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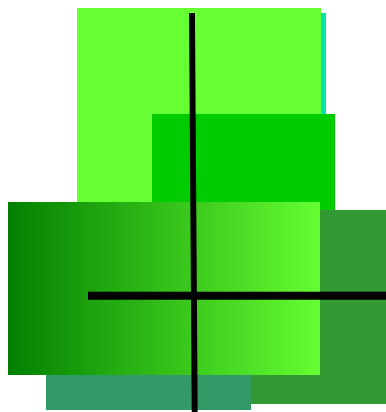
ANNUAL REPORT TO CONGRESS

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2000



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Research Working Group of Military and Veterans Health Coordinating Board



Annual Report to Congress – 2000

Research on Gulf War Veterans' Illnesses

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EXECUTIVE SUMMARY

I. INTRODUCTION

The Secretary of Veterans Affairs is required 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 Working Group (RWG) of the Military and Veterans Health Coordinating Board (MVHCB) prepared this document, the *2000 Annual Report to Congress*, which is the seventh report on research and research activities. (PGVCB, 1995a; 1996a; 1997; 1998; 1999a; 2001)

This Annual Report is divided into six 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 the management of Federal Gulf War veterans' illnesses research programs, including research oversight, peer review, and coordination. Section VI discusses priorities established in 1995, 1996, and 1998 for future research, and highlights the progress made to date.

II. RESEARCH RESULTS IN 2000

In the past year, 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 2000 to January 2001. The RWG tracks all Federally funded research projects related to Gulf War veterans' illnesses. As in previous reports to Congress, the research reports summarized in Section II are grouped according to nine focus areas: symptoms and general health status, brain and nervous system function, diagnosis, reproductive health, mortality, depleted uranium, chemical weapons, pyridostigmine bromide, and interactions of exposures.

1. Symptoms and General Health Status:

Nine large studies were published that focused on symptoms and general health. (Kang, et al, 2000; Doebbeling, et al, 2000; Knoke, et al, 2000; Bell, et al, 2000; Nisenbaum, et al, 2000; Ismail, et al, 2000; Hotopf, et al, 2000; Steele, 2000; Smith, et al, 2000) These publications included the results of studies conducted at four large research centers in Washington, DC, Iowa, San Diego, and London, UK. Each of the nine studies included several hundred to thousands of individuals. Four of the studies have included some form of medical evaluation, such as causes of hospitalization. (Knoke, et al, 2000; Bell, et al, 2000; Nisenbaum, et al, 2000; Smith, et al, 2000) 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. (Kang, et al, 2000; Doebbeling, et al, 2000; Bell, et al, 2000; Ismail, et al, 2000; Hotopf, et al, 2000; Smith, et al, 2000)

One of the most significant conclusions based on these recent studies and others is that Gulf War veterans do not suffer from a unique, previously unrecognized "syndrome." Four large studies have evaluated the health of thousands of Gulf War veterans and non-deployed veterans, involving the US Air Force; US Navy; US Army, Navy, and Air Force, combined; and all three services from the United Kingdom, combined. (Fukuda, et al, 1998; Knoke, et al, 2000; Doebbeling, et al, 2000; Ismail, et al, 1999) In each study, the patterns of symptoms reported by Gulf War veterans were similar to the patterns of symptoms reported by non-deployed veterans.

