were sacrificed after the test battery on day 15. The second treatment also involved four groups of animals with the same administration protocol of agents as described above. No sensorimotor performance assessments were performed in the second treatment group; instead, the animals were sacrificed 3 hours after the last treatment.

Treatment with sarin alone at the 1.0XLD_{50} level resulted in convulsions and cholinergic toxicity. Death occurred in 7 of the 15 animals treated. No deaths occurred at the lower sarin dose levels. Treatment with PB in combination with sarin resulted in the death of 5 of 15 animals at the 1.0XLD_{50} level. Neurobehavioral tests revealed significant sensorimotor impairments in each treatment group (PB alone, sarin alone, PB plus sarin), compared to the control group, at each time point (day 7 and day 15) and each dose of sarin. At the termination of both sets of experiments, specimens were taken for the determination of plasma butyrylcholinesterase (BChE) and the determination of regional brain acetylcholinesterase (AChE) activity. At day 15, pretreatment with PB prior to sarin exposure, as well as PB alone, resulted in an increase in plasma BChE activity compared to the other two groups. In contrast, when assessed 3 hours after sarin exposure, plasma BChE activities were inhibited in the sarin alone group and in the sarin plus PB group, compared to the controls. At 3 hours, the plasma BChE activity of the sarin alone group was significantly more inhibited than that of the sarin plus PB group. This suggested that pretreatment with PB afforded a protective effect against a short-term response to a high dose of sarin in the peripheral nervous system (PNS).

The AChE activity level in the cerebral cortex was significantly inhibited in the sarin alone group, as well as the sarin plus PB group, at 3 hours and at 15 days after sarin exposure, compared to the other two groups. The PB alone group showed significantly higher AChE activity compared to the control group on day 15. However, at 3 hours after exposure, the brain AChE activity level in the PB plus sarin group was significantly less inhibited than the sarin alone group. This demonstrated the protective

effect of PB against a short-term response to sarin exposure in the central nervous system (CNS). There was no inhibition of AChE activity 15 days after sarin exposure in other regions of the brain (brain stem, cerebellum, and midbrain). In fact, AChE activity significantly increased in all three treatment groups 15 days after exposure to sarin. These results demonstrated regional brain differences in response to sarin alone and to sarin and PB exposure.

Regarding the protective effect seen with PB pretreatment, the authors commented: "Our results on the effects of PB on the CNS are at variance from those reported by Friedman, et al., (1996) in that we did not detect an inhibition in brain region AChE activity. Whether PB could have a direct access to CNS AChE is still debatable (Grauer, et al., 2000; Lallement, et al., 1998; Sinton, et al., 2000)." The authors concluded: "Pretreatment with PB afforded protection in the PNS as well as in the CNS AChE following acute treatment with sarin. The anatomic and physiological mechanisms of the effects of PB and sarin on sensorimotor performance and the role of biochemical changes are uncertain and could be central, peripheral, or nonspecific."

4. Chaney, LA, Rockhold, RW, and Hume, AS. Cardiorespiratory effects following acute exposure to pyridostigmine bromide and/or N,N-diethyl-m-toluamide (DEET) in rats. *International Journal of Toxicology* 2002 July-August; 21(4):287-300. **(Funded by University of Mississippi Medical Center)**

The objective of this study was to explore the immediate lethal interaction between pyridostigmine bromide (PB) and DEET when administered in combination at high doses, to determine the possible biological mechanism for this interaction. (Chaney, et al., 2002) PB elicits responses, among many others, that mimic parasympathetic stimulation of the respiratory system. This effect is due to the accumulation of acetylcholine in the periphery. While the exact mechanism of DEET toxicity is unknown, it is speculated that high concentrations of DEET somehow interact with the CNS. DEET may interfere with the central respiratory control centers resulting in the inhibition of respiratory drive. Thus, the hypothesized mechanism of increased lethality when PB and DEET are administered in combination is due to differential contributions from the parasympathetic nervous system and CNS to decrease ventilation, compared with PB or DEET alone.

Male Sprague-Dawley rats received a single intraperitoneal injection to high doses of PB and DEET (approximately 60% of the LD_{50}), alone and in combination. Various parameters of respiration were monitored before and at various time points up to 1 hour after agent administration. In addition, arterial blood gases and pH were determined before and 15 to 20 minutes after drug administration. In the DEET + PB group, a blood sample was taken 5 minutes after drug administration, due to the immediate drop in blood pressure. Finally, cardiovascular system parameters, such as blood pressure and heart rate were monitored since both PB and DEET can cause hypotensive effects. A large drop in blood pressure could cause secondary failure of the respiratory center if the blood flow proved inadequate. There were only mild clinical signs of toxicity observed in rats exposed to 2 mg/kg PB. In contrast, rats exposed to 300 mg/kg DEET experienced ataxia, prolonged prostration, and seizure activity. The combined exposure of DEET and PB produced ataxia, tremors, severe seizures, and respiratory distress. Only one rat survived the combined dose, with death occurring within 10-15 minutes of drug dosing.

PB alone caused an increase in respiratory rate, increased tidal volume, and minute volume, while DEET alone had virtually no respiratory effects, except at a much higher dose (1.0 X LD_{50}). The combination of DEET and PB did not appear to have a synergistic effect on respiratory function, other than a small increase in tidal volume. The arterial blood CO_2 concentration was significantly increased and the blood pH decreased in rats exposed to DEET plus PB. No effects were seen in blood gases or pH among the other treatment groups. Finally, neither DEET nor PB administered alone affected heart rate. However, when given together, there was a profound decrease of 15 to 60% in heart rate and a significant drop in blood pressure, reaching serious levels within 8 minutes.

Pre-treatment with atropine methyl nitrate (AMN) reduced the occurrence of tremors and seizure activity in PB-treated rats. It also reduced the lethality from 92% to 22% in rats exposed to PB + DEET. AMN is a peripherally

selective cholinergic antagonist; and it protected against circulatory collapse by preventing PB-induced bradycardia. The authors concluded that respiratory failure might have contributed to the lethality of the concurrent administration of high doses of DEET and PB; however, the primary cause of death appeared to be circulatory failure. These results in laboratory rats cannot be directly extrapolated to humans, because these massive doses caused seizures and death within minutes.

5. Wilson, BW, Henderson, JD, Coatney, EM, Nieberg, PS, and Spencer, PS. Actions of pyridostigmine and organophosphate agents on chick cells, mice, and chickens. *Drug and Chemical Toxicology* 2002 May; 25(2):131-139. **(Funded by DoD-56 and the National Institute of Environmental Health Sciences)**

The objective of this study was to determine if combined exposure to PB, sarin, and/or diisopropyl phosphofluoridate (DFP) is more neurotoxic to sensitive animals than if given separately, by examining inhibition of two enzymes. (Wilson, et al., 2002) These enzymes were brain acetylcholinesterase (AChE), a major target of organophosphate (OP) chemicals, and neuropathy target esterase (NTE), an enzyme whose inhibition is associated with OP-induced delayed neuropathy (OPIDN). Sarin and DFP are organophosphate chemicals, while PB is in a related class of chemicals, the carbamates. Experiments were performed using live chickens, tissue homogenates, and cell cultures to determine if the inhibitory effects of the combination of PB and an organophosphate (sarin or DFP) were additive, synergistic, or antagonistic.

In range finding experiments, 1 to 10 mg/kg of PB was administered intramuscularly to chickens and survivors were sacrificed 24 hours later. These were very high doses; therefore, mortality occurred as low as 2 mg/kg. One hour after injection, blood cholinesterase levels (AChE) were depressed to 34% at the 1mg/kg dose and almost to zero at the 2 mg/kg dose. Twenty-four hours later, the 1mg/kg birds had recovered to 72% of baseline and the single surviving bird at 2 mg/kg had recovered to 58% of its initial AChE activity. PB did not inhibit brain NTE activity, regardless of dose. The researchers concluded that PB did cross the blood-brain barrier of chickens at these lethal or sub-lethal doses of PB. These results in chickens cannot be directly extrapolated to humans, because the massive doses of PB caused death.

Sarin and PB were tested in mouse or chicken brain tissue homogenates. Sarin alone, PB alone, and the combination of sarin and PB inhibited brain AChE, regardless of whether sarin or PB was added first. Thus, in these *in vitro* experiments, the presence of PB did not reduce the extent of the AChE inhibition. In contrast, PB alone did not cause inhibition of chicken brain NTE. This indicated that PB alone is unable to induce OPIDN. Sarin alone, or sarin combined with PB caused significant inhibition of NTE.

In additional experiments evaluating AChE inhibition, DFP alone, PB alone, and DFP in combination with PB were added to cell cultures of chicken embryo brain cells. DFP alone or PB alone inhibited AChE activity. There was an additive effect of AChE inhibition, when DFP and PB were added to the cells in combination. Furthermore, AChE levels in cells did not recover from DFP and PB in combination, as well as the AChE levels in cells treated with DFP alone or PB alone. Overall, the authors concluded that there was little direct interaction on the enzyme, AChE, between sarin and PB or between DFP and PB. The authors planned to continue their research on neurotoxic OP, including sarin and tri-ortho cresyl phosphate, to determine if PB may exacerbate OPIDN and neuromuscular damage, including dose-response, biochemistry, and morphometry.

6. Usmani, KA, Rose, RL, Goldstein, JA, Taylor, WG, Brimfeld, AA, and Hodgson, E. In vitro human metabolism and interactions of repellent N,N-diethyl-m-toluamide. *Drug Metabolism and Disposition* 2002 March; 30(3):289-294. **(DoD-103)**

The objectives of this study were to quantify the metabolism of DEET by human microsomes; to identify the human P450 isoenzymes responsible for the metabolism of DEET; and to investigate the potential for inhibition or activation of DEET biotransformation, in combination with chlorpyrifos, permethrin and pyridostigmine bromide. (Usmani, et al., 2002) N-N Diethyl-m-toluamide, also known as DEET, is a very widely used insect repellant in the U.S. Although generally regarded as quite a benign chemical, there are isolated reports of toxic reactions from extremely high exposure. Given

there was very limited information on the biotransformation of DEET in humans, this study was undertaken to answer some fundamental questions regarding DEET metabolism. Because DEET was widely used during in the Gulf War, there has been interest in evaluating the potential for adverse interactions with other chemicals, as a possible explanation for neurological symptoms experienced by some Gulf War veterans. Pyridostigmine bromide (PB), chlorpyrifos, an organophosphate pesticide, and permethrin, a pyrethroid pesticide, were used during the Gulf War.

Oxidative metabolism of DEET was investigated using purified P450 cytochromes, as well as microsomes extracted from pooled human liver specimens. In order to identify the most active isoenzymes in the oxidative biotransformation of DEET, fifteen different human P450 cytochromes were screened. Only four isoenzymes showed any oxidative metabolic activity, and only four others demonstrated de-ethylation activity. In addition, DEET was incubated with liver microsomes, pooled from human donors of both genders with wide-ranging activities of these eight P450 isoenzymes, to determine and compare metabolic efficiency. It was determined that the metabolite produced by oxidation occurs more frequently than the one produced by de-ethylation. Also, individuals with varying activities of these eight isoenzymes will be more or less efficient in the metabolism of DEET, regardless of gender.

Among the four isoenzymes with DEET oxidative metabolism activity, the isoenzyme with the most activity was CYP2B6. This isoenzyme was pre-incubated with chlorpyrifos and its desulfuration metabolite, chloropyrifos-oxon, to evaluate potential inhibition of DEET oxidation. Pre-incubation of the CYP2BG with chlorpyrifos resulted in total inhibition of the oxidative metabolite of DEET, while pre-incubation with chloropyrifos-oxon resulted in 58% inhibition. This indicated that chlorpyrifos exposure could inhibit the subsequent metabolism of DEET in humans by inhibiting the isoenzymes involved in DEET metabolism.

Finally, DEET was incubated with pooled human microsomes pre-treated with chlorpyrifos, permethrin, or pyridostigmine bromide, alone or in combination, to determine if the metabolism of DEET was affected by the presence of these chemicals. The oxidative metabolism of DEET was increased for every chemical or combination of chemicals, with the exception of chlorpyrifos or any combination including chlorpyrifos. Conversely, the oxidative metabolism of DEET was significantly decreased, when pooled human microsomes were pre-incubated with chlorpyrifos or any combination of chemicals including chlorpyrifos. These results cannot be extrapolated directly to humans because the experiments were performed in test tubes, rather than whole animals. In addition, the experiments were designed solely to test interactions of the isoenzymes or microsomes with the chemicals, rather than to assess any potential adverse health effects.

7. Vogel, JS, Keating, GA, and Buchholz, BA. Protein binding of isofluorophate *in vivo* after coexposure to multiple chemicals. *Environmental Health Perspectives* 2002 December; 110(Supplement 6):1031-1036. **(HHS-8)**

The objective of this study was to use accelerator mass spectrometry (AMS) to quantify radio-labeled diisopropylfluorophosphate (DFP) as a tracer at attomolar levels (10^{-18} molar), after co-exposures to two different classes of pesticides, alone or in combination. (Vogel, et al., 2002) DFP was chosen as a tracer because it is an organophosphate chemical, and a simulant of organophosphate (OP) nerve agents that inhibit target proteins through covalent binding. Bound tissue concentrations of DFP were quantified to determine if these levels could be altered due to repeated exposures to pesticides at the very low doses relevant to household exposures. The chemical mixture used for repeated pre-exposures included parathion, an OP pesticide, permethrin, a pyrethroid pesticide, as well as pyridostigmine bromide (PB), a carbamate cholinesterase inhibitor that exhibits a protective effect against the action of OP. The authors stated that while this chemical mixture has minor relevance to exposures that may have occurred during the Gulf War, it is more relevant to household exposures to pesticides.

In this experiment, male CD2/F1 mice were orally administered these chemicals alone or in combination through a 5-day fast/feed cycle. Animals from each chemical mixture group were then given a 1μg/kg dose of radio-labeled DFP. The animals were sacrificed 48 hours later, a time period determined as optimal from earlier pharmacokinetic experiments. Blood and tissue

from the brain, liver, muscle and spleen were removed from the animals and then processed for AMS analysis. Pre-exposure to the chemical mixtures did not affect absorption or distribution of DFP in plasma, muscle, liver or spleen tissues. PB demonstrated an overall protective effect against binding of DFP in plasma, red blood cells, muscle, and brain tissue. Higher levels of protein-bound DFP were demonstrated in brain tissue only, when combined with other chemicals. DFP levels in brain tissue increased by 32% with parathion, 27% with permethrin, and 43% with parathion and permethrin combined, respectively. These percent increases persisted with co-administered doses of PB.

These experiments have little direct relevance to human health, because the DFP concentrations detected in these experiments were in the parts per trillion range (measured in picograms), a concentration far below any that has been demonstrated to cause adverse health effects in humans or animals. In addition, the percentage increases of DFP seen in the brain tissue after co-exposure to the other pesticides were minute in terms of actual concentrations. Finally, the determination of molecules of chemicals bound to proteins was only a measure of concentration. It was not an indication of an adverse health effect.

III. RESEARCH FUNDING TRENDS

A. Overview

Appendix A provides details of the research database on Gulf War veterans' illnesses. It was last updated as of December 31, 2002. Research projects are grouped according to the Department that is responsible for their funding. Each entry in the database includes:

- Project Title
- Responsible Federal Agency
- Study Location
- Project Start-up Date
- Project Completion Date (estimated if ongoing)
- Overall Objectives of Project
- Specific Aims of Project
- Methods of Approach
- Expected Products (Milestones)
- Current Status/Results
- Publications

Two descriptors categorize each research project. The first descriptor is a series of **Research Focus Areas**. The research focus areas are categorized as follows:

- Prevalence and risk factors for symptoms and alterations in general health status
- Brain and nervous system function
- Chemical weapons
- Environmental toxicology (e.g. studies focused on specific environmental toxicants such as pesticides, oil well fires, etc.)
- Reproductive health
- Depleted uranium
- Leishmaniasis
- Immune function
- Pyridostigmine bromide
- Mortality experience
- Interactions of exposures (chemical, biological, pharmacological, physiological, etc.)
- Prevention of diseases (i.e. studies that will produce knowledge that could lead to disease prevention strategies)
- Treatment
- Diagnosis (i.e. studies that will improve the ability to diagnose previously unexplained conditions, or to better refine diagnoses with new tools)

Each project is assigned up to three focus areas as categorical descriptors. This allows accounting for projects that cover multiple focus areas. For example, a project on the neurophysiological effects of exposure to sarin in animals would have a focus on the brain and nervous system, and a focus on chemical weapons. The number of focus areas (between one and three) assigned to a project depends on the project itself.

The second descriptor for each project is **Research Type**. The Federal Government defines **Research** as systematic investigation designed to develop or contribute to generalizable knowledge. Each research project on Gulf War veterans' illnesses uses a method of approach to test a specific research hypothesis. Approaches range in type from mechanistic research, addressing potential biological mechanisms of causation, to clinical and epidemiological research that attempt to determine illness prevalence and risk factors. Although precise categorization of research types can be difficult because of overlapping methodologies, research projects can be divided into the following general types:

MECHANISTIC RESEARCH: Research into underlying mechanisms of diseases and illnesses using in vitro and in vivo models.

CLINICAL RESEARCH: Application of an intervention, such as in a controlled drug trial, or use of methodologies such as case-control studies to define risk factors for disease.

EPIDEMIOLOGY RESEARCH: Study of the distribution and determinants of disease in human populations. It includes population-based studies focused on outcomes such as mortality, symptoms, hospitalizations, etc., using devices such as postal surveys, telephone interviews, and reviews of medical records.

In addition to the research on Gulf War veterans' illnesses, the Deployment Health Working Group (DHWG) also tracks development work. In general, development is the systematic use of the knowledge or understanding gained from research directed toward the production of materials; devices; systems; or methods, including design, development, and improvement of prototypes and new processes. Within the context of Gulf War veterans'

illnesses, the DHWG categorizes activities as development as follows:

DEVELOPMENT: An activity that satisfies the general definition of development described above, and is directed toward new biologically based prevention, intervention, and treatment measures.

The research database on Gulf War veterans' illnesses catalogs only research and development activities that either directly involve Gulf War veterans, or has been initiated to answer specific questions about risk factors. An example of the latter is a research project using animal models to determine health effects of low-level chemical warfare agents. The database does not account for the vast accumulated knowledge derived from the nation's investment in biomedical research over the past 50 years.

The research database on Gulf War veterans' illnesses contains research that is Federally sponsored only. This includes research conducted by Federal scientists, as well as that by non-federal scientists supported by Federal research funds through grants, contracts, and cooperative agreements. It is not possible to accurately track research efforts that fall within the private sector or otherwise outside of the purview of the Federal government.

Nonetheless, the DHWG attempts to stay abreast of all research relevant to Gulf War veterans' illnesses. The DHWG accomplishes this by monitoring the peer reviewed published scientific literature, attending scientific meetings, and even using newspaper reports and personal accounts of researchers.

An interim assessment of the nature and causes of illnesses in Gulf War veterans was included in Appendix C of the Annual Report to Congress for 2000. (MVHCB, 2001a) In 1996, the Persian Gulf Veterans Coordinating Board identified 21 major research questions. The comprehensive Gulf War research portfolio has addressed each of these questions, and relevant results have been published on each one. Appendix C provided a formal assessment of the progress made on each of these 21 questions.

The following sections provide a quantitative overview of the current research portfolio on Gulf War veterans' illnesses and the evolution of the portfolio over time since 1994. Topics that are covered include overall research expenditures from 1994-2002 (projected), and the types and areas of research in which the Federal Government has invested.

B. Research Funding

All current Federal research projects directly related to Gulf War veterans' illnesses that VA, DoD, or HHS has sponsored. From 1994 through early 2002, the Departments have sponsored 239 distinct research projects on Gulf War veterans' illnesses. This does not include research projects that recently have been selected for funding, but are currently in final contract negotiations. This also does not account for anticipated projects arising from competition of proposals submitted in response to new initiatives, such as the VA Program Announcement on Deployment Health Research, which was released in 2002.

A table in Appendix A lists all of the research and development projects and programs supported now or in the past by the Federal government. The appropriated funds, centrally distributed to each program or project, are shown in the fiscal years that funds were obligated. Many extramural projects are multi-year efforts for which funds are obligated at the beginning of the project period.

Table III-1 is a summary of research expenditures by DoD, VA, and HHS between FY94 and FY02, and a projection of funding into FY03. From FY94 through FY02, Federal Government funding for the direct costs of Gulf War research exceeded $227 million. This total does not include indirect costs of conducting the research such as facility, administrative and operational costs. Estimates of these indirect costs are $70 million. As of September 30, 2002, 152 projects were completed, and this total is expected to rise to 182 by the end of FY03. As of September 30, 2003, a total of 182 projects will be completed (76% of total of 239 projects), and 57 projects will be ongoing.

Table III-2 is a year-by-year account of new and completed projects.

Table III-1. Funding for Research FY'94-02 in $Millions

Department	FY'94	FY'95	FY'96	FY'97	FY'98	FY'99	FY'00	FY'01	FY'02	Direct Costs FY'94-02	Indirect Costs FY'94-02	Total Costs FY'94-02
DoD	$6.5	$11.0	$11.9	$28.9	$13.2	$23.5	$25.2	$23.5	$24.8	$168.5	$50.6	$219.1
VA	$1.2	$2.3	$3.9	$2.8	$4.7	$9.0	$12.0	$8.5	$4.1	$48.5	$16	$64.5
HHS	$0.0	$2.5	$1.6	$0.0	$1.6	$1.6	$1.6	$1.0	$0.8	$10.7	$3.2	$13.9
Total	**$7.7**	**$15.8**	**$17.4**	**$31.7**	**$19.5**	**$34.1**	**$38.8**	**$33.0**	**$29.7**	**$227.7**	**$69.8**	**$297.5**

Table III-1. Direct costs cover the actual research such as testing and lab supplies. Indirect costs cover expenses for administration, infrastructure, utilities etc. These expenses are estimated because indirect costs can be computed only by facility and not by project. Table III-1 does not include funding for activities performed by members of the DHWG (salaries, travel, etc.).

Table III-2. Number of New and Completed Projects by Year*

Fiscal Year	New	Completed
1992 – 1994	62	3
1995	21	8
1996	16	4
1997	36	10
1998	17	15
1999	30	16
2000	14	42
2001	17	25
2002	19	29

*For programs/centers with multiple projects, each project is counted as an individual project for accounting purposes.

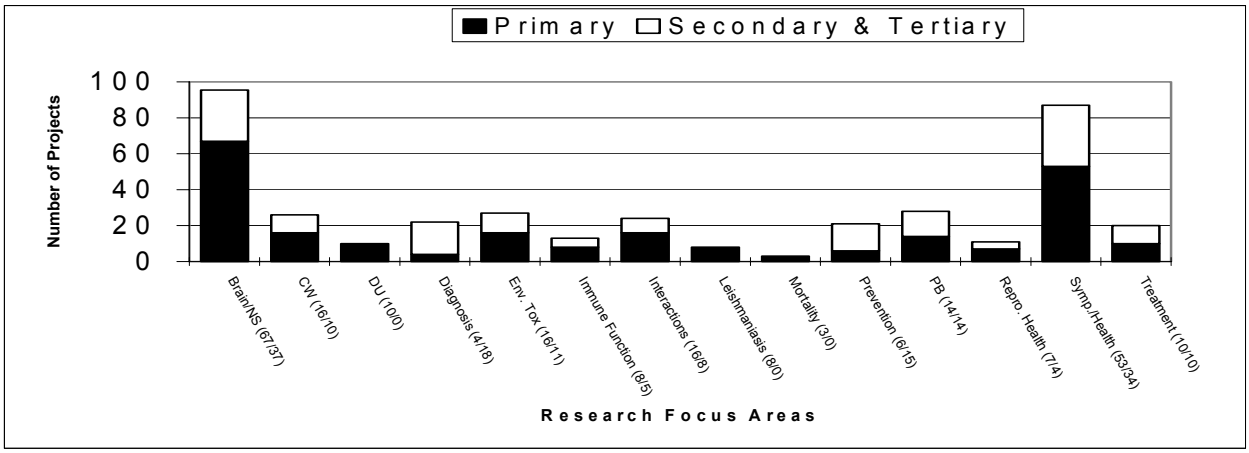

Figure III-1. Number of projects in each research focus area. Closed bars represent the number of projects with the focus area as primary; open bars represent the number of projects with the focus area as either secondary or tertiary. The first number within the parenthesis represents the number of projects with a primary research focus area. The second number represents the number of projects with a secondary or tertiary research focus area.

C. Diversity of Research Approaches

The funds that have been invested in research on Gulf War veterans' illnesses over the years have gone into a broad-based portfolio with respect to research type and research focus area. On average, epidemiology and clinical research have each comprised approximately one third of the total number of projects. The remaining third has been divided between mechanistic research and development, with the larger share going to mechanistic research.

The distribution of projects across different research focus areas is illustrated in **Figure III-1.** Projects for each focus area are categorized by the focus areas, which are listed as one of the three areas assigned to each project. The total number of projects by research focus areas is shown in **Figure III-1** in two ways. For each focus area, a black bar represents the total number of projects for which that focus area is listed as primary. A clear bar represents the total number of projects for which that focus area is listed as secondary or tertiary. Thus the total height of a bar represents the total number of projects for which the focus area is listed as primary, secondary, or tertiary. By showing the data this way, the multiplicative effects of research investments are demonstrated. For example, a project that examines the effects of Pyridostigmine Bromide on the Brain and Nervous System is counted under both of these focus areas.

As can be seen in **Figure III-1**, the overall emphasis of research has been greatest in the focus areas of the Brain and Nervous System Function and in Symptoms and General Health Status. This reflects the focus of epidemiological efforts on the prevalence of symptoms and illnesses in Gulf War veterans, and the focus of clinical research efforts on risk factors for illnesses. The focus on the brain and nervous system is a result of both the dominance of health complaints in this area, and the fact that there were several potential exposures to neurotoxic chemicals during the Gulf War.

The number of research projects in the various research focus areas has changed over time since 1994 as a reflection of the evolution of issues centered on Gulf War veterans' illnesses. The relatively greater increase over the years of research on chemical warfare agents, pyridostigmine bromide, and interactions of chemicals is noteworthy. These increases are an outgrowth of increased concern about potential health risks posed to veterans by exposures to multiple toxic agents at low concentrations.

IV. NEW RESEARCH PROJECTS AND INITIATIVES

Several new research projects and initiatives that have been undertaken since last year's *Annual Report to Congress* are highlighted in this Section. These include the awarding of new research projects and the development of new research initiatives. In addition, this section provides an update of important accomplishments in 2002 for key research projects and initiatives.

Many of the new research projects and initiatives are responsive to recommendations from a variety of sources, including the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC, 1996a; PAC, 1996b; PAC, 1997); the Institute of Medicine Committee on the Health Consequences of Service During the Persian Gulf War (IOM, 1995; IOM, 1996); the Senate Veterans' Affairs Committee (SVAC, 1998); the Presidential Special Oversight Board (PSOB, 2000); and the Persian Gulf Veterans Coordinating Board (PGVCB, 1995b; PGVCB, 1996b).

IV.A. NEW RESEARCH PROJECTS

An overview of a new VA research initiative, two new projects, and a new DoD research initiative are highlighted in this section:

- VA Program Announcement on Deployment Health Research;
- a new jointly funded VA/DoD project entitled: Prospective Assessment of Neurocognition in Future Gulf-Deployed and Gulf-Nondeployed Military Personnel;
- a new VA-funded project entitled: the National Registry of Veterans with Amyotrophic Lateral Sclerosis; and
- DoD Broad Agency Announcement on Low-Level Chemical Exposures in Gulf War Veterans.

IV.A.1. VA Program Announcement on Deployment Health Research

VA places a high priority on the development of improved methods of diagnosis, treatment, and prevention of illnesses related to hazardous deployments, such as the Gulf War, Bosnia/Kosovo, Afghanistan, and the current war in Iraq. In 2002, VA released a Program Announcement on Deployment Health Research to expand its research portfolio. VA recognizes five major research 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

The complete Program Announcement can be accessed at: www.va.gov/resdev/fr/ProgramAnnouncementDeploymentHealthIssues.pdf

Deployments often present unique and difficult challenges for active-duty service members and veterans. 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;
- 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, 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 (such as 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 that can lead to significant long-term disability, including sequelae from chronic infectious diseases, traumatic injuries, and chronic physical and psychological symptoms.

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 and the current war in Iraq; however, it is too soon to assess their long-term health effects systematically. Very little is known about long-term effects of several smaller, recent deployments, such as to Panama, Haiti, and Somalia.

VA will support a broad spectrum of research that focuses on deployment health and force health protection. VA investigators are encouraged to collaborate with DoD investigators, particularly for studies that require the acquisition of DoD data for subject selection or exposure assessment. The five major categories of research priorities are described briefly, and in each category, the relevant VA research projects are listed, that were funded in 2002.

1. Long-term health impacts of hazardous deployments

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;
- 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); and
- Use of existing health databases, if possible (such as, national VA and DoD hospitalization databases).

Relevant Projects Funded in 2002:

- VA-82: Pituitary Adrenal Function in People with Fatiguing Illnesses (East Orange, NJ VAMC)

- VA-85: Associative Learning in Veterans with and without Combat Experience (Columbia, SC VAMC)

2. Health impacts of specific military occupational and environmental exposures

This category focuses 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.

Examples include potential exposure to depleted uranium during the Gulf War, exposure to air pollution during deployment to Bosnia/Kosovo, and exposure to hepatitis and tuberculosis in Afghanistan.

Relevant Projects Funded in 2002:

- VA-80: Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress (East Orange, NJ VAMC)

- VA-81: Stress, Pro-Inflammatory Cytokines, and Coping Behavior (East Orange, NJ VAMC)

3. Improvements in 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. Clearly, central nervous system symptoms are a recurring phenomenon after hazardous deployments.

Further research is justified to determine whether evaluations of subtle neurological function can provide information on the pathophysiology of illnesses in veterans of hazardous deployments. Some Gulf War studies 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.

Relevant Projects Funded in 2002:

- VA-83: Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls (Washington, DC VAMC)

- VA-84: Neurobiology of Severe Psychological Trauma in Women (San Diego, CA VAMC)

- VA-88: Prospective Assessment of Neurocognition in Future Gulf-Deployed and Gulf-Nondeployed Military Personnel (New Orleans, LA VAMC) (This project is described in the next section.)

4. Improvements in treatment of deployment-related illnesses

This category focuses on treatment trials for veterans of hazardous deployments, such as the Gulf War, Bosnia/Kosovo, or Afghanistan.

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. (IOM, 2001) IOM evaluated certain therapies as definitely or likely to be beneficial for multiple conditions. For example, 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).

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. VA also encourages submission of proposals for innovative approaches to treating veterans with complex, disabling medical conditions, or with complex psychosocial problems, such as substance abuse or unemployment. (i.e., case management)

Relevant Projects Funded in 2002:

- VA-86: A Clinical Trial of Magnetic Stimulation in Depression (Gainesville, FL VAMC)

- VA-87: Improving Outcomes of Depression in Primary Care (Portland, OR VAMC)

- VA-89: National Registry of Veterans with Amyotrophic Lateral Sclerosis (Durham, NC VAMC) (This project is described in the next section.)

5. Health risk communication for veterans and health care providers

This category focuses on research that would lead to improved methods of health risk communication for veterans and their health care

providers. The long-term goal is to provide more timely, understandable, and effective communications. Research is needed to identify effective methods or tools of delivering information, with an aim to developing general guiding principles.

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 the vaccine for tick-borne encephalitis in Bosnia; and
- use of malaria prophylaxis in Afghanistan.

Relevant Projects Funded in 2002:

- VA-79: VHA Clinicians and Bioterror Events: Interactive Web-Based Learning (Birmingham, AL VAMC)

IV.A.2. National Registry of Veterans with Amyotrophic Lateral Sclerosis (Project VA-89)

Amyotrophic lateral sclerosis (ALS) is a rapidly fatal neuromuscular disease of unknown etiology. In December 2001, VA and DoD released the preliminary results of a study of ALS in Gulf War veterans (VA-61/DoD-118). The incidence of ALS was increased almost two-fold in Gulf War veterans, compared to non-deployed veterans. Therefore, VA determined that systematic identification and tracking of veterans with ALS was a high research priority. Accordingly, in 2002, VA funded a National Registry of veterans diagnosed with ALS (VA-89). This Registry is directed by the Epidemiologic Research and Information Center at the Durham, NC VAMC, in collaboration with the Lexington, KY VAMC.

There are three objectives for this Registry:

- to provide VA with data on the current number and characteristics of veterans with ALS, as well as the ongoing identification of new cases;
- to provide VA with an important data resource for future studies examining the causes and treatment of ALS; and
- to provide a mechanism for VA to inform veterans with ALS about treatment trials and other studies for which they may be eligible.

ALS is a very rare disease, therefore it is very difficult to identify and enroll adequate numbers of patients in clinical trials of promising new treatments. This National Registry is the first step to develop the capability to set up national treatment trials.