2. Brain and Nervous System Function:

Seven studies were published that focused on brain and nervous system function, including posttraumatic stress disorder, major depression, and neuropsychological functioning. (Storzbach, et al, 2000; Storzbach, et al, 2001; King, et al, 2000; Sharkansky, et al, 2000; Benotsch, et al, 2000; Fiedler, et al, 2000; Engel, et al, 2000) These publications presented the results of studies conducted at five federally funded research centers in Portland, Oregon, Boston, New Orleans, East Orange, New Jersey, and Washington, DC. Six of these studies included several hundred to several thousand individuals. Four of these publications relied upon neurological and/or psychiatric evaluations, rather than relying solely on self-administered

surveys. (Storzbach, et al, 2000; Storzbach, et al, 2001; Fiedler, et al, 2000; Engel, et al, 2000)

Two of these seven studies, which focused on brain and nervous system function, were published by the Portland Environmental Hazards Research Center. 241 Gulf War veterans who reported unexplained symptoms, which could not be diagnosed after a thorough evaluation, were compared with 113 healthy Gulf War veterans (controls). (Storzbach, et al, 2000) 87% of the 241 cases had unexplained cognitive or psychological symptoms, 38% had unexplained musculoskeletal symptoms, and 42% had unexplained fatigue. There were 12 psychological tests and 6 neurobehavioral tests. Cases differed significantly from controls on all psychological test scales, in the direction of increased distress. Case performance on all neurobehavioral tests was deficient compared to the controls. However, the deficiencies were statistically significant in only 2 of the 6 tests. The performance of about 90% of the cases on the neurobehavioral tests was similar to the controls. (Storzbach, et al, 2001) In contrast, about 10% of the cases performed significantly worse than the controls on almost all the neurobehavioral tests.

3. Diagnosis:

Two studies were published that focused on the diagnosis of infectious diseases in Gulf War veterans, including one study on *Mycoplasma fermentans*, and one study on infectious diseases that are endemic to the Persian Gulf region. (Lo, et al, 2000; Specht, et al, 2000) The prevalence of antibodies to *Mycoplasma fermentans* was compared among chronically ill Gulf War veterans (cases) and healthy Gulf War veterans (controls), based on specimens obtained before and after the war. (Lo, et al, 2000) Some scientists and veterans have proposed that previously undetected infections with this organism might be a cause of symptoms in some Gulf War veterans. Before the war, 34 out of 718 cases (4.8%) and 116 out of 2,233 controls (5.2%) tested positive for antibodies to *Mycoplasma fermentans*. After the war, an additional 1.1% of cases and 1.2% of controls tested positive for antibodies. These results provided no evidence that infection with this organism was associated with the development of chronic illnesses in the cases.

4. Reproductive Health:

Two studies were published that focused on reproductive health among Gulf War veterans. These included one study on the prevalence of major congenital abnormalities among infants of veterans in Hawaii, and one study on the rates of abnormalities in cervical cytology among women veterans. (Araneta, et al, 2000; Frommelt, et al, 2000) Between 1989 and 1993, 17,182 infants were born to military parents in Hawaii, including 22% Gulf War veterans and 78% non-deployed veterans. (Araneta, et al, 2000) There were no differences in infants born to the two groups of veterans in the rates of low birth weight or prematurity. 367 infants were identified with one or more of 48 major birth defects (2% of live births). The prevalence of birth defects was similar for infants born to the two veteran groups, in the prewar and postwar periods.

5. Mortality:

One study was published that focused on mortality of Gulf War veterans in the United Kingdom. (Macfarlane, et al, 2000) The rates of mortality in all 53,462 British Gulf War veterans were compared with the rates among the same number of non-deployed British veterans. There were 395 deaths among Gulf War veterans (0.7%) and 378 deaths among non-deployed veterans (0.7%). Mortality rates due to diseases (natural causes) were slightly lower among Gulf War veterans. Mortality rates due to external causes were slightly higher among Gulf War veterans, mostly due to motor vehicle accidents. These British results are very similar to results of a mortality study in US Gulf War veterans. (Kang and Bullman, 1996) Both the UK and US mortality studies will continue indefinitely.