Eligible participants include all veterans with a physician diagnosis of ALS, regardless of when they served in the military. Veterans with possible ALS are identified through VA medical records, the Veterans Benefits Administration (VBA), and self-referral. Neurologists with expertise in ALS review veterans' medical records to verify the diagnosis according to appropriate diagnostic criteria. When invited to participate, veterans are asked to complete a brief telephone interview. Registry participants will also be contacted by telephone periodically to assess health and functional status. The VA will notify Registry participants about clinical trials for which they may be eligible. An executive committee will evaluate all studies that request use of Registry data. It will also determine when participants should be notified about appropriate clinical trials.

IV.A.3. DoD Broad Agency Announcement on Low-Level Chemical Exposures in Gulf War Veterans

In the summer of 2002, the U.S. Army Medical Research and Materiel Command (USAMRMC) released a solicitation (Broad Agency Announcement) for research proposals on persons who served on active duty in the Southwest Asia theatre of operations during the Gulf War. The focus of this solicitation was research on: 1) possible health effects of exposures to low-levels of hazardous chemicals; and 2) individual susceptibility of humans to such exposures under environmentally controlled conditions. These funds were provided by

Congress, with explicit language in the law for their use, including "competitively funded research studies," and the two topics, exactly as published in the Broad Agency Announcement.

Following an independent review by scientific experts, including researchers who specialized in the field of multiple chemical sensitivities, one proposal was recommended for funding on the basis of scientific merit and highest relevance to the Congressional law. In 2003, this four-year project will start at Rutgers University, focusing on the effects of diesel exhaust and stress on symptoms in chemically intolerant individuals. This research effort follows up on the conclusions of an earlier conference sponsored by the USAMRMC on chemical intolerance and neuroplasticity. (Sorg and Bell, 2001)

IV.B. 2002 UPDATE OF KEY RESEARCH PROJECTS AND INITIATIVES

Four research initiatives are described in this section:

- Deployment Health Working Group;
- VA Research Advisory Committee on Gulf War Veterans' Illnesses;
- Medsearch: Gulf War Veterans Medical Library Web Site; and
- Conference on Post-Deployment Care: Risk Communication and Terrorism-New Clinical Approaches.

IV.B.1. Deployment Health Working Group

The Persian Gulf Veterans Coordinating Board (PGVCB) was established in January 1994 to enhance interagency coordination on research and clinical care of Gulf War veterans. Senior scientists, health care providers, and administrators from VA, DoD, and HHS were appointed as members of the PGVCB. In 2000, the scope of the Board's mission was broadened, and it transitioned to become the Military and Veterans Health Coordinating Board (MVHCB). (PGVCB, 2001) In 2002, the scope of interagency coordination was broadened once again; and the MVHCB was replaced by the Deployment Health Working Group (DHWG). The charter for the DHWG was developed through an interagency process; and in October 2002, the VA Under Secretary of Health and the DoD Assistant Secretary for Health Affairs approved the charter for implementation. The overall purpose of the DHWG is to enhance coordination between the agencies, regarding the health of active-duty service personnel and veterans, related to past, current, and future deployments.

The DHWG charter outlines its responsibilities, which include: "collaboration between VA, DoD and HHS on a broad range of military and veterans' health matters to achieve the nation's commitment to maintain, protect and preserve the health of the men and women who serve in the U.S. Armed Forces. The work group will address health matters that relate to military service with a primary focus of military members, veterans, and their families during and after mobilization, combat, and other operations. The responsibilities of the work group include coordination of those responsibilities and activities that are statutorily prescribed for the participating agencies. The work group provides recommendations and coordination for deployment health research activities, health risk communication efforts, and other matters related to deployment health as they arise."

Research is one of the major DHWG responsibilities. The charter states that the DHWG will "assess the state and direction of research in deployment and post-deployment health, facilitate discussion on the future research activities by the participating agencies, and assist in the completion of statutorily required deployment research reporting activities."

Subcommittee's major responsibilities is the writing and publication of this *Annual Report to Congress*.

IV.B.2. VA Research Advisory Committee on Gulf War Veterans' Illnesses

In January 2002, the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) was appointed. This Committee was established by Congress to provide advice on research studies to the Secretary of the VA on a regular basis.

The Committee was established by Public Law 105-368, Section 104, which required VA to "establish an advisory committee consisting of members of the general public, including Persian Gulf War veterans and representatives of such veterans, to provide advice to the head of that

department or agency on proposed research studies, research plans, or research strategies relating to the health consequences of military service in the Southwest Asia theater of operations during the Persian Gulf War."

The Secretary of the VA approved the charter for the RACGWVI in January 2002. The charter defines its scope of activity as follows: "The VA RACGWVI shall provide advice and make recommendations to the Secretary of the VA on proposed research studies, research plans, and research strategies relating to the health consequences of military service in the Southwest Asia theater of operations during the Persian Gulf War." The charter also states that: "It shall not be a function of the Committee to conduct scientific research." The charter requires the Committee to hold open public meetings at least two times per year.

The Committee is chaired by James Binns, Jr., who is a Vietnam veteran and a former Principal Deputy Assistant Secretary of Defense. There are eleven additional members who are scientists who work for universities or private industry, Gulf War veterans, or veteran advocates.

The Committee held its first meeting in April 2002, and two additional meetings in 2002. It released an *Interim Report* in June 2002, which contained seven recommendations for future research on illnesses in Gulf War veterans. It also published a brief *Annual Report* in November 2002. These reports are accessible at: www.appc1.va.gov/rac-gwvi/

IV.B.3. Medsearch: Gulf War Veterans Medical Library Web Site

DoD, CDC, and VA have collaborated to create a web-based library of Gulf War-related research, entitled Medsearch. Accessible at http://www.gulflink.osd.mil/medsearch/, the library was developed to help service members, veterans, families, and the public learn about research efforts into health concerns related to service during the Gulf War. In addition, the library provides scientists and medical professionals with information about initiatives and important findings in Gulf War-related medical research.

In 2001, CDC made funding available to develop a web site that was designed to provide accessibility to the medical literature to veterans and the interested public. CDC collaborated with the DoD Deployment Health Support Directorate, because of its experience in building the GulfLINK web site since 1997. GulfLINK was designed to provide information on numerous issues of interest to Gulf War veterans; however, it did not focus on medical research.

The Medsearch web site was launched on June 18, 2002. The three major sections of Medsearch contain descriptions of government funded research projects that link to abstracts of articles published in peer-reviewed journals; explanations of the major research areas such as exposure to low-level chemical weapons; and a compilation of the most important, relevant government reports, such as the reports by the Senate Veterans' Affairs Committee and the Presidential Special Oversight Board. (SVAC, 1998; PSOB, 2000)

The primary target audience of Medsearch is veterans; therefore, there has been an emphasis on making the site's functions user-friendly, and on the of use plain English, whenever possible. As the overall framework of the web site was being constructed, the developers decided that the *1999 Annual Report to Congress* should be used as the starting point and model for the overall web structure. (PGVCB, 2001) This report was chosen because it was comprehensive in scope, and because of the utility of its classification system for various types of medical studies. A glossary of medical terms was developed to improve comprehension. Approximately 2,800 persons per month have visited the Medsearch site.

IV.B.4. Conference on Post-Deployment Care: Risk Communication and Terrorism-New Clinical Approaches

On September 9 to 11, 2002, a conference was held in Alexandria, VA, entitled: Conference on Post-Deployment Care: Risk Communication and Terrorism-New Clinical Approaches. The Conference Co-Chairs were Dr. Charles Engel of the Walter Reed Army Medical Center and Dr. Maria Pavlova of the Department of Energy. The purpose was to provide cutting-edge information on clinical risk communication to strengthen health provider-patient relationships. There were four objectives:

- To describe clinical risk communication and its application to provider relationships in the context of war and terrorism.
- To provide clinicians and health care professionals with information about practical risk communication using case studies and standardized community and patient-centered scenarios.
- To increase the knowledge and skills of providers by fostering collaboration and dialogue between risk communication experts and health care providers.
- To develop a set of recommendations for clinical risk communication for future use by DoD in the areas of research, policy, and practice.

The sessions were organized into several major topics, as follows:

- Patient-Centered Communication
- New Technologies for Clinical Risk Communication
- Building Patient-Provider Trust
- National Risk Communication Initiatives
- Risk Perception
- Vaccination Risk Communication
- Occupational Health, Terrorism and Risk Communication

Four initiatives funded by VA and CDC, specifically related to illnesses in Gulf War veterans, were highlighted during this conference. In 2001, VA funded two War-Related Illness and Injury Study Centers at the East Orange, NJ VAMC and the Washington, DC VAMC. Both Centers have developed new research initiatives on risk communication. At the conference, Dr. Drew Helmer of the East Orange VAMC and Dr. Aaron Schneiderman of the Washington DC VAMC provided an update of these new initiatives. In 2001, CDC funded two new research projects focusing on the development of improved methods of risk communication. These projects are located at Rutgers University and Walter Reed Army Medical Center (Projects HHS-9 and HHS-10). At the conference, Dr. Drue Barrett of CDC provided an update of these two projects. About 200 physicians, university scientists, government officials, and active-duty service members attended this conference. Detailed information about this conference, including the agenda, is accessible at www.pdhealth.mil/education/conference.asp

V. RESEARCH PRIORITIES

The Persian Gulf Veterans Coordinating Board (PGVBC) identified three sets of research priorities in 1995, 1996, and 1998. (PGVCB, 1995b; 1996b; 1999a) (The PGVCB was the interagency committee that previously coordinated research on Gulf War veterans' illnesses. The Deployment Health Working Group is the committee that succeeded the PGVCB.) Substantial progress has been made on each of these priorities, as summarized here.

A. RESEARCH PRIORITIES FOR 1995

In 1995, the scope and magnitude of the research activities required implementation of a comprehensive plan. This resulted in the publication of *A Working Plan for Research on Persian Gulf Veterans' Illnesses* on August 5, 1995. (PGVCB, 1995b) The *Working Plan* was coordinated by the Department of Veterans Affairs (VA), in conjunction with the PGVCB. The plan mapped out the course to pursue the following overarching goals:

- Establish the nature and prevalence of symptoms, diagnosable illnesses, and unexplained conditions among Persian Gulf veterans in comparison to appropriate control groups.

- Identify the possible risk factors for any illnesses, beyond those expected to occur, among Persian Gulf veterans.

- Identify appropriate diagnostic tools, treatment methods, and prevention strategies for any excess illness conditions found among Persian Gulf veterans.

A key component of the 1995 *Working Plan* was an assessment of current knowledge and research on Gulf War veterans' illnesses. This assessment led to the identification of 19 research questions, which are included below, in the section on research priorities for 1996.

This assessment also led to the identification of the following issues for which significant gaps in knowledge existed in 1995:

1. Information on the prevalence of symptoms, illnesses, and/or diseases within other coalition forces.
2. Information on the prevalence of symptoms, illnesses, and/or diseases within indigenous populations within the Persian Gulf area including Saudi Arabia and Kuwait.
3. Information on the prevalence of adverse reproductive outcomes among Persian Gulf veterans and their spouses.
4. Simple and sensitive tests for *L. tropica* infection that could lead to quantification of the prevalence of *L. tropica* infection among Persian Gulf veterans.
5. Information on the long-term, cause-specific mortality among Persian Gulf veterans.

Each of these research issues has been addressed since 1995, as follows:

The US government has coordinated its research effort with the UK and Canada, as coalition partners in the Gulf War. The UK fielded the second largest force during the Gulf War, including 53,000 service members. The US DoD has funded epidemiological research in the UK, which has compared the health of British Gulf War veterans, Bosnia veterans, and non-deployed veterans (projects DoD-39, DoD-106, DoD-142, DoD-151). The results of the first and second phases of the three-phase British investigation have been published. (Unwin, et al., 1999; Ismail, et al., 1999; Hotopf, et al., 2000; Ismail, et al., 2000; Chalder, et al., 2001; Reid, et al., 2001; Unwin, et al., 2002; Hull, et al., 2002; Higgins, et al., 2002; Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002) In addition, a second large epidemiological study of a separate cohort of British Gulf War veterans has been published. (Cherry, et al., 2001a; Cherry, et al., 2001b)

The Canadian government has published a comprehensive study of the health of Canadian Gulf War veterans, compared to non-deployed veterans. (Goss Gilroy, 1998) Denmark also participated in the Gulf War as a coalition partner, primarily in the postwar period after April 1991. American scientists have collaborated with Danish scientists on a study of neuropsychological function in Danish veterans (project HHS-5). The French began an epidemiological study of their entire cohort of 25,000 Gulf War veterans in February 2002, and it will take two years.

1. Because the health status of Saudi Arabian soldiers had not been systematically addressed, a team of US researchers from

DoD and CDC started an epidemiology study of the Saudi Arabian National Guard in 1999 (DoD-120). The objective is to examine available computerized databases for unusual health trends, comparing soldiers who were stationed in a combat area in January 1991 (Al Khafji), with soldiers who were stationed in a non-combat area (Riyadh). Mortality rates are being compared, as are rates and causes of hospitalizations.

2. Nine projects include research objectives related to the prevalence of adverse reproductive outcomes among Gulf War veterans and their spouses. Four of these projects have been completed (HHS-4, DoD-1C, DoD-1G, VA-2A), and their results have been published. (Penman and Tarver, 1996; Cowan, et al., 1997; Araneta, et al., 1997; Araneta, et al., 2000; Kang, et al., 2001) The other five projects have been completed, but have not been published yet (VA-2C, VA-47, DoD-1D, DoD-35, DoD-44). In addition, DoD developed an ongoing, national surveillance system, the Birth Defects Registry, in 1998. (Bush, et al., 2001; Ryan, et al., 2001)

3. Eight projects have focused on the development of simple, sensitive tests for leishmaniasis that could lead to quantification of the prevalence of infection, as well as new treatment methods. Six of these projects have been completed and have led to several publications (VA-6E, VA-16, DoD-8A, DoD-8B, DoD-9, and DoD-38). Two of these projects are ongoing (VA-15 and DoD-95).

4. The long-term mortality of Gulf War veterans will be followed by VA indefinitely (project VA-1). Four publications have focused on the causes of mortality among American Gulf War veterans, compared to non-deployed veterans. (Helmkamp, 1994; Writer, et al., 1996; Kang and Bullman, 1996; Kang and Bullman, 2001) The major finding was that there was an increased mortality rate due to external causes among Gulf War veterans, in particular, motor vehicle accidents. To date, this is the only difference in mortality rates. The British also published a mortality study of Gulf War veterans and non-deployed veterans in the UK, and there were very similar results. (Macfarlane, et al., 2000)

B. RESEARCH PRIORITIES FOR 1996

In 1995 and 1996, the number of research programs investigating Gulf War veterans' illnesses increased substantially. Many research programs began to produce results. One major development in 1996 was the information about potential exposures to chemical weapons due to the demolitions at Khamisiyah. The addition of new research, results of ongoing research, and new information about potential exposures formed the basis of a new assessment of knowledge and research. This changed the context in which the research was conducted and necessitated a revision of the 1995 *Working Plan*. The 1996 report was entitled *A Working Plan for Research on Persian Gulf Veterans' Illnesses, First Revision*. (PGVCB, 1996b) This report identified three sets of research objectives: a) shorter-term objectives; b) long-term objectives; and c) a comprehensive list of 21 research questions.

a. Short-Term Objectives

Emerging findings from ongoing research in 1995 and 1996, and new factual information on the potential for chemical weapons exposure in southern Iraq in 1991 led to the following specific, near-term recommendations for additional research:

1. More longitudinal follow-up studies of the health of Persian Gulf veterans, including those with illnesses that are difficult to diagnose.
2. Critical peer review of models used to predict exposure concentrations of environmental pollution (such as the Kuwait oil well fires) and chemical warfare agents (such as the demolition of weapons storage sites at Khamisiyah in March 1991, and aerial bombing of chemical weapons facilities during the air war).
3. Assessment of the potential for clinical investigations of the health status of the service members in the vicinity of Khamisiyah when weapons bunker 73 and the storage pit were detonated in March 1991. If deemed possible, such clinical investigations should be carried out.

Each of these research issues has been addressed since 1996, as follows:

1. Five studies include longitudinal follow-up of Gulf War veterans, in Boston, New Orleans, New Jersey, Iowa, and the United Kingdom. These studies were described in detail in Section IV.C.4. of the *Annual Report for 1999*. (PGVCB, 2001) Funding was approved in 2002 to perform longitudinal follow-up of the survey participants of the VA National Health Survey (DoD-149).

2. Several publications have described the results of models of the oil well fire smoke and potential releases of chemical weapons, all of which have been peer reviewed. The modeling of environmental pollution released by the Kuwaiti oil well fires has been described in detail. (Office of the Special Assistant for Gulf War Illnesses (OSAGWI), 1998b; Spektor, 1998; OSAGWI, 2000b; OSAGWI, 2000c) The results of modeling of the potential release of chemical weapons, due to the demolitions at Khamisiyah in March 1991, have been reported by two agencies. (OSAGWI, 1997; CIA, 1997; OSAGWI, 2000f) The results of modeling of the potential release of chemical weapons, due to aerial bombing of facilities during the air war, have also been published by two agencies. (CIA, 1996; CIA, 2002; OSAGWI, 2000e) Only three sites that were bombed during the air war might have released chemical weapons-Muhammadiyat, Al Muthanna, and Ukhaydir. (OSAGWI, 2001b; OSAGWI, 2001f; OSAGWI, 2001e) The results of investigations about potential exposure of US troops to the oil well fires and to chemical weapons were summarized in Appendix C. of the *Annual Report to Congress for 2000*. (MVHCB, 2001a)

3. Three investigations have focused on the potential health effects among service members who were near Khamisiyah at the time of the demolitions in 1991 (DoD-1B, DoD-63, and DoD-69). The first two studies have been published. (Gray, et al., 1999c; McCauley, et al., 2002b; Shapiro, et al., 2002) In addition to these three projects, three other studies relevant to Khamisiyah have been outgrowths of other projects. These have evaluated mortality rates, clinical diagnoses, and self-reported symptoms (VA-1, DoD-94, and VA-4). The first two studies have been published. (Kang and Bullman, 2001; Smith, 2002b)

b. Long Term-Objectives

Additional research on health-related issues arising from the Gulf War experience, but with potential for more general applicability to future conflicts, was also recommended in 1996, including:

1. Investigation of the risk factors for the development of stress-related disorders including, but not limited to, post-traumatic stress disorder (PTSD).
2. Investigation of the risk factors responsible for the observed excess mortality due to external causes (e.g., motor vehicle accidents) in veterans of all wars and conflicts.
3. Exploration of the development of practical, sensitive, and specific biomarkers of exposure to chemical agents, including organophosphate nerve agents and vesicants such as sulfur mustard.
4. Toxicological and, where feasible, epidemiological research on the potential for long-term health effects resulting from low-level, sub-clinical exposures to chemical agents, particularly organophosphate agents such as sarin.
5. Development of a strategic plan for research into the potential long-term health consequences of exposure to low-levels of chemical warfare agents.

Each of these research issues has been addressed since 1996, as follows:

1. Many projects are focusing on the risk factors for the development of stress-related disorders, including post-traumatic stress disorder and major depression. Several studies that focused on stress-related disorders were published in 2002. (Gray, et al., 2002b; McCauley, et al., 2002b; Unwin, et al., 2002; Ismail, et al., 2002; David, et al., 2002; Barrett, et al., 2002; Orcutt, et al., 2002)

2. An increased risk for mortality due to external causes has been observed in veterans of both the Vietnam War and the Gulf War. One project is evaluating the risk

factors responsible for the observed increase in mortality due to motor vehicle accidents in Gulf War veterans (DoD-102). Another project (DoD-73) evaluated the risk factors for the significantly increased risk of unintentional injuries in Gulf War veterans, which resulted in an important report in 2000. (Bell, et al., 2000)

3. Eight projects are focusing on the development of sensitive, specific biomarkers of exposure to chemical agents, including organophosphate nerve agents and vesicants such as sulfur mustard. Three of these projects have been completed (VA-6D, VA-47, DoD-49), which resulted in several publications. In 2001 and 2002, five new projects were funded (DoD-135, DoD-136, DoD-137, DoD-138, DoD-152).

4. Twenty toxicological projects are focusing on the potential long-term health effects resulting from low-level exposures to organophosphate agents. Eleven of these projects are focusing on sarin. (Olson, et al., 1998; Wilson, et al., 1998; Wilson, et al., 2002; Spruit, et al., 2000; Henderson, et al., 2002; Conn, et al., 2002; Kalra, et al., 2002; Khan, et al., 2000; Jones, et al., 2000; Abdel-Rahman, et al., 2002; Abou-Donia, et al., 2002) Five epidemiological research projects are focusing on the potential long-term health effects resulting from low-level, subclinical nerve agent exposures. Three projects are focusing on possible sarin exposures due to the demolitions at Khamisiyah (DoD-1B, DoD-63, DoD-69). (Gray, et al., 1999c; McCauley, et al., 2002b; Shapiro, et al., 2002) Two projects are evaluating the long-term effects of sarin and other nerve agents on volunteers who participated in experiments at Aberdeen Proving Grounds in the 1950s to 1970s (DoD-116A/VA-63A, DoD-93).

5. A strategic research plan was developed, entitled "Effects of Low-Level Exposure to Chemical Warfare Agents: A Research Strategy." An interagency committee wrote it, including members from VA, DoD, CDC, and the Environmental Protection Agency (EPA). It was published in the *Annual Report to Congress for 1997*. (PGVCB, 1998a)

c. Comprehensive List of 21 Research Questions

In 1995, it was recommended that a contextual framework be provided for the results of completed and ongoing studies, to develop an approach for the interpretation of research results. In 1995, the PGVCB identified 19 major research questions, to which two additional questions were added in 1996. (PGVCB, 1996b) The comprehensive Gulf War research portfolio has addressed each of these 21 questions, and relevant results have been published on each one. A comprehensive assessment of the progress made on each of these 21 questions was provided in Appendix C of the *Annual Report to Congress for 2000*. (MVHCB, 2001a)

21 Research Questions Highlighted in the 1996 *A Working Plan for Research*

1. WHAT IS THE PREVALENCE OF SYMPTOMS/ILLNESSES IN THE PERSIAN GULF VETERAN POPULATION? HOW DOES THIS PREVALENCE COMPARE TO THAT IN AN APPROPRIATE CONTROL GROUP?

2. WHAT WAS THE OVERALL EXPOSURE OF TROOPS TO LEISHMANIA TROPICA?

3. WHAT WERE THE EXPOSURE CONCENTRATIONS TO VARIOUS PETROLEUM PRODUCTS, AND THEIR COMBUSTION PRODUCTS, IN TYPICAL USAGE DURING THE PERSIAN GULF CONFLICT?

4. WHAT WAS THE EXTENT OF EXPOSURE TO SPECIFIC OCCUPATIONAL/ENVIRONMENTAL HAZARDS KNOWN TO BE COMMON IN THE PERSIAN GULF VETERANS EXPERIENCE? WAS THIS EXPOSURE DIFFERENT FROM THAT OF AN APPROPRIATE CONTROL GROUP?

5. WHAT WERE THE POTENTIAL EXPOSURES OF TROOPS TO ORGANOPHOSPHORUS NERVE AGENT AND/OR SULFUR MUSTARD AS A RESULT OF ALLIED BOMBING AT MUHAMMADIYAT AND AL MUTHANNA, OR THE DEMOLITION OF A WEAPONS BUNKER AT KHAMISIYAH?

6. WHAT WAS THE EXTENT OF EXPOSURE TO CHEMICAL AGENT, OTHER THAN AT KHAMISIYAH, IRAQ, IN THE PERSIAN GULF AS A FUNCTION OF SPACE AND TIME?

7. WHAT WAS THE PREVALENCE OF PB USE AMONG PERSIAN GULF TROOPS?

8. WHAT WAS THE PREVALENCE OF VARIOUS PSYCHOPHYSIOLOGICAL STRESSORS AMONG GULF WAR VETERANS? IS THE PREVALENCE DIFFERENT FROM THAT OF AN APPROPRIATE CONTROL POPULATION?

9. ARE PERSIAN GULF VETERANS MORE LIKELY THAN AN APPROPRIATE COMPARISON GROUP TO EXPERIENCE NON-SPECIFIC SYMPTOMS AND SYMPTOM COMPLEXES?

10. DO PERSIAN GULF VETERANS HAVE A GREATER PREVALENCE OF ALTERED IMMUNE FUNCTION OR HOST DEFENSE WHEN COMPARED WITH AN APPROPRIATE CONTROL GROUP?

11. IS THERE A GREATER PREVALENCE OF BIRTH DEFECTS IN THE OFFSPRING OF PERSIAN GULF VETERANS THAN IN AN APPROPRIATE CONTROL POPULATION?

12. HAVE PERSIAN GULF VETERANS EXPERIENCED LOWER REPRODUCTIVE SUCCESS THAN AN APPROPRIATE CONTROL POPULATION?

13. IS THE PREVALENCE OF SEXUAL DYSFUNCTION GREATER AMONG PERSIAN GULF VETERANS THAN AMONG AN APPROPRIATE COMPARISON POPULATION?

14. DO GULF WAR VETERANS REPORT MORE PULMONARY SYMPTOMS, OR DIAGNOSES, THAN PERSONS IN APPROPRIATE CONTROL GROUPS?

15. DO GULF WAR VETERANS HAVE A SMALLER BASELINE LUNG FUNCTION IN COMPARISON TO AN APPROPRIATE CONTROL GROUP? DO GULF WAR VETERANS HAVE A GREATER DEGREE OF NON-SPECIFIC AIRWAY REACTIVITY IN COMPARISON TO AN APPROPRIATE CONTROL GROUP?

16. IS THERE A GREATER PREVALENCE OF ORGANIC NEUROPSYCHOLOGICAL AND NEUROLOGICAL DEFICITS IN PERSIAN GULF VETERANS COMPARED TO APPROPRIATE CONTROL POPULATIONS?

17. CAN SHORT-TERM, LOW-LEVEL EXPOSURES TO PYRIDOSTIGMINE BROMIDE, THE INSECT REPELLANT DEET, AND THE INSECTICIDE PERMETHRIN, ALONE OR IN COMBINATION, CAUSE SHORT-TERM AND/OR LONG-TERM NEUROLOGICAL EFFECTS?

18. DO PERSIAN GULF VETERANS HAVE A SIGNIFICANTLY HIGHER PREVALENCE OF PSYCHOLOGICAL SYMPTOMS AND/OR DIAGNOSES THAN DO MEMBERS OF AN APPROPRIATE CONTROL GROUP?

19. WHAT IS THE PREVALENCE OF LEISMANIASIS AND OTHER INFECTIOUS DISEASES IN THE GULF WAR VETERAN POPULATION?

20. DO GULF WAR VETERANS HAVE A GREATER RISK OF DEVELOPING CANCERS OF ANY TYPE WHEN COMPARED WITH AN APPROPRIATE CONTROL POPULATION?

21. ARE GULF WAR VETERANS EXPERIENCING A HIGHER MORTALITY RATE THAN THAT OF AN APPROPRIATE CONTROL POPULATION? ARE SPECIFIC CAUSES OF DEATH RELATED TO SERVICE IN THE PERSIAN GULF REGION?

C. RESEARCH PRIORITIES FOR 1998

In 1998, the PGVCB reevaluated the issue of research priorities. (PGVCB, 1999a) Key factors that guided the PGVCB in its discussions were recent research findings, the current breadth and depth of the research portfolio in key areas, and the availability of resources to develop needed new initiatives.

1. Research on Treatments for Gulf War Veterans' Illnesses

Some Gulf War veterans with unexplained illnesses are suffering from a complex of symptoms such as fatigue, musculoskeletal pain, and cognitive problems. These symptom complexes significantly overlap with other symptom complexes identified in the civilian population such as chronic fatigue syndrome (CFS) and fibromyalgia (FM). As with illnesses in Gulf War veterans, no clearly defined etiologic agent has been identified for CFS and FM.

The PGVCB concluded that experimental treatment methods that have been applied to persons with CFS or FM deserved further exploration in the context of Gulf War veterans' illnesses. Consequently, the PGVCB determined that the development of treatment protocols for unexplained illnesses was a research priority. In

1999, VA and DoD jointly began two major multi-site treatment trials. These were the Exercise Behavioral Therapy Trial (VA-62 and DoD-115) and the Antibiotic Treatment Trial (VA-55 and DoD-119). Details of these two trials were provided in Section IV.C.1. of the *Annual Report for 1999*. (PGVCB, 2001) Total investment by VA and DoD for these two trials was more than $9.6 million and $5.6 million, respectively. These treatment trials have been completed and will be published in 2003.

In 1998, VA funded five treatment demonstration projects (VA-56, VA-57, VA-58, VA-59, and VA-60). A key goal was to test new and innovative clinical approaches for treating Gulf War veterans who have medically unexplained symptoms. The primary sources of patients were the Gulf War Registries located at eight VA Medical Centers (Birmingham, Boston and Brockton, Cincinnati and Cleveland, Portland and Seattle, and Tampa). Some of the approaches included: case management to improve the treatment of medical and psychiatric diseases and/or patient satisfaction; evaluation of the impact of comorbidity on effectiveness of treatment; and use of a multidisciplinary approach to treatment, with integration of primary care medicine and behavioral medicine/psychiatry.

These projects were completed in 2000, and results of some of the five projects have been published. (Baker, et al., 2001; Richardson, et al., 2001; Richardson, et al., 2002; Everson, et al., 2002) The final progress reports for all five projects are accessible at www.va.gov/health/environ/persgulf.htm

VA funded an Institute of Medicine study to identify effective treatments for health problems in Gulf War veterans. This study started in 1999, and it was published in July 2001. (IOM, 2001) This IOM study focused on seven diagnoses that are prevalent in Gulf War veterans: chronic fatigue syndrome, depression, fibromyalgia, headache, irritable bowel syndrome, panic disorder, and PTSD. The IOM study was described in the *Annual Report for 2001*. (MVHCB, 2002)

In 2001 and 2002, three relevant studies were funded to improve the treatment of diseases that are prevalent in veterans, and that were specifically addressed the 2001 IOM book. (IOM, 2001) In 2001, VA and DoD jointly funded a treatment trial for PTSD in women active-duty personnel and veterans (VA-74/DoD-125). This study was described in the *Annual Report for 2001*. (MVHCB, 2002) In 2002, VA funded two studies designed to improve the treatment of depression (VA-86 and VA-87).

2. Longitudinal Follow-Up for Gulf War Veterans' Illnesses

The PGVCB concluded that research approaches to determine the long-term health of veterans are a high priority. Several research projects funded by the Federal Government have longitudinal components built into them. These projects are directed toward understanding the progress of Gulf War veterans' illnesses over time. In 2002, there were five studies that included longitudinal follow-up, in Boston, New Orleans, East Orange, New Jersey, Iowa, and the United Kingdom. These studies were described in detail in Section IV.C.4. of the *Annual Report for 1999*. (PGVCB, 2001) Preliminary results of these follow-up studies were published in the *Proceedings of the 2001 Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research*. (MVHCB, 2001b) In addition, funding was approved in 2002 to perform follow-up of the participants of the VA National Survey (DoD-149).

The scientists in Boston and New Orleans have studied their cohorts four times. The British scientists have studied their cohort three times, and the Iowa and New Jersey scientists have studied their cohorts twice. Results for follow-up of the Boston cohort of veterans at Times 2, 3, and 4 have been published. (Time 2: Wolfe, et al., 1996; Wolfe, et al., 1998; Wolfe, et al., 1999a; Wagner, et al., 2000; King, et al., 2000; Sharkansky, et al., 2000; Erickson, et al., 2001; Orcutt, et al., 2002; Time 3: Proctor, et al., 1998; Wolfe, et al., 1999b; Proctor, et al., 2001a; Proctor, et al., 2001b; White, et al., 2001; Time 4: Wolfe, et al., 2002) Results for follow-up of the New Orleans cohort at Times 2 and 3 have been published. (Time 2: Sutker, et al., 1994a; Sutker, et al., 1994b; Benotsch, et al., 2000; Time 3: Proctor, et al., 1998; Wolfe, et al., 1999b; White, et al., 2001) Results for follow-up of the British cohort at Time 2 have been published. (Time 2: Ismail, et al., 2002; David, et al., 2002; Sharief, et al., 2002; Higgins, et al., 2002)

3. Disease Prevention

The substantial proportion of veterans who have reported ill health following deployment to the Gulf War represents a significant level of morbidity that might be preventable. To ensure that future health problems in future deployments can be prevented, the PGVCB has endorsed future research aimed generally at disease prevention, and more specifically at prevention of stress-related symptoms and conditions. This is consistent with the recommendations of a number of oversight committees. The Federal investment focusing on the pathophysiology of stress-related illnesses has markedly increased, and now there are more than 100 projects with a primary or secondary focus on Brain and Nervous System Function. This investment in improved understanding of the pathophysiology of stress-related illnesses should lead to better methods of disease prevention and treatment.

4. Improved Hazard Assessment

The Presidential Review Directive-5 recognized that the ability to better anticipate environmental and occupational hazards prior to deployments could potentially reduce morbidity associated with unintended or unanticipated exposures. (NSTC, 1998; Joint Chiefs of Staff, 1999) The PGVCB, in conjunction with the working groups that developed the PRD-5, recommended enhanced research efforts aimed at improving methods of hazard identification and risk assessment for environmental and occupational hazards. Such research efforts should emphasize the reality of complex multiple exposures to more than one hazardous agent.