6. Depleted Uranium:

One study was published that focused on the effects of depleted uranium (DU) in Gulf War veterans. (McDiarmid, et al, 2001) VA and DoD initiated a national effort in August 1998 to offer a DU medical evaluation to any concerned Gulf War veteran. This study described the results of the first 169 veterans who volunteered for this program through December 1999. Of the 169 veterans who submitted 24-hour samples for determination of urinary uranium concentration, there were only 3 individuals with validated, elevated results. One of these individuals

probably had retained DU metal fragments from a friendly fire incident. The sources of the elevated results in the other 2 persons were unknown. The authors concluded “Those with normal uranium values now are unlikely to develop any uranium-related toxicity in the future regardless of what their DU exposure may have been during the Gulf War.”

7. Chemical Weapons:

Three studies were published that focused on the effects of chemical weapons in laboratory animals. These studies focused on sarin, and included one study in guinea pigs and two studies in rats. (Spruit, et al, 2000; Khan, et al, 2000; Jones, et al, 2000)

8. Pyridostigmine Bromide:

One study was published that focused on the effects of pyridostigmine bromide in rats. (Li, et al, 2000)

9. Interactions of Exposures:

Nine animal studies were published that focused on the health effects of interactions of exposures. These included five animal studies of the effects of pyridostigmine bromide (PB), in combination with stressors (forced swimming stress, heat stress, severe cold stress, restraint stress, or exercise training). (Grauer, et al, 2000; Sinton, et al, 2000; Servatius, et al, 2000; Somani, et al, 2000; Verma-Ahuja, et al, 2000) Four animal studies evaluated the effects of PB, in combination with other chemicals, in particular, DEET or permethrin. (Hoy, et al, 2000a; Hoy, et al, 2000b; van Haaren, et al, 2000; Chaney, et al, 2000)

III. RESEARCH FUNDING TRENDS

The Gulf War Veterans’ Illnesses research portfolio currently includes 193 projects. It was last updated during the second quarter of Fiscal Year 2001 (through March 31, 2001). These 193 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. Currently,

the Federal Government is projecting cumulative expenditures of \$173.6 million for research from FY 1994 through FY 2001. As of March 31, 2001, 116 projects were completed and 77 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 examined 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 in 2000 for key research projects and initiatives.

IV.A. NEW RESEARCH PROJECTS

IV.A.1. New Projects Funded by the 2000 DoD Broad Agency Announcements

In 1998, DoD established new funding for programmed research. The purpose of this program element funding is to address Gulf War veterans’ illnesses issues, which may also be of concern in future deployments. This planned funding is approximately \$20 million per year for FY 1999 through FY 2002 and \$5 million per year thereafter. DoD published four Broad Agency Announcements (BAAs) in 2000. The new projects funded by these BAAs will be announced in 2001. The specific requests focused on the following areas of research interest:

- Epidemiological Investigations of Deployment Health Monitoring Methods
- Deployment Stress Health and Performance Consequences
- Biochemical and Physiological Markers to Assess Toxic Chemical Exposures and Health Effects in Deployed Military Personnel
- Toxicity of Militarily Relevant Heavy Metals

IV.B. 2000 UPDATE OF KEY RESEARCH PROJECTS AND INITIATIVES

IV.B.1. Institute of Medicine Study of Health Effects Associated with the Gulf War

In 1998, the VA contracted with the Institute of Medicine (IOM) to perform a review of the scientific and medical literature regarding adverse health effects associated with the exposures experienced during the Gulf War. The first phase of this study focused on the medical literature on pyridostigmine bromide, depleted uranium, sarin and cyclosarin, and the anthrax and botulinum toxoid vaccines. A report on this first phase was published in September 2000, entitled *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, Vaccines*. (IOM, 2000) The findings and research recommendations in this IOM report are summarized in Section IV.B.1. In 2000, planning started for the second phase of the IOM project, which will focus on a review of the scientific literature on pesticides and solvents used during the Gulf War.