In 1998, the DoD established new funding for programmed research. The purpose of this program element funding, explicitly put into DoD's budget requests, was to address issues of Gulf War veterans' illnesses, which may also be of concern in future deployments. The funding is approximately $20 million per year for fiscal years 1999 to 2002, and about $10 million per year thereafter. The overall objective is to enhance force health protection in future deployments. The program is guided by a tri-service DoD panel and is coordinated with the Deployment Health Working Group. Specific research areas in 1999 to 2002 have included:

1. prevention and treatment of persistent stress symptoms;
2. methods to assess health hazards from toxic chemicals and mixtures and to monitor exposures;
3. improved safety assessments of medical materiel, including potential interactions in operational environments; and
4. epidemiological studies to continue long-term follow-up of Gulf War veterans and to improve health status monitoring in future deployments.

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Appendix A

Federally Funded Research Projects

Appendix A 1

Project Index By Department

DEPARTMENT OF DEFENSE PROJECTS

DoD-1	Naval Health Study Program
DoD-1 A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; A Study of Symptoms Among 1500 Seabees
DoD-1 B	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not.
DoD-1 C	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among Gulf War veterans and other active-duty personnel
DoD-1 D	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in Gulf War Veterans
DoD-1 E	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study
DoD-1 F	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: GWV vs. NDV
DoD-1G	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans
DoD-2	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET
DoD-4	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey
DoD-7 A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling
DoD-7 B	Carcinogenicity of Depleted Uranium Fragments
DoD-8 A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)
DoD-8 B	Development of a Leishmania Skin Test Antigen (LSTA)
DoD-9	Identification of the Genetic Factors Which Control Tropism in Leishmania
DoD-10	Pyridostigmine Synergistic Toxicity Study

DoD-11	Male/Female Differential Tolerances to Pyridostigmine Bromide
DoD-13	Effects of Persian Gulf War Service on Military Working Dogs
DoD-14	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry
DoD-15	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm
DoD-16	Kuwait Oil Fire Health Risk Assessment
DoD-17	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning
DoD-18	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)
DoD-19	Persian Gulf Veterans Health Tracking System
DoD-21	Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm
DoD-22	Chronic Organophosphorus Exposure and Cognition
DoD-23	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families
DoD-30	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study
DoD-31	Dysregulation of the Stress Response in the Persian Gulf Syndrome
DoD-32	Neuropsychological Functioning in Persian Gulf Era Veterans
DoD-33	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
DoD-34	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents
DoD-35	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.
DoD-36	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms
DoD-37	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats

DoD-38	Diagnostic Antigens of Leishmania tropica
DoD-39	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces
DoD-40	Psychological and Neurobiological Consequences of the Gulf War Experience
DoD-41	Evaluation of Muscle Function in Persian Gulf Veterans
DoD-42	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment
DoD-44	Investigation of Seminal Plasma Hypersensitivity Reactions
DoD-45	Air Force Women's Health Surveillance Study
DoD-46	Exploratory Data Analysis with the CCEP Database
DoD-47	Study of Mycoplasmal Infections in Gulf War Veterans
DoD-48	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups
DoD-49	Diagnosis and Dosemitry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts
DoD-50	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways
DoD-51	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
DoD-52	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans
DoD-53	Long-Term Effects of Subclinical Exposures to Sarin
DoD-54	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure
DoD-55	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects
DoD-56	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine
DoD-57	Physiologic Effects of Stress in Gulf War Veterans

DoD-58	Illness Among Persian Gulf War Veterans: Case Validation Studies
DoD-59	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis
DoD-60	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness
DoD-61	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid
DoD-62	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice
DoD-63	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity
DoD-64	Individual Differences in Neurobehavioral Effects of Pyridostigmine
DoD-65	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment
DoD-66	Testing for mycoplasmal infection replicability of nucleoprotein gene tracking and forensic polymerase chain reaction
DoD-67	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
DoD-69	Five Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents
DoD-70	War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes
DoD-71	A Comparison of Post Deployment Hospitalization Between Vietnam and Gulf War Veterans
DoD-72	Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
DoD-73	Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes
DoD-74	Relationship of Stress Exposures to Health in Gulf War Veterans
DoD-75	Toxic Interactions of Prophylactic Drugs and Pesticides
DoD-76	Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel
DoD-77	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War

DoD-78	Experimental Models of Gulf War Syndrome
DoD-79	Time Course of Stress-induced Impairment of Blood Brain Barrier
DoD-80	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells
DoD-81	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress
DoD-82	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs
DoD-83	Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism
DoD-84	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD
DoD-85	CNS Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms
DoD-86	Effects of Combat Stress on Structure and Function of the Hippocampus
DoD-87	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs
DoD-88	Clinical Relevance of Novel Immunological Markers in PTSD
DoD-89	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder
DoD-90	SPECT Benzodiazepine Receptor and MR Imaging in PTSD
DoD-91	Neurological and Circadian Substrates of PTSD-like Behaviors
DoD-92	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder
DoD-93	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up
DoD-94	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans
DoD-95	Development of Diagnostic tools and alternative treatment drugs for Leishmania
DoD-96	Deployment Health Center

DoD-97	Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis
DoD-98	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans
DoD-99	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations
DoD-100	Antibodies to Squalene
DoD-101	Mechanisms in Chronic Multisymptom Illnesses
DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans
DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals
DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome
DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala
DoD-106	The Role of Th1/Th2 cytokine balance in Gulf War-related illness
DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity
DoD-108	Health Status of Current National Guard Members
DoD-109	Disordered Responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms
DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy
DoD-111	Autonomic Dysfunction in Gulf War Veterans
DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?
DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans

DoD-115 A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)

DoD-116 VA/DoD Core Funding of the Medical Follow-Up Agency (See also VA-63; formerly VA-DoD-2D/2V)

DoD-116 A Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA)

DoD-116 B Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)

DoD-117 Patterns of Pre-Persian Gulf War Illness and Health Care Seeking

DoD-118 An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also VA-61)

DoD-119 Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also VA-55)

DoD-120 Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents

DoD-121 Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel During Pregnancy and Offspring Development

DoD-122 Carcinogenic Potential of Depleted Uranium and Tungsten Alloys

DoD-123 Immunotoxicity of Depleted Uranium and Heavy Metal Tungsten Alloys

DoD-124 Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin

DoD-125 A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)

DoD-126 Blood-Brain Barrier Transport of Uranium

DoD-127 Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man

DoD-128 Multifactorial Assessment of Depleted Uranium Neurotoxicity

DoD-129 Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness

DoD-130 Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents

DoD-131 Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses

DoD-132 Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness

DoD-133 Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome

DoD-134 Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin

DoD-135 Biochemical Markers for Exposure to Low Doses of Organophosphorous Exposure

DoD-136 A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure

DoD-137 Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin

DoD-138 Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents

DoD-139 Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses

DoD-140 US Department of Defense Surveillance for Neoplasms in Infancy

DoD-141 Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans

DoD-142 Illnesses Among Persian Gulf War Veterans: Case Validation Studies (Iowa / Great Britain)

DoD-143 Millennium Cohort Study (See also VA-78)

DoD-144 Psychological Health Screening: Methods and Metrics for Deployed Forces

DoD-145 Early Intervention Research Program to Enhance Soldier Resilience

DoD-147 Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications

DoD-149 Longitudinal Health Study of Gulf War Veterans

DoD-150 Validation Study of Gulf War Deployment Files

DoD-151 Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War Veterans

DoD-152 Characterization of Intracellular Signaling Pathways Activated by Nerve Agents

DoD-153 Gulf War Illness Research

DoD-154 Prospective Assestment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also VA-88)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PROJECTS

HHS-1	Health Assessment of Persian Gulf War Veterans from Iowa
HHS-2	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18
HHS-3	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires
HHS-4	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans In Mississippi
HHS-5	Cognitive Function and Symptom Patterns in Persian Gulf Veterans
HHS-6	Defining Gulf War Illness
HHS-7	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
HHS-8	Strategy to Identify Non-Additive Response to Chemical Mixtures
HHS-9	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
HHS-10	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
HHS-11	Deployment to the Gulf War and the Subsequent Development of Cancer

DEPARTMENT OF VETERANS AFFAIRS PROJECTS

VA-1	Mortality Follow-up Study of Persian Gulf Veterans
VA-2	National Health Survey of Persian Gulf Veterans
VA-2 A	VA National Survey of Persian Gulf Veterans - Phase I
VA-2 B	VA National Survey of Persian Gulf Veterans - Phase II
VA-2 C	VA National Survey of Persian Gulf Veterans - Phase III
VA-3	Use of Roster of Veterans Who Served in Persian Gulf Area
VA-4	Boston Environmental Hazards Research Center Program
VA-4 A	Evaluation of Cognitive Functioning of Persian Gulf Veterans
VA-4 B	Evaluation of Neurological Functioning in Persian Gulf Veterans
VA-4 C	Gulf War And Vietnam Veterans Cancer Incidence Surveillance
VA-4 D	Evaluation of Respiratory Dysfunction Among Gulf War Veterans
VA-4 E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility
VA-4 F	Validity of Computerized Tests
VA-5	East Orange Environmental Hazards Research Center Program
VA-5 A	Health and Exposure Survey of Persian Gulf Veterans
VA-5 B	Physiological and Psychological Assessments of Persian Gulf Veterans
VA-5 C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans
VA-5 D	Effects of Genetics and Stress on Responses to Environmental Toxins

VA-6	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research
VA-6 A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)
VA-6 B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
VA-6 C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)
VA-6 D	DNA Damage from Chemical Agents and Its Repair (Project IV)
VA-6 E	Clinical and Epidemiology Leishmania Research
VA-7	Desert Storm Reunion Survey
VA-8	Psychological Test Data of Gulf War Veterans Over Time
VA-9	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems
VA-10	Memory and Attention in PTSD
VA-11	Neuropsychological Functioning in Veterans
VA-12	Psychological Assessment of Operation Desert Storm Returnees
VA-13	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study
VA-15	Vaccine-Mediated Immunity Against Leishmaniasis
VA-16	Protective Immunity in Experimental Visceral Leishmaniasis
VA-17	Immunological Evaluation of Persian Gulf Veterans
VA-18	Chronic Gastrointestinal Illness in Persian Gulf Veterans
VA-20	Psychological Adjustment in Operation Desert Shield/Storm Veterans
VA-21	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS

VA-36	Stress Symptoms and Their Causal Attribution in Desert Storm Veterans
VA-40	Musculoskeletal Symptoms in Gulf War Syndrome
VA-46	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder
VA-47	Retrospective Verification of Mustard Gas Exposure
VA-48	Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance
VA-49	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
VA-50	Neuropsychological findings in a sample of Operation Desert Storm veterans
VA-51	Psychobiological Assessment of Desert Storm Veterans
VA-53	Spouses and Children Program
VA-54	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress
VA-55	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also DoD-119)
VA-56	Birmingham's Gulf War Veterans' Illness Demonstration Clinic (13)
VA-57	Case Management and Residential Rehabilitation for Persian Gulf War Veterans (13)
VA-58	Implementation and Evaluation of Gulf War Veterans' Demonstration Project (13)
VA-59	Demonstration Treatment Program for Gulf War Veterans With Unexplained Physical Symptoms (13)
VA-60	Identification and Management of Sleep Disorders in Gulf War Veterans
VA-61	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also DoD-118)
VA-62	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
VA-63	VA/DoD Core funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)

VA-63 A	Follow-Up Investigation of troops exposed to nerve agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)
VA-63 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)
VA-64	Boston Environmental Hazards Research Center
VA-64 A	Functional Neuroimaging in Lead Exposed Adults
VA-64 B	Quantification and Validation of Structure-Function relationships through visuospatial test performance
VA-64 C	Development of a structured neurotoxicant assessment checklist (SNAC) for clinical use in veteran populations
VA-65	San Antonio Environmental Hazards Research Center
VA-65 A	Does a variant of the human SOD2 gene increase sensitivity to hazards?
VA-65 B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress
VA-65 C	The importance of hydrogen peroxide detoxification in cellular protection
VA-65 D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental hazards?
VA-66	Physiological Responding in Posttraumatic Stress Disorder
VA-67	Olfactory Functioning in Gulf War Veterans
VA-68	Family Study of Fibromyalgia
VA-69	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans
VA-70	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8
VA-71	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
VA-72	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
VA-73	Pain Sensitivity in Gulf War Veterans with Medically Unexplained Musculoskeletal Pain

VA-74	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
VA-75	ALS and Veterans: Are Veterans at Increased Risk?
VA-76	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD
VA-77	HPA Axis Reactivity in Men and Women with Chronic PTSD
VA-78	Millenium Cohort Study (See also DoD-143)
VA-79	VHA Clinicians and Bioterror Events: Interactive Web-based Learning
VA-80	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
VA-81	Stress, Pro-Inflammatory Cytokines and Coping Behavior
VA-82	Pituitary Adrenal Function in People with Fatiguing Illness
VA-83	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls
VA-84	Neurobiology of Severe Psychological Trauma in Women
VA-85	Associative Learning in Veterans with and without Combat Experience
VA-86	A Clinical Trial of Magnetic Stimulation in Depression
VA-87	Improving Outcomes of Depression in Primary Care
VA-88	Prospective Assestment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also DoD-154)
VA-89	National Registry of Veterans with Amyotrophic Lateral Sclerosis

Appendix A 2

Project List by Research Focus Areas

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Brain & Nervous System				
Clinical			DoD-101	Mechanisms in Chronic Multisymptom Illnesses
Clinical			DoD-111	Autonomic Dysfunction in Gulf War Veterans
Clinical			DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses
Clinical			DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat
Clinical			DoD-86	Effects of Combat Stress on Structure and Function of the Hippocampus
Clinical			VA-12	Psychological Assessment of Operation Desert Storm Returnees
Clinical			VA-13	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot
Clinical			VA-20	Psychological Adjustment in Operation Desert Shield/Storm Veterans
Clinical			VA-21	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in
Clinical			VA-50	Neuropsychological findings in a sample of Operation Desert Storm veterans
Clinical			VA-64 B	Quantification and Validation of Structure-Function relationships through visuospatial test performance
Clinical			VA-66	Physiological Responding in Posttraumatic Stress Disorder
Clinical			VA-67	Olfactory Functioning in Gulf War Veterans
Clinical			VA-69	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans

Major Focus Area / Research Type	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Brain & Nervous System				
Clinical			VA-71	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
Clinical			VA-73	Pain Sensitivity in Gulf War Veterans with Medically Unexplained Musculoskeletal Pain
Clinical			VA-76	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD
Clinical			VA-77	HPA Axis Reactivity in Men and Women with Chronic PTSD
Clinical			VA-83	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls
Clinical			VA-84	Neurobiology of Severe Psychological Trauma in Women
Clinical			VA-85	Associative Learning in Veterans with and without Combat
Clinical	Chemical Weapons		DoD-63	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity
Clinical	Diagnosis		DoD-147	Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications
Clinical	Diagnosis		DoD-32	Neuropsychological Functioning in Persian Gulf Era Veterans
Clinical	Diagnosis		VA-4 F	Validity of Computerized Tests
Clinical	Environmental Toxicology		VA-64 A	Functional Neuroimaging in Lead Exposed Adults
Clinical	Prevention	History of Alcoholism	DoD-83	Risk for Stress-related Substance Abuse: the Effects of Family
Clinical	Symptoms & General Health		DoD-36	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms

Major Focus Area / *Research Type*	Primary Focus Area: Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Brain & Nervous System				
Clinical	Symptoms & General Health		DoD-40	Psychological and Neurobiological Consequences of the Gulf War Experience
Clinical	Symptoms & General Health		DoD-41	Evaluation of Muscle Function in Persian Gulf Veterans
Clinical	Symptoms & General Health		DoD-84	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD
Clinical	Symptoms & General Health		DoD-89	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder
Clinical	Symptoms & General Health		HHS-5	Cognitive Function and Symptom Patterns in Persian Gulf Veterans
Clinical	Symptoms & General Health		VA-10	Memory and Attention in PTSD
Clinical	Symptoms & General Health		VA-11	Neuropsychological Functioning in Veterans
Clinical	Symptoms & General Health		VA-4 A	Evaluation of Cognitive Functioning of Persian Gulf Veterans
Clinical	Symptoms & General Health		VA-4 B	Evaluation of Neurological Functioning in Persian Gulf
Clinical	Symptoms & General Health		VA-51	Psychobiological Assessment of Desert Storm Veterans
Clinical	Symptoms & General Health		VA-54	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress
Clinical	Symptoms & General Health		VA-6 A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)
Clinical	Symptoms &	General Health	VA-7	Desert Storm Reunion Survey
Clinical	Symptoms & General Health		VA-9	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Brain & Nervous System				
Clinical	Symptoms & General Health	Diagnosis	DoD-31	Dysregulation of the Stress Response in the Persian Gulf Syndrome
Clinical	Symptoms & General Health	Diagnosis	DoD-67	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
Clinical	Symptoms & General Health	Environmental Toxicology	VA-5 C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans
Clinical	Symptoms and General Health		DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome
Clinical	Symptoms and General Health		DoD-153	Gulf War Illness Research
Clinical	Treatment		DoD-90	SPECT Benzodiazepine Receptor and MR Imaging in PTSD
Clinical	Treatment		VA-89	National Registry of Veterans with Amyotrophic Lateral Sclerosis
Clinical	Treatment	Symptoms & General Health	DoD-85	CNS Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms
Epidemiology			DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans
Epidemiology			DoD-118	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also
Epidemiology			DoD-82	Feasibility of Developing a Registry of PTSD Affected Veteran
Epidemiology			VA-36	Stress Symptoms and Their Causal Attribution in Desert Storm
Epidemiology			VA-61	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also
Epidemiology			VA-64	Boston Environmental Hazards Research Center

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Brain & Nervous System				
Epidemiology			VA-72	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
Epidemiology			VA-75	ALS and Veterans: Are Veterans at Increased Risk?
Epidemiology	Prevention		DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces
Epidemiology	Prevention		DoD-87	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life
Epidemiology	Symptoms & General Health		DoD-23	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families
Epidemiology	Symptoms & General Health		DoD-52	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans
Epidemiology	Symptoms & General Health		VA-68	Family Study of Fibromyalgia
Epidemiology	Symptoms and General Health		DoD-154	Prospective Assestment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military
Epidemiology	Symptoms and General Health		VA-88	Prospective Assestment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military
Mechanistic			DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala
Mechanistic			DoD-80	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells
Mechanistic			DoD-91	Neurological and Circadian Substrates of PTSD-like Behaviors

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Brain & Nervous System				
Mechanistic			DoD-92	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder
Mechanistic			VA-81	Stress, Pro-Inflammatory Cytokines and Coping Behavior
Chemical Weapons				
Clinical	Diagnosis		VA-47	Retrospective Verification of Mustard Gas Exposure
Clinical	Pyridostigmine Bromide	Prevention	DoD-60	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness
Development	Diagnosis		DoD-49	Diagnosis and Dosemitry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein
Epidemiology			DoD-116 A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA)
Epidemiology			VA-63 A	Follow-Up Investigation of troops exposed to nerve agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)
Epidemiology	Symptoms & General Health		DoD-69	Five Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents
Epidemiology	Symptoms & General Health		DoD-93	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up
Mechanistic			DoD-137	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Chemical Weapons				
Mechanistic			DoD-50	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways
Mechanistic	Brain & Nervous System		DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents
Mechanistic	Brain & Nervous System		DoD-53	Long-Term Effects of Subclinical Exposures to Sarin
Mechanistic	Diagnosis		VA-6 D	DNA Damage from Chemical Agents and Its Repair (Project IV)
Mechanistic	Environmental Toxicology		DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorous Exposure
Mechanistic	Environmental Toxicology		DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure
Mechanistic	Environmental Toxicology		DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
Mechanistic	Prevention		DoD-51	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
Mechanistic	Pyridostigmine Bromide	Brain & Nervous System	DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
Depleted Uranium				
Mechanistic			DoD-126	Blood-Brain Barrier Transport of Uranium
Mechanistic			DoD-127	Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man
Mechanistic			DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity

Major Focus Area / *Research Type*	Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Chemical Weapons				
Mechanistic			DoD-129	Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness
Mechanistic			DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents
Mechanistic	Environmental Toxicology		DoD-7 A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling
Mechanistic	Environmental Toxicology		DoD-7 B	Carcinogenicity of Depleted Uranium Fragments
Depleted Uranium				
Mechanistic	Immune Function		DoD-123	Immunotoxicity of Depleted Uranium and Heavy Metal
Mechanistic	Reproductive Health		DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel During Pregnancy and Offspring Development
Mechanistic	Symptoms & General Health		DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys
Diagnosis				
Clinical			DoD-47	Study of Mycoplasmal Infections in Gulf War Veterans
Development			DoD-100	Antibodies to Squalene
Development			DoD-66	Testing for mycoplasmal infection replicability of nucleoprotein gene tracking and forensic polymerase chain reaction
Development			DoD-97	Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis

Major Focus Area / Research Type	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Environmental Toxicology				
Clinical	Brain & Nervous System	Interactions	VA-48	Cross-Sensitization as a CNS Model for Gulf War Chemical
Clinical	Diagnosis		VA-64 C	Development of a structured neurotoxicant assessment checklist (SNAC) for clinical use in veteran populations
Clinical	Symptoms & General Health		VA-4 D	Evaluation of Respiratory Dysfunction Among Gulf War Veterans
Development			DoD-16	Kuwait Oil Fire Health Risk Assessment
Development			DoD-18	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)
Development			DoD-19	Persian Gulf Veterans Health Tracking System
Development	Interactions		DoD-34	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents
Epidemiology			DoD-13	Effects of Persian Gulf War Service on Military Working Dogs
Mechanistic			DoD-134	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin
Mechanistic			VA-65	San Antonio Environmental Hazards Research Center
Mechanistic			VA-65 A	Does a variant of the human SOD2 gene increase sensitivity to
Mechanistic			VA-65 B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress
Mechanistic			VA-65 C	The importance of hydrogen peroxide detoxification in cellular protection
Mechanistic			VA-65 D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental hazards?

Major Focus Area / *Research Type*	Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Environmental Toxicology				
Mechanistic	Brain & Nervous System	Chemical Weapons	DoD-22	Chronic Organophosphorus Exposure and Cognition
Mechanistic	Prevention		HHS-3	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires
Mechanistic	Prevention		VA-4 E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility
Immune Function				
Clinical			DoD-106	The Role of Th1/Th2 cytokine balance in Gulf War-related illness
Clinical			DoD-48	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups
Clinical	Brain & Nervous System		DoD-88	Clinical Relevance of Novel Immunological Markers in PTSD
Clinical	Symptoms & General Health		VA-17	Immunological Evaluation of Persian Gulf Veterans
Clinical	Symptoms & General Health		VA-6 B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
Mechanistic			DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War Veterans
Mechanistic	Interactions	Environmental Toxicology	HHS-7	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
Mechanistic	Pyridostigmine Bromide	Interactions	DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?
Interactions				
Clinical	Pyridostigmine Bromide		DoD-124	Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin

Major Focus Area				Primary Focus Area
Research Type	Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Immune Function				
Development	Environmental Toxicology		HHS-8	Strategy to Identify Non-Additive Response to Chemical Mixtures
Mechanistic	Brain & Nervous System	Chemical Weapons	DoD-54	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure
Mechanistic	Chemical Weapons	Brain & Nervous System	DoD-72	Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
Mechanistic	Chemical Weapons	Brain & Nervous System	DoD-78	Experimental Models of Gulf War Syndrome
Mechanistic	Chemical Weapons	Pyridostigmine Bromide	DoD-55	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects
Mechanistic	Chemical Weapons	Pyridostigmine Bromide	DoD-56	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine
Mechanistic	Chemical Weapons	Pyridostigmine Bromide	DoD-61	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid
Mechanistic	Chemical Weapons	Pyridostigmine Bromide	DoD-62	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice
Mechanistic	Environmental Toxicology		DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals
Mechanistic	Immune Function	Pyridostigmine Bromide	DoD-81	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and
Mechanistic	Pyridostigmine Bromide		DoD-77	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War
Mechanistic	Pyridostigmine Bromide	Brain & Nervous System	DoD-2	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET
Mechanistic	Pyridostigmine Bromide	Brain & Nervous System	DoD-37	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Interactions				
Mechanistic	Pyridostigmine Bromide	Brain & Nervous System	DoD-75	Toxic Interactions of Prophylactic Drugs and Pesticides
Mechanistic	Pyridostigmine Bromide	Immune Function	DoD-76	Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel
Leishmaniasis				
Clinical	Diagnosis	Treatment	VA-6 E	Clinical and Epidemiology Leishmania Research
Development	Diagnosis		DoD-38	Diagnostic Antigens of Leishmania tropica
Development	Diagnosis		DoD-8 A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)
Development	Diagnosis		DoD-8 B	Development of a Leishmania Skin Test Antigen (LSTA)
Development	Diagnosis	Treatment	DoD-95	Development of Diagnostic tools and alternative treatment drugs for Leishmania
Mechanistic	Prevention		VA-15	Vaccine-Mediated Immunity Against Leishmaniasis
Mechanistic	Prevention		VA-16	Protective Immunity in Experimental Visceral
Mechanistic	Treatment		DoD-9	Identification of the Genetic Factors Which Control Tropism in Leishmania
Mortality				
Epidemiology			DoD-15	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm
Epidemiology			VA-1	Mortality Follow-up Study of Persian Gulf Veterans
Epidemiology	Prevention		DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans
Clinical	Diagnosis	Treatment	VA-79	VHA Clinicians and Bioterror Events: Interactive Web-based Learning

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Prevention				
Epidemiology			DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy
Epidemiology			HHS-9	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
Epidemiology	Symptoms and General Health		DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy
Epidemiology	Treatment		HHS-10	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
Epidemiology	Treatment	Brain & Nervous System	DoD-145	Early Intervention Research Program to Enhance Soldier Resilience
Pyridostigmine Bromide				
Clinical			DoD-11	Male/Female Differential Tolerances to Pyridostigmine
Clinical	Brain & Nervous System	Prevention	DoD-64	Individual Differences in Neurobehavioral Effects of Pyridostigmine
Epidemiology			DoD-17	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning
Epidemiology	Prevention		DoD-21	Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm
Mechanistic	Brain & Nervous System		DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity
Mechanistic	Brain & Nervous System		DoD-59	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Pyridostigmine Bromide				
Mechanistic	Brain & Nervous System		DoD-79	Time Course of Stress-induced Impairment of Blood Brain Barrier
Mechanistic	Brain & Nervous System		VA-49	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
Mechanistic	Brain & Nervous System	Interactions	VA-80	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment
Mechanistic	Environmental Toxicology		VA-6 C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)
Mechanistic	Interactions		DoD-10	Pyridostigmine Synergistic Toxicity Study
Mechanistic	Interactions		DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses
Mechanistic	Interactions		VA-5 D	Effects of Genetics and Stress on Responses to Environmental
Mechanistic	Prevention		DoD-33	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
Reproductive Health				
Clinical			VA-53	Spouses and Children Program
Clinical	Symptoms & General Health	Immune Function	DoD-44	Investigation of Seminal Plasma Hypersensitivity Reactions
Epidemiology			DoD-1 C	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among Gulf War veterans and other active-duty
Epidemiology			DoD-1 D	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in Gulf War

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Reproductive Health				
Epidemiology			DoD-1G	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans
Epidemiology			DoD-35	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.
Epidemiology			HHS-4	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans In Mississippi
Symptoms & General Health				
Clinical			DoD-1 A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; A Study of Symptoms Among 1500 Seabees
Clinical			DoD-65	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment
Clinical			VA-18	Chronic Gastrointestinal Illness in Persian Gulf Veterans
Clinical			VA-40	Musculoskeletal Symptoms in Gulf War Syndrome
Clinical	Brain & Nervous System		DoD-57	Physiologic Effects of Stress in Gulf War Veterans
Clinical	Brain & Nervous System		DoD-58	Illness Among Persian Gulf War Veterans: Case Validation Studies
Clinical	Brain & Nervous System		VA-4Core	Boston Environmental Hazards Research Center Program
Clinical	Brain & Nervous System		VA-5 B	Physiological and Psychological Assessments of Persian Gulf Veterans

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Symptoms & General Health				
Clinical	Brain & Nervous System		VA-5 Core	East Orange Environmental Hazards Research Center Program
Clinical	Brain & Nervous System		VA-8	Psychological Test Data of Gulf War Veterans Over Time
Clinical	Brain & Nervous System	Reproductive Health	DoD-45	Air Force Women's Health Surveillance Study
Clinical	Brain and Nervous System		VA-82	Pituitary Adrenal Function in People with Fatiguing Illness
Clinical	Diagnosis		DoD-109	Disordered Responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms
Clinical	Immune Function	Brain & Nervous System	DoD-42	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment
Epidemiology			DoD-1 B	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not.
Epidemiology			DoD-1 E	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study
Epidemiology			DoD-1 F	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: GWV vs. NDV
Epidemiology			DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome

Major Focus Area / Research Type	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Symptoms & General Health				
Epidemiology			DoD-116 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)
Epidemiology			DoD-120	Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents
Epidemiology			DoD-14	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry
Epidemiology			DoD-39	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces
Epidemiology			DoD-4	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey
Epidemiology			DoD-46	Exploratory Data Analysis with the CCEP Database
Epidemiology			DoD-70	War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes
Epidemiology			DoD-71	A Comparison of Post Deployment Hospitalization Between Vietnam and Gulf War Veterans
Epidemiology			DoD-73	Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes
Epidemiology			DoD-74	Relationship of Stress Exposures to Health in Gulf War Veterans
Epidemiology			DoD-94	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans
Epidemiology			DoD-98	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans

Major Focus Area / Research Type	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Symptoms & General Health				
Epidemiology			DoD-99	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations
Epidemiology			HHS-1	Health Assessment of Persian Gulf War Veterans from Iowa
Epidemiology			HHS-11	Deployment to the Gulf War and the Subsequent Development of
Epidemiology			HHS-6	Defining Gulf War Illness
Epidemiology			VA-2	National Health Survey of Persian Gulf Veterans
Epidemiology			VA-2 A	VA National Survey of Persian Gulf Veterans - Phase I
Epidemiology			VA-2 B	VA National Survey of Persian Gulf Veterans - Phase II
Epidemiology			VA-3	Use of Roster of Veterans Who Served in Persian Gulf Area
Epidemiology			VA-4 C	Gulf War And Vietnam Veterans Cancer Incidence Surveillance
Epidemiology			VA-46	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder
Epidemiology			VA-5 A	Health and Exposure Survey of Persian Gulf Veterans
Epidemiology			VA-6 Core	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research
Epidemiology			VA-63 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)
Epidemiology			VA-70	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8

Major Focus Area / *Research Type*	Primary Focus Area: Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Symptoms & General Health				
Epidemiology	Brain & Nervous System		DoD-141	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans
Epidemiology	Brain & Nervous System		DoD-142	Illnesses Among Persian Gulf War Veterans: Case Validation Studies (Iowa / Great Britain)
Epidemiology	Brain & Nervous System		DoD-143	Millennium Cohort Study
Epidemiology	Brain & Nervous System		VA-78	Millenium Cohort Study
Epidemiology	Brain & Nervous System	Diagnosis	VA-2 C	VA National Survey of Persian Gulf Veterans - Phase III
Epidemiology	Chemical Weapons		DoD-116	VA/DoD Core Funding of the Medical Follow-Up Agency (See also VA-63; formerly
Epidemiology	Chemical Weapons		VA-63	VA/DoD Core funding of the Medical Follow-Up Agency (See also DoD-116; formerly
Epidemiology	Diagnosis		HHS-2	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18
Epidemiology	Prevention		DoD-108	Health Status of Current National Guard Members
Epidemiology	Prevention		DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
Epidemiology	Reproductive Health		DoD-30	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study
Epidemiology	Reproductive Health	Treatment	DoD-96	Deployment Health Center
Epidemiology	Brain and Nervous System		DoD-149	Longitudinal Health Study of Gulf War Veterans
Epidemiology	Symptoms and General Health		DoD-150	Validation Study of Gulf War Deployment Files

Major Focus Area / *Research Type*	Primary Focus Area / Secondary Focus Area	Tertiary Focus Area	Project Number	Project Title
Treatment				
Clinical			VA-56	Birmingham's Gulf War Veterans' Illness Demonstration Clinic (13)
Clinical			VA-57	Case Management and Residential Rehabilitation for Persian Gulf War Veterans (13)
Clinical			VA-60	Identification and Management of Sleep Disorders in Gulf War Veterans
Clinical	Brain & Nervous System		DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)
Clinical	Brain & Nervous System		VA-59	Demonstration Treatment Program for Gulf War Veterans With Unexplained Physical Symptoms (13)
Clinical	Brain & Nervous System		VA-74	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
Clinical	Brain & Nervous System		VA-86	A Clinical Trial of Magnetic Stimulation in Depression
Clinical	Brain & Nervous System		VA-87	Improving Outcomes of Depression in Primary Care
Clinical	Symptoms & General Health		DoD-115	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)
Clinical	Symptoms & General Health		DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also VA-55)
Clinical	Symptoms & General Health		VA-55	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also DoD-119)
Clinical	Symptoms & General Health		VA-62	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
Clinical			VA-58	Implementation and Evaluation of Gulf War Veterans' Demonstration Project (13)

Appendix A 3

Project Funding

(As of December 31, 2002)

NOTES ON REVISED TABLE OF SPENDING FOR GULF WAR VETERANS' ILLNESSES RESEARCH

April 2004

NOTE: These notes and the attached table replace and supercede Appendix A-3 of the *Annual Report to Congress: Federally Sponsored Research on Gulf War Veterans' Illnesses for 2002* issued April 2004.