IV.B.2. White House Report: *Health Consequences of the Gulf War: An Ongoing Analysis*

In mid-2000, White House staff requested that an interagency report be coordinated and edited by the MVHCB, which would summarize the activities of the Federal Government to address illnesses in Gulf War veterans. This report was completed in December 2000, and was entitled *Health Consequences of the Gulf War: An Ongoing Analysis*. (White House, 2000) This report provides an overview of the clinical programs, research and investigations, compensation initiatives, outreach efforts, and lessons learned. The report includes a chapter on Research, which summarizes the findings to date. The major research conclusions are provided in Section IV.B.2.

IV.B.3. Conference on Federally Sponsored Gulf War Veterans' Illnesses Research

The RWG organized and hosted an international meeting, entitled "2001 Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research," on January 24-26, 2001, in Alexandria, Virginia. The purpose of the

meeting was to bring together Federally sponsored researchers on Gulf War veterans' illnesses in a common forum. This was the fifth such conference, and almost 400 scientists, clinicians, government officials, and veterans attended it. The *Proceedings* for this conference were published in early 2001. (MVHCB, 2001b)

V. RESEARCH MANAGEMENT

The RWG has accomplished several notable achievements, including:

- Development, production, and dissemination of the 1995 *A Working Plan for Research on Persian Gulf Veterans' Illness* (PGVCB, 1995b), and its 1996 revision (PGVCB, 1996b).
- Production and dissemination of *Annual Reports to Congress* for 1994 through 2000 on results, status, and priorities of Federal research activities (PGVCB, 1995a; 1996a; 1997; 1998a; 1999a; 2001; MVHCB, 2001a).
- Secondary programmatic review and recommendations on research proposals that have been competitively reviewed by funding agencies.
- Organization of five conferences of Federally funded researchers, including publication of three *Proceedings* (PGVCB, 1998b; PGVCB, 1999b; MVHCB, 2001b).
- Coordination and oversight of implementation of relevant recommendations of the Institute of Medicine, Presidential Advisory Committee, Senate Veterans' Affairs Committee, the Presidential Review Directive 5, and the Presidential Special Oversight Board (IOM, 1995, 1996; PAC, 1996a, 1996b, 1997; SVAC, 1998; NSTC, 1998; PSOB, 2000).

- Two national treatment trials (exercise/behavior therapy trial and antibiotic treatment trial).

VI. RESEARCH PRIORITIES

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

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 research-coordinating role through the Research Working Group (RWG) of the Military and Veterans Health Coordinating Board (MVHCB). The Secretaries of the Department of Defense (DoD), Health and Human Services (HHS), and VA chair the MVHCB.

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 2000 *Annual Report to Congress*, is the seventh report on research and research activities. (PGVCB, 1995a; 1996a; 1997; 1998; 1999a; 2001) The 2000 *Annual Report to Congress* reports on research funded by Federal and non-federal institutions. All new peer reviewed reports of high quality research add to and build upon existing knowledge, regardless of funding source.

This Annual Report is divided into six 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 new research projects and initiatives since the last Annual Report. Section V discusses the management of Federal Gulf War veterans' illnesses research programs, including research oversight, peer review, and coordination. Section VI discusses priorities established in 1995, 1996, and 1998 for future research, and highlights the progress made to date.

II. RESEARCH RESULTS IN 2000

New Research Publications

In the past year, several research studies 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 2000 to January 2001. Because all scientifically peer reviewed research must be considered in any future assessments of Gulf War veterans' illnesses, these summaries include both Federally funded and non-federally funded research. The primary source of information on research is from the peer reviewed scientific literature. The RWG tracks all Federally funded research projects related to Gulf War veterans' illnesses. These projects are described in detail in Appendix A.

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

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

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

As in previous reports to Congress, research has been categorized according to particular focus areas. The research reports summarized below are grouped according to nine focus areas: symptoms and general health status, brain and nervous system function, diagnosis, reproductive health, mortality, depleted uranium, chemical weapons, pyridostigmine bromide, and interactions of exposures. In each category, an

overview section highlights the results of relevant reports, followed by a summary of each individual report.