General

1. All entries for research funding reflect money centrally committed to researchers (both intramural and extramural) to carry out the specific projects. These funds do not cover operational costs for administration, infrastructure, etc. Each department allocates these costs in slightly different ways, making it difficult to accurately account for these funds. For example, in VA the research appropriation does not pay for clinician/investigator salaries. By law those funds must come from the patient care appropriation.
2. A "blank" funding entry generally reflects years in which a project was not active (e.g. it had not started or it had come to an end).
3. Some multiyear projects receive all of their funding in the fiscal year of the authorization and appropriation. For those, the dollars authorized and appropriated are shown for that fiscal year. The remaining funding entries show $0 for the years that the project is active.
4. Some intramural projects/programs are supported out of operational costs. For those projects, $0 is entered for the funds in the fiscal years that the project is active.
5. Programs consisting of multiple projects are represented in one of two ways depending on how funds are centrally allocated:
   a**. Funds centrally allocated to the program**: These programs are shown in the table as a main program indicated by project designation such as DoD-1, and projects in the program as DoD-1A, DoD-1B, etc. All funds are shown under the main program. Blank funding entries are shown for the individual projects.
   b. **Funds centrally allocated to projects within a program**: The funds for these programs are only indicated by their projects without a main program identifier, for example, VA-2A and VA-2B.
6. Funds listed under FY'03 are only projections at this time.

Specific

1. DoD-4 is part of a larger US Army study conducted at Walter Reed Army Institute of Research. Funding for this project has been combined into project DoD-23. In addition, projects DoD-8A and 8B are part of a larger US Army study in which all funding has been combined and is shown under program DoD-8.
2. HHS-3 was funded from the FY'91 appropriation, which is not included in this accounting.
3. HHS-4 was funded from the FY'93 appropriation, which is not included in this accounting.
4. Funds for VA-1 for FY'94 through FY'97 represent an aggregate of funds for both the VA Mortality Study and the VA National Survey of Persian Gulf Veterans. Beginning in FY'98, VA-1 reflects continuation of the VA Mortality Study. Beginning in FY'98, VA–2A, 2B, and 2C reflect funding for separate components of the VA National Survey of Persian Gulf Veterans.
5. In seven instances (DoD-115 & VA-62, DoD-116 & VA-63, DoD-118 & VA-61, DoD-119 &VA-55, DoD-125 & VA-74, DoD-143 & VA-78 ,and DoD154 & VA-88), two different designations represent the same project because they were funded jointly by both DoD and VA. The total funding appropriated for each of these five projects is broken down and reported separately by funding agency.

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-1	Naval Health Study Program	C	$725,000	$1,010,000	$2,250,000	$2,000,000	$2,654,000					$8,639,000	
DoD-1A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 1: A Study of Symptoms among 1500 Seabees.	C										$0	
DoD-1B	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not.	C										$0	
DoD-1C	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among Gulf War veterans and other active-duty personnel.	C										$0	
DoD-1D	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in Gulf War Veterans.	C										$0	
DoD-1E	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study.	C										$0	

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-1F	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: PGW vs. NDV.	C										$0	
DoD-1G	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans.	C										$0	
DoD-2	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET.	C	$90,000	$0	$0	$0						$90,000	
DoD-4	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey.	C	$0									$0	
DoD-7A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling.	C	$897,000	$0	$0	$0	$0					$897,000	
DoD-7B	Carcinogenicity of Depleted Uranium Fragments.	C	$897,814	$0	$0	$0	$0	$121,400	$0			$1,019,214	
DoD-8	Program DoD-8.	C	$773,000	$895,000	$652,000	$695,000	$694,000	$0				$3,709,000	
DoD-8A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL).	C	$0	$0	$0							$0	

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-8B	Development of a Leishmania Skin Test Antigen (LSTA).	C	$0	$0	$0	$0	$0	$0	$0	$0	0	$0	$0
DoD-9	Identification of the Genetic Factors Which Control Tropism in Leishmania.	C	$0	$150,000	$0	$0	$0					$150,000	
DoD-10	Pyridostigmine Synergistic Toxicity Study.	C	$42,000	$44,000								$86,000	
DoD-11	Male/Female Differential Tolerances to Pyridostigmine Bromide.	C	$549,000	$359,000	$0	$0	$0					$908,000	
DoD-13	Effects of Persian Gulf War Service on Military Working Dogs.	C	$0	$0	$97,000	$200,000	$120,000	$200,000	$0			$617,000	
DoD-14	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry.	C	$120,000	$0	$0	$0						$120,000	
DoD-15	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm.	C	$20,000	$0								$20,000	
DoD-16	Kuwait Oil Fire Health Risk Assessment.	C	$345,000	$137,000	$50,000	$127,000						$659,000	
DoD-17	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning.	C	$21,000									$21,000	
DoD-18	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM).	C	$68,000	$151,000	$770,000	$193,000	$290,000	$295,000	$295,000	$306,000	$195,000	$2,563,000	$175,000
DoD-19	Persian Gulf Veterans Health Tracking System.	C		$25,000	$0	$0	$450,000	$450,000	$0	$0	$100,000	$1,025,000	$100,000

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-21	Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm.	C	$38,000	$100,000	$0	$0						$138,000	
DoD-22	Chronic Organophosphorus Exposure and Cognition.	C	$375,000	$0	$0	$0	$0					$375,000	
DoD-23	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families.	C	$621,000	$688,000	$764,000	$985,000						$3,058,000	
DoD-30	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study.	C		$779,000	$0	$0	$0	$0	$0	$0		$779,000	
DoD-31	Dysregulation of the Stress Response in the Persian Gulf Syndrome.	C		$971,000	$0	$0	$0	$0	$0			$971,000	
DoD-32	Neuropsychological Functioning in Persian Gulf Era Veterans.	C		$353,000	$0	$0	$0	$0				$353,000	
DoD-33	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity.	C		$354,000	$0	$0	$0	$0				$354,000	
DoD-34	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents.	C		$283,000	$0	$0	$0	$0				$283,000	

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-35	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.	C		$427,000	$10,000	$63,000	$0	$10,500	$0	$0		$510,500	
DoD-36	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms.	C		$416,000	$138,000	$0	$0	$0				$554,000	
DoD-37	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats.	C		$934,000	$5,000	$0	$0	$0				$939,000	
DoD-38	Diagnostic Antigens of Leishmania tropica.	C		$612,000	$0	$0	$0					$612,000	
DoD-39	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces.	C		$865,000	$0	$28,400	$155,000	$0	$124,868	$0		$1,173,268	
DoD-40	Psychological and Neurobiological Consequences of the Gulf War Experience.	C		$264,000	$0	$0	$0	$0	$0	$0		$264,000	
DoD-41	Evaluation of Muscle Function in Persian Gulf Veterans.	C		$906,000	$0	$0	$0	$0	$0			$906,000	
DoD-42	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment.	C			$700,000	$0	$0	$0	$0	$0		$700,000	

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-44	Investigation of Seminal Plasma Hypersensitivity Reactions.	C			$634,000	$0	$5,000	$14,200				$653,200	
DoD-45	Physical and Emotional Health of Gulf War Veterans Women.	C	$247,068	$0	$299,274	$0	$456,732	$20,505	$0	$99,628	$0	$1,123,207	
DoD-46	Exploratory Data Analysis with the CCEP Database.	C			$60,000	$100,000						$160,000	
DoD-47	Study of Mycoplasmal Infections in Gulf War Veterans.	C			$112,000	$0	$0					$112,000	
DoD-48	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf War Syndrome Cohort vs. Selected Control Groups.	C			$74,000	$0	$0					$74,000	
DoD-49	Diagnosis and Dosemitry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts.	C			$927,000	$0	$0	$0	$0			$927,000	
DoD-50	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways.	C			$699,000	$0	$0	$0				$699,000	
DoD-51	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses.	C			$864,000	$0	$0	$0	$0			$864,000	

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-52	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans.	C	$414,000	$0	$0	$0	$0	$0				$414,000	
DoD-53	Long-Term Effects of Subclinical Exposures to Sarin.	C			$1,000,000	$400,000	$0	$0	$217,137	$0		$1,617,137	
DoD-54	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure.	C			$315,000	$100,000	$0	$0	$0			$415,000	
DoD-55	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects.	C			$500,000	$136,000	$0	$0	$0	$0		$636,000	
DoD-56	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine.	C			$685,000	$100,000	$0	$0	$0	$0		$785,000	
DoD-57	Physiologic Effects of Stress in Gulf War Veterans.	C				$909,000	$0	$0	$0	$0	$0	$909,000	
DoD-58	Illness Among Persian Gulf War Veterans: Case Validation Studies.	C				$2,208,000	$0	$0	$0	$0	$0	$2,208,000	$0
DoD-59	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis.	C				$625,000	$0	$0	$0	$0		$625,000	
DoD-60	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness.	C				$125,000	$0	$0				$125,000	

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-61	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid.	C				$1,586,000	$0	$0	$0			$1,586,000	
DoD-62	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice.	C				$201,000	$0	$0				$201,000	
DoD-63	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity.	C				$1,626,000	$0	$0	$0			$1,626,000	
DoD-64	Individual Differences in Neurobehavioral Effects of Pyridostigmine.	C				$1,900,000	$18,516	$0	$190,595	$0		$2,109,111	
DoD-65	Multi-Disciplinary Pathophysiologic Studies of Neurotoxic Gulf War-Related Neurologic Syndromes Leading to Diagnosis and Treatment.	C				$3,000,000	$0	$0	$0	$0		$3,000,000	
DoD-66	Testing for Micoplasmal Infection Replicability of Nucleoprotein Gene Tracking and Forensic Polymerase Chain Reaction.	C			$49,940	$100,000	$40,000	$403,000	$140,319	$0		$733,259	
DoD-67	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria.	C				$3,400,000	$0	$0				$3,400,000	

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-69	Five Year Follow-Up of Army Personnel Potentially Exposed to Chemical Warfare Agents.	C				$946,160	$0	$0	$110,000	$0	$245,910	$1,302,070	$0
DoD-70	War Syndromes from 1900 to the Present: Symptom Patterns and Long Term Health Outcomes.	C				$734,687	$0	$115,000	$0	$0		$849,687	
DoD-71	A Comparison of Post-Deployment Hospitalization Incidence between Vietnam and Gulf War Veterans.	C				$566,000	$0	$0	$0			$566,000	
DoD-72	Long-Term Effects of Subchronic Exposure to Sarin, Alone and with Stress and Other Chemicals.	C				$996,000	$0	$0	$0	$0	$0	$996,000	
DoD-73	Post-Deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes.	C				$500,000	$0	$0	$0	$0		$500,000	
DoD-74	Relationship of Stress Exposures to Health in Gulf War Veterans.	C				$161,489	$1,991,330	$0	$0	$0	$0	$2,152,819	
DoD-75	Toxic Interactions of Prophylactic Drugs and Pesticides.	C					$1,380,157	$0	$0	$0	$0	$1,380,157	$0
DoD-76	Evaluation of Immunotoxicity Due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel.	C					$448,369	$0	$0	$0	$0	$448,369	$0

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-77	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War.	C					$760,031	$0	$0	$0	$0	$760,031	
DoD-78	Experimental Models of Gulf War Syndrome.	C					$2,179,097	$444,800	$0	$0	$0	$2,623,897	
DoD-79	Time-course of Stress-Induced Impairment of the Blood Brain Barrier.	C				$100,200	$0	$0	$0			$100,200	
DoD-80	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells.	C				$297,400	$0	$0	$0	$0	$0	$297,400	
DoD-81	Immunotoxicity Due to Coexposure of DEET, Pyridostigmine, and Stress.	C				$300,000	$0	$0	$0	$0	$0	$300,000	
DoD-82	Feasibility of Developing a Registry of PTSD-Affected Veteran Sib Pairs.	C				$172,000	$0	$0	$0	$0	$0	$172,000	
DoD-83	Risk for Stress-Related Substance Abuse: Effects of Family History of Alcoholism.	C				$299,700	$0	$0	$0	$0	$0	$299,700	
DoD-84	Psychobiological Alterations Of Persian Gulf War Veterans with and without PTSD.	C				$300,000	$0	$0	$0	$0	$0	$300,000	
DoD-85	Central Nervous System Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms.	C				$149,900	$149,200	$0	$0	$0	$0	$299,100	
DoD-86	Effects of Combat Stress on the Structure and Function of the Hippocampus.	C				$300,000	$297,800	$0	$0	$0	$0	$597,800	$0

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Department of Defense Gulf War Research Funding

PROJECT NO	Project Title	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-87	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs.	C				$289,100	$0	$0	$0	$68,044	$0	$357,144	$0
DoD-88	Clinical Relevance of Novel Immunological Markers in PTSD.	C				$242,300	$0	$0	$0	$0	$0	$242,300	
DoD-89	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder.	C				$288,500	$0	$0	$0	$0	$0	$288,500	
DoD-90	SPECT Benzodiazepine Receptor and MR Imaging in PTSD.	C				$200,000	$100,000	$0	$0	$0	$0	$300,000	
DoD-91	Neurological and Circadian Substrates of PTSD-Like Behaviors.	C				$300,000	$299,000	$0	$0	$0		$599,000	
DoD-92	Traumatic Experiences Persistently Enhance Cue-dependeent Learning: Toward and Animal Model of Chronic Stress and Posttraumatic Stress Disorder.	C				$249,700	$0	$0	$0	$0	$0	$249,700	
DoD-93	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up.	C						$970,700	$0	$0		$970,700	

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Department of Defense Gulf War Research Funding

PROJECT NO	Project Title	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-94	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans.	C						$1,318,069	$206,727	$0	$0	$1,524,796	
DoD-95	Development of Diagnostic tools and alternative treatment drugs for Leishmania.	C						$1,500,000	$1,500,000	$1,500,000	$1,500,000	$6,000,000	
DoD-96	Deployment Health Center.	O						$1,500,000	$1,500,000	$2,250,000	$1,750,000	$7,000,000	$1,250,000
DoD-97	Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis.	C						$177,300	$146,742	$151,202	$151,000	$626,244	
DoD-98	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans.	O						$332,500	$188,000	$364,182	$0	$884,682	$0
DoD-99	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations.	C						$207,876	$204,205	$224,265	$0	$636,346	$0
DoD-100	Antibodies to Squalene.	C						$582,756	$0	$50,000	$487,333	$1,120,089	$0
DoD-101	Mechanisms in Chronic Multisymptom Illnesses.	O						$2,903,408	$5,558,000	$0	$5,431,062	$13,892,470	$5,200,000

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-102	Case-control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-deployed Veterans.	C						$249,908	$254,047	$253,793	$0	$757,748	$0
DoD-103	Human Metabolism & Interactions of Deployment-related Chemicals.	C						$686,332	$46,315	$0	$0	$732,647	$0
DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome.	C						$999,998	$9,311	$0	$0	$1,009,309	
DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala.	O						$950,490	$0	$0	$0	$950,490	$0
DoD-106	The role of Th1/Th2 cytokine balance in Gulf War-related Illness.	C						$292,411	$0	$0	$0	$292,411	
DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity.	O						$875,373	$10,825	$0	$0	$886,198	$0
DoD-108	Health Status of Current National Guard Members.	C						$498,166	$0	$264,375	$174,651	$937,192	$0
DoD-109	Disordered responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms.	C						$917,762	$147,523	$397,243	$0	$1,462,528	$0
D0D-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy.	C						$127,920	$63,705	$0	$0	$191,625	
DoD-111	Autonomic Dysfunction in Gulf War Veterans.	C						$999,481	$0	$0	$0	$999,481	$0

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?	C						$256,916	$0	$0	$0	$256,916	
DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine-Neurochemical, Behavioral, and Physiological Effects.	O						$857,140	$56,000	$57,000	$0	$970,140	$0
DoD-114	A Re-Examination of Neuropsychological Functioning in Persian Gulf War Veterans.	C						$593,712	$0	$0	$0	$593,712	$0
DoD-115	A Randomized Multi-Center Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (see also VA-62; formerly VA/DoD-1D).	C						$1,000,000	$2,000,000	$0	$0	$3,000,000	
DoD-116	VA/DoD Core Funding of the Medical Follow-up Agency (See also VA-63; formerly VA/DoD-2D).	O	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$2,250,000	$250,000
DoD-116A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground, (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA).	C			$0		$0					$0	

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-116B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly listed as VA/DoD-2DB).	C				$0	$0	$0				$0	
DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking.	C							$1,232,050	$0	$0	$1,232,050	$0
DoD-118	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) among GWVs (See also VA-61).	C							$1,500,000	$0	$202,400	$1,702,400	$0
DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT). (See also VA-55.)	C						$500,000	$1,000,000	$0	$0	$1,500,000	
DoD-120	Assessing Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents.	C						$239,000	$316,000	$0	$0	$555,000	
DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel on Pregnancy and Offspring Development.	C				$300,000	$250,000	$25,000	$15,000	$15,000		$605,000	
DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys.	C				$25,000	$25,000	$25,000	$30,000	$35,000		$140,000	
DoD-123	Immunotoxicity of Depleted Uranium and Heavy Metal Tungsten Alloys.	C						$15,000	$20,000	$15,000		$50,000	

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-124	Randomized, Controlled Trial of Combination Treatment with Pyridostigmine, DEET, and Permethrin.	O						$1,283,218	$0	$0	$0	$1,283,218	$0
DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women. (See also VA-74.)	O							$445,078	$477,000	$384,600	$1,306,678	$0
DoD-126	Blood-Brain Barrier Transport of Uranium	O							$790,884	$0	$0	$790,884	$0
DoD-127	Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man	C								$399,582	$0	$399,582	$0
DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity	O							$661,156	$0	$0	$661,156	$0
DoD-129	Inhalation of Uranium Oxide Aerosols: CNS Deposition, Neurotoxity, and Role in Gulf War Illness	O								$1,276,220	$0	$1,276,220	$0
DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents	O								$983,164	$0	$983,164	$0
DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illness	O								$5,377,526	$0	$5,377,526	$500,000
DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness	O								$792,198	$0	$792,198	$0

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome	O								$884,087	$0	$884,087	$0
DoD-134	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin	O							$775,155	$0	$0	$775,155	$0
DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorus Insecticides	O							$786,408	$0	$0	$786,408	$0
DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure	O								$748,858	$0	$748,858	$0
DoD-137	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin	O								$600,000	$0	$600,000	$0
DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents	O								$434,795	$0	$434,795	$0
DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses	O							$892,399	$434,512	$0	$1,326,911	$0

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy	O								$764,879	$0	$764,879	$0
DoD-141	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans	C								$149,993	$0	$149,993	$0
DoD-142	Illness Among Persian Gulf War Veterans: Case Validation Studies	C								$267,337	$0	$267,337	$0
DoD-143	Millennium Cohort Study (See also VA-78)	O							$3,000,000	$1,000,000	$1,250,000	$5,250,000	$3,000,000
DoD-144	Psychological Health Screening: Methods & Metrics for Deployed Forces	O						$109,000	$295,000	$250,000	$300,000	$954,000	$0
DoD-145	Early Intervention Research Program to Enhance Soldier Resilience	O								$250,000	$275,000	$525,000	$275,000
DoD-147	Development of Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications	O				$105,000	$200,000	$190,000	$260,000	$412,000	$696,111	$1,863,111	$292,530
DoD-149	Longitudinal Health Study of Gulf War Veterans	O								$1,689,945	$0	$1,689,945	$0
DoD-150	Validation Study of Gulf War Deployment Files	O									$134,348	$134,348	$0
DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War	O									$491,946	$491,946	$0
DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents	O									$1,000,000	$1,000,000	$1,000,000

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
DoD-153	Gulf War Illness Research	O									$9,644,500	$9,644,500	$1,000,000
DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also VA-88)	O									$100,000	$100,000	$447,285
	DoD Total Funds		**$6,492,882**	**$10,973,000**	**$11,905,214**	**$28,880,536**	**$13,213,232**	**$23,508,841**	**$25,238,449**	**$23,492,828**	**$24,763,861**	**$168,468,843**	**$13,489,815**

Status: C=Complete; O=Ongoing

Department of Health and Human Services Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*		FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
HHS-1	Health Assessment of Persian Gulf War Veterans from Iowa	C		$1,764,762	$1,616,755	$0	$0	$162,000	$0	$0		$3,543,517	
HHS-2	Disease Cluster in a PA Air National Guard Unit	C		$750,000	$0	$0	$16,055	$0	$0			$766,055	
HHS-3	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and Blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil	C	$0	$0	$0	$0	$0					$0	
HHS-4	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans in Mississippi	C	$0	$0	$0							$0	
HHS-5	Cognitive Function and Symptom Patterns in Gulf War Veterans	C					$600,000	$558,000	$660,000	$0	$0	$1,818,000	$0
HHS-6	Defining Gulf War Illnesses	C					$600,000	$480,000	$719,792	$200,000	$0	$1,999,792	$0

Status: C=Complete; O=Ongoing

Department of Health and Human Services Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*		FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	TOTALS FY '94-'02	FY 2003 Projection
HHS-7	Immunotoxicity of Dermal Permethrin and Cis-Urcanic Acid	C					$175,706	$192,445	$187,647	$0		$555,798	
HHS-8	Strategy to Identify Non-additive Response to Chemical Mixtures	C					$242,586	$247,933	$0	$0		$490,519	
HHS-9	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments	O								$337,693	$339,814	$677,507	$400,000
HHS-10	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline	O								$461,177	$460,000	$921,177	$400,000
HHS-11	Deployment to the Gulf War and the Subsequent Development of Cancer	O											$170,000
	Total HHS Funds		**$0**	**$2,514,762**	**$1,616,755**	**$0**	**$1,634,347**	**$1,640,378**	**$1,567,439**	**$998,870**	**$799,814**	**$10,772,365**	**$970,000**

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-1	Mortality Follow-up Study of Persion Gulf Veterans, Second Update.	O	$546,000	$340,000	$1,980,000	$440,032	$178,197	$166,848	$176,440	$171,154	$128,496	$4,127,167	$0
VA-2	National Health Survey of Persian Gulf Veterans.	C									$0	$0	
VA-2A	National Health Survey of Persian Gulf Veterans - Phase I.	C	$0	$0	$0	$0	$18,111					$18,111	
VA-2B	National Health Survey of Persian Gulf Veterans - Phase II.	C			$0	$0	$0	$0				$0	
VA-2C	National Health Survey of Persian Gulf Veterans - Phase III.	C					$1,601,280	$3,571,932	$3,400,000	$2,344,427	$30,000	$10,947,639	
VA-3	Use of Roster of Veterans Who Served In Persian Gulf Area.	C	$0	$0	$0	$0	$0	$0				$0	
VA-4 TOTAL	Boston Environmental Hazards Research Center Program.	C	$98,300	$500,000	$500,000	$500,000	$500,000	$500,000	$229,500			$2,827,800	
VA-4Core	Boston Environmental Hazards Research Center Program.	C											
VA-4A	Evaluation of Cognitive Functioning in Persian Gulf Veterans.	C											
VA-4B	Evaluation of Neurological Functioning in Persian Gulf Veterans.	C											

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-4C	Gulf War and Vietnam Veterans Cancer Incidence Surveillance.	C											
VA-4D	Evaluation of Respiratory Dysfunction among Gulf War Veterans.	C											
VA-4E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker for Susceptibility.	C											
VA-4F	Validity of Computerized Tests	C											
VA-5 TOTAL	East Orange Environmental Hazards Research Center Program	C	$100,000	$500,000	$500,000	$500,000	$500,000	$500,000	$326,900			$2,926,900	
VA-5 Core	East Orange Environmental Hazards Research Center Program	C											
VA-5A	Health and Exposure Survey of Persian Gulf Veterans	C											
VA-5B	Physiological and Psychological Assessments of Persian Gulf Veterans.	C											
VA-5C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans.	C											
VA-5D	Effects of Genetics and Stress on Responses to Envionmental Toxins.	C											

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-6 TOTAL	Portland Enviromental Hazards Research Center: Environment, Veterans' Gulf War Syndrome. Core: Clinical and Epidemiology Research.	C	$99,279	$499,583	$498,695	$499,198	$499,926	$499,098	$233,290			$2,829,069	
VA-6 Core	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and Gulf War Syndrome. Core Project for Clinical and Epidemiology Research.	C											
VA-6A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I).	C											
VA-6B	Clinical and Neuroendrocrine Aspects of Fibromalgia (Project II).	C											
VA-6C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III).	C											
VA-6D	DNA Damage from Chemical Agents and Its Repair (Project IV).	C											
VA-6E	Clinical and Epidemiology of Leishmania Research.	C											

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-7	Desert Storm Reunion Survey.	C	$0	$50,000								$50,000	
VA-8	Psychological Test Data of Gulf War Veterans Over Time.	C	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	
VA-9	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems.	C		$20,000								$20,000	
VA-10	Memory and Attention in PTSD	C			$63,700	$57,000	$57,600	$0				$178,300	
VA-11	Neuropsychological Functioning in Veterans	C	$0	$0								$0	
VA-12	Psychological Assessment of Operation Desert Storm Returnees	C	$0	$0	$0	$0						$0	
VA-13	Neurobehavioral Aspects of Persian Gulf Experiences : A Pilot Study	C	$0	$50,000								$50,000	
VA-15	Vaccine-Mediated Immunity against Leishmaniasis	C	$64,300	$64,300	$0	$82,600	$80,000	$79,400	$41,540	$114,336	$119,600	$646,076	$59,800
VA-16	Protective Immunity in Experimental Leishmaniasis	C		$60,200	$60,700	$54,900						$175,800	
VA-17	Immunological Evaluation of Persian Gulf Veterans	C	$0	$0								$0	
VA-18	Chronic Gastrointestinal Illness in Persian Gulf Veterans	C		$0	$0							$0	

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-20	Psychological Adjustment in Operation Deset Shield/ Storm Veterans	C	$0									$0	
VA-21	A Comparison of PTSD Symptomology among Three Army Medical Units Involved in ODS	C	$0	$0								$0	
VA-36	Stress Symptoms and their Casual Attribution in Desert Storm Veterans.	C		$0	$0	$0						$0	
VA-40	Musculoskeletal Symptoms in Gulf War Syndrome.	C	$0	$0	$0	$0	$0	$0				$0	
VA-46	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder.	C		$0	$0	$0	$0	$0	$0			$0	
VA-47	Louisville Center for the Study of Environmental Hazards to Reproductive Health.	C				$349,700	$299,700	$299,700	$139,960			$1,089,060	
VA-48	Cross-Sensitization as a CNS Model for Chemical Intolerance.	C					$99,900	$89,400	$92,840	$45,000		$327,140	
VA-49	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction	C					$112,090	$147,950	$141,696	$144,024	$125,862	$671,622	
VA-50	Neuropsychological findings in a sample of Desert Storm Veterans.	C		$0	$0							$0	

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-51	Psychobiological Assessment of Desert Storm Veterans.	C	$0	$0	$0	$0	$0	$0	$0	$0		$0	
VA-53	Spouses and Childrens Program.	O				$101,360	$98,651	$51,088	$33,655	$12,934	$25,000	$322,688	$20,690
VA-54	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress	O						$53,400	$90,131	$86,895	$86,350	$316,776	$72,700
VA-55	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (see also DoD-115).	C						$447,742	$1,466,375	$1,981,963	$254,000	$4,150,080	
VA-56	Birmingham's Gulf War Veterans' Illness Demonstration Clinic (13).	C					$54,100	$261,625	$161,175			$476,900	
VA-57	Case Management and Residential Rehabilitation for Persian Gulf War Veterans (13).	C					$71,625	$253,625	$174,750			$500,000	
VA-58	Implementation and Evaluation of Gulf WarVeterans' Demonstration Project (13).	C					$84,714	$349,805	$262,496			$697,015	
VA-59	Demonstration Treatment Program for Gulf War Veterans with Unexplained Physical Symptoms (13)	C					$45,750	$348,225	$259,500			$653,475	
VA-60	Identification and Management of Sleep Disorders in Gulf War Veterans (13).	C					$121,125	$328,500	$246,375			$696,000	

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-61	An Epidemiological Investigation into the Occurrences of Amyotrophic Lateral Sclerosis (ALS) among Gulf War Veterans.(See also DoD-118).	C							$0	$0	$110,600	$110,600	
VA-62	A Randomized, Multi-Center Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD 115; formerly VA/DoD 1V).	C						$788,000	3,756,826	$1,971,233	$44,250	$6,560,309	
VA-63	VA/DoD Core funding of Medical Follow-Up Agency (See also DoD 116; formerly VA/DoD-2V/2D).	O	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$2,250,000	$250,000
VA-63A	Follow-up Investigation of troops exposed to nerve agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A;formerly VA/DoD-2VA/2DA) .	C				$0	$0					$0	
VA-63B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD 116B; previously VA/DoD-2VB).	C				$0	$0	$0				$0	

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-64	Boston Environmental Hazards Research Center Program	O							$112,360	$299,700	$300,000	$712,060	$297,000
VA-64A	Functional Neuroimaging in Lead Exposed Adults.	O											
VA-64B	Quantification and Validation of Structure-Function relationships through visuospatial test performance.	O											
VA-64C	Development of a structural neurotoxicant asessment checklist (SNAC) for clinical use in veteran populations.	O											
VA-65	San Antonio Environmental Hazards Research Center	O							$116,750	$350,000	$300,000	$766,750	$300,000
VA-65A	Does a variant of human SOD2 gene increase Sensitivity to hazards?	O											
VA-65B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress.	O											
VA-65C	The importance of hydrogen peroxide detoxification in cellular protection.	O											
VA-65D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental exposure?	O											

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-66	Physiological Responding in Posttraumatic Stress Disorder	C						$0	$0	$0		$0	
VA-67	Olfactory Functioning in Gulf War Veterans.	C							$7,500	$7,500		$15,000	
VA-68	Family Study of Fibromyalgia	C							$46,700	$50,000	$50,000	$146,700	
VA-69	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans	C							$122,243	$135,487	$141,815	$399,545	$48,947
VA-70	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8	C					$50,051	$19,817	$6,204	$4,884	$4,900	$85,856	$0
VA-71	Central Nervous System Modulation of Visceral Pain in Persian Gulf War Syndrome	C							$125,313	$181,692	$186,524	$493,529	$47,975
VA-72	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illness	C									$50,000	$50,000	$50,000
VA-73	Pain Sensitivity in Gulf War Vets with Medically Unexplained Musculoskeletal Illness	C									$50,000	$50,000	$50,000
VA-74	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (see also DoD-125)	O								$291,804	$896,550	$1,188,354	$1,386,700

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-75	ALS and Veterans: Are Veterans at Increased Risk?	O								$73,000	$139,600	$212,600	$139,600
VA-76	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD	O									$145,100	$145,100	$135,000
VA-77	HPA Axis Reactivity in Men and Women with Chronic PTSD	O									$101,400	$101,400	$101,300
VA-78	Millennium Cohort Study (see also DoD-143)	O							$0	$0	$0	$0	$75,000
VA-79	VHA Clinicians and Bioterror Events: Interactive Web-Based Learning	O									$0		$254,100
VA-80	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress	O											$203,400
VA-81	Stress, Pro-Inflammatory Cytokines, and Coping Behavior	O											$193,800
VA-82	Pituitary Adrenal Function in People with Fatiguing Illness	O									$88,000	$88,000	$135,000

Status: C=Complete; O=Ongoing

Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS*	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY94-02	FY 2003 Projection
VA-83	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls	O									$18,988	$18,988	$50,000
VA-84	Neurobiology of Severe Psychological Trauma in Women	O									$135,000	$135,000	$135,000
VA-85	Associative Learning in Veterans with and without Combat Experience	O									$60,400	$60,400	$74,000
VA-86	A Clinical Trial of Magnetic Stimulation in Depression	O									$131,400	$131,400	$131,400
VA-87	Improving Outcomes of Depression in Primary Care	O									$152,065	$152,065	$201,926
VA-88	Prospective Assessment of Neurocognition in Future Gulf-Deployed and Gulf-Nondeployed Military Personnel (see also DoD-154)	O											$55,700
VA-89	National Registry of Veterans with ALS	O											$319,300
TOTALS			**$1,157,879**	**$2,334,083**	**$3,853,095**	**$2,834,790**	**$4,722,820**	**$9,006,155**	**$12,020,519**	**$8,516,033**	**$4,125,900**	**$48,571,274**	**$4,788,338**

Status: C=Complete; O=Ongoing

Department of Veterans Affairs
Veterans Health Administration
Office of Research and Development
Washington, DC 20420

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