A. Symptoms and General Health Status

Overview:

Nine large studies were published in 2000 that focused on symptoms and general health. These publications included the results of studies conducted at four large research centers in Washington, DC, Iowa, San Diego, and London, UK. Each of the nine studies included several hundred to thousands of individuals. Four of the studies have included some form of medical evaluation, such as causes of hospitalization. (Knoke, et al, 2000; Bell, et al, 2000; Nisenbaum, et al, 2000; Smith, et al, 2000) 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. (Kang, et al, 2000; Doebbeling, et al, 2000; Bell, et al, 2000; Ismail, et al, 2000; Hotopf, et al, 2000; Smith, et al, 2000)

In almost all published studies, Gulf War veterans have reported significantly higher frequencies of symptoms and medical conditions, in comparison with non-deployed veterans. In contrast, the rates of objectively validated medical conditions among Gulf War veterans have generally been similar to the rates in non-deployed veterans. These patterns have been demonstrated again in the VA National Survey and in a survey of veterans in Kansas (Kang, et al, 2000; Steele, 2000)

In 1995, VA initiated a population-based, mailed survey, entitled the "National Health Survey of Gulf War Era Veterans and Their Families." (Kang, et al, 2000) A total of 11,441 Gulf War veterans responded (75%), and 9,476 non-deployed veterans responded (64%). Gulf War veterans reported many chronic medical conditions significantly more frequently than the controls, such as recurrent headaches, frequent diarrhea, and arthritis. In addition, Gulf War veterans reported an increased frequency of all 48 of the 48 symptoms on the survey, compared to the controls. 7.8% of Gulf War veterans reported having been hospitalized overnight during the past year, compared with 6.4% of non-deployed veterans. However, there were no reported differences in the rates of several

serious conditions, such as cancer, coronary heart disease, stroke, diabetes, or cirrhosis of the liver. These results were consistent with other large population-based studies of Gulf War veterans in Iowa, Canada, and the United Kingdom. (Iowa, 1997; Goss Gilroy, 1998; Unwin, et al, 1999)

The state of Kansas conducted a statewide survey in 1998 to describe the prevalence and risk factors for health problems in 1,548 Gulf War veterans and 482 non-deployed veterans (65% participation rate). (Steele, 2000) This study included only veterans who had retired or separated by 1998 or who were current Reserve/National Guard members. There were 55% Reserve/National Guard in the Kansas sample, compared to 17% of all Gulf War veterans. Gulf War veterans reported significantly higher rates of 10 of 21 medical conditions that were diagnosed or treated by a physician, such as depression, arthritis, migraine headache, or posttraumatic stress disorder (PTSD). Gulf War veterans reported significantly higher rates of all 37 of 37 symptoms. Notably, there were no reported differences in the rates of hospitalizations (1991 to 1998) or rates of application for VA disability benefits (1991 to 1998). The prevalence of the Centers for Disease Control and Prevention (CDC) working case definition of multisymptom illness was also evaluated. (Fukuda, et al, 1998) This CDC case definition was reported by 47% of Gulf War veterans in Kansas and 20% of non-deployed veterans. Overall, the Kansas data indicated that Gulf War veterans and non-deployed veterans reported similar patterns of symptoms, although Gulf War veterans reported higher rates.

Four major studies have been published that used a statistical technique, factor analysis, to identify patterns of symptoms. The health of thousands of Gulf War veterans has been evaluated in these four studies, involving the US Air Force; the US Navy; the US Army, Navy, and Air Force combined; and all three armed services in the United Kingdom, combined. (Fukuda, et al, 1998; Knoke, et al, 2000; Doebbeling, et al, 2000; Ismail, et al, 1999) In each of these studies, the patterns of symptoms reported by Gulf War veterans were similar to the patterns reported by non-deployed veterans. The results of these four studies are consistent with the conclusion of a recent Institute of Medicine report, which was, "Thus far, there is insufficient

evidence to classify veterans' symptoms as a new syndrome. . . All Gulf War veterans do not experience the same array of symptoms. Thus, the nature of the symptoms suffered by many Gulf War veterans does not point to an obvious diagnosis, etiology, or standard treatment." (Institute of Medicine, 2000)

Differences in demographic variables, health behaviors, risk-taking behaviors, and mental or physical health could influence a soldier's postwar health status. Such factors could also influence the chance of selection for deployment. 675,626 active duty Army soldiers were followed from 1980 to the beginning of the Gulf War. (Bell, et al, 2000) About 38% of these soldiers were deployed to the Gulf War. In comparison to non-deployed soldiers, Gulf War veterans were more likely to have the following characteristics: male, fewer than 5 years of time in service, younger than 25 years of age, black, single, high school education, fewer dependents, and junior enlisted rank. Deployed soldiers were more likely to be in certain military occupational specialties: infantry/gun crews, mechanical repair, or crafts workers (e.g., plumbers, metal workers). Deployed soldiers were more likely to have received hazardous duty pay before July 1990; and deployed soldiers received this hazardous duty pay more frequently for parachuting or for potential exposure to hostile fire before July 1990. Rates of hospitalizations for all injuries in military hospitals were evaluated from 1980 to August 1, 1990. The risk of hospitalization for injuries was higher among the deployed soldiers in most years. In addition, male gender, young age, less education, single marital status, less time in service, and receipt of two or more types of hazardous duty pay during one pay period were all significant predictors of prewar hospitalization for injuries. The authors concluded that "postwar excess injury risk may be explained in part by a propensity for greater risk-taking, which was evident before and persisted throughout the war."

Several studies have demonstrated a significant association between demographic, lifestyle, and occupational risk factors and increased symptoms among Gulf War veterans. For example, in the VA National Survey, Gulf War veterans who were in the Army or in the Reserve/National Guard consistently reported higher rates of symptoms and medical conditions, than veterans in other services or on active-duty. (Kang, et al, 2000) In the Kansas

study, there was a significant association between increasing symptoms in multiple organ systems in Gulf War veterans, and female gender, lower household incomes, lower education, enlisted status, and service in the Army. (Steele, 2000) The CDC evaluated the association between several risk factors and a working case definition of chronic multisymptom illness in 1,002 Air Force veterans of the Gulf War. (Fukuda, et al, 1998; Nisenbaum, et al, 2000) The multisymptom illness was significantly associated with increasing age, female gender, non-white race, current smoking, and enlisted rank.

In 1997-98, a mailed survey was conducted among a randomly selected sample of 3,297 British servicemen, who had deployed to the Gulf War (70% response rate). (Unwin, et al, 1999; Ismail, et al, 2000) The authors used two physical health status measures and two mental health status measures. Physical ill health was measured as fatigue, and as a measure of multisymptom illness, based on the CDC working case definition. (Fukuda, et al, 1998) Psychological ill health was measured as psychological distress, and as a measure of post-traumatic stress reaction. There was a significant relationship between decreasing military rank and all four health outcomes. Privates were about two to three times more likely to report ill health than officers were. At the time of the survey, 57% of the Gulf War veterans had left the armed forces. Veterans who had been discharged were about two times more likely to report all four health outcomes. There was a highly significant linear trend between smoking and all four health outcomes.

Some studies have shown a significant association between reported environmental exposures and increased symptoms among Gulf War veterans, while other studies have shown no association. In the CDC study of multisymptom illness, 6% and 39% of Gulf War veterans fulfilled the case definition of severe illness and mild-to-moderate illness, respectively. (Fukuda, et al, 1998) The rates of severe and mild-to-moderate illness were significantly associated with self-reports of pyridostigmine bromide (PB) use; insect repellent use on a regular basis; and the belief that chemical or biological weapons were used against them. (Nisenbaum, et al, 2000) Severe illness was also associated with injuries during the war that required medical attention. The authors cautioned, however, that

these self-reports of exposures could be subject to recall bias. In particular, the reports could be strongly influenced by extensive media coverage or by psychological states, such as PTSD, which were not controlled in the analysis.

In the British study of Gulf War veterans, it was hypothesized that Royal Army personnel might have been in closer geographical proximity to some of the environmental exposures implicated during the war, than Royal Navy or Royal Air Force personnel. (Ismail, et al, 2000) Nonetheless, Army personnel reported the same levels of health problems as Navy and Air Force personnel. In addition, combat troops, such as the infantry, reported the same levels of health problems as support troops, such as engineering or medical personnel. One possible explanation of this finding is that the ground war only lasted four days, whereas chemical and biological weapons were considered to be a real threat for several months and beyond the immediate geographical frontline.

A second analysis of the British Gulf War cohort focused on the relationship between ill health after the Gulf War and vaccines received before or during the conflict. (Hotopf, et al, 2000) This study used data only from veterans who reported that they still had their vaccine records (n=923; 28% of responders). The patterns of vaccines given before and during deployment were different, with more “routine” vaccines and fewer biological warfare vaccines given before deployment. The associations of vaccines with six health outcomes were evaluated. Multiple vaccines (defined as 5 or more vaccines) received before deployments were associated with only one of the six health outcomes (post-traumatic stress reaction). In contrast, five of the six outcomes were associated with multiple vaccines received during deployment (all but post-traumatic stress reaction). The strongest association was with the CDC case definition of multisymptom illness. The authors concluded that multiple vaccines, combined with the “stress” of deployment, might be associated with ill health. This study has raised a number of methodological concerns, in particular, that the restricted sample of 923 veterans who kept their vaccine records might be biased in some way. (Shaheen, 2000; Bolton, et al, 2001)

The rates of three diseases were compared among Gulf War and non-deployed veterans, due to concern among some veterans: systemic lupus

erythematosus (SLE), amyotrophic lateral sclerosis (ALS; also called Lou Gehrig’s disease), and fibromyalgia (FM). (Smith, et al, 2000) This included 551,841 service members who were deployed to the Gulf War and 1,478,704 service members who were not deployed. All military hospitalization data were evaluated for the three specific diseases during the follow-up period of August 1, 1991 to July 31, 1997 (six years). There were 36 Gulf War veterans and 160 non-deployed veterans who were diagnosed with SLE (relative risk of 0.94; not significant). There were 6 Gulf War veterans and 12 non-deployed veterans who were diagnosed with ALS (relative risk of 1.66; not significant). It is noteworthy that in 2000, the VA and DoD initiated an evaluation of the rates of ALS in Gulf War and non-deployed veterans, which will include data from VA, DoD, and civilian sources. There were 239 Gulf War veterans and 621 non-deployed veterans who were diagnosed with FM (relative risk of 1.23; significantly increased). Comprehensive Clinical Evaluation Program (CCEP) participation was a strong independent risk factor for FM. In particular, CCEP participants had 26.4 times the risk of being hospitalized for FM compared with non-participants.

Symptoms and General Health Status- Individual Studies:

1. Kang, HK, Mahan, CM, Lee, KY, Magee, CA, and Murphy, FM. Illnesses among United States veterans of the Gulf War: a population-based survey of 30,000 veterans. *Journal of Occupational and Environmental Medicine* 2000; 42(5):491-501. (VA-2)

In 1995, VA initiated a population-based, mailed survey, entitled the “National Health Survey of Gulf War Era Veterans and Their Families.” (Kang, et al, 2000) The purpose of the survey was to compare the health status of a sample of 15,000 Gulf War veterans with the health status of a sample of 15,000 non-deployed veterans. Women and members of the Reserve and National Guard were over-sampled. In 1995 to 1996, 15,817 veterans responded to the mailed survey. In 1996 to 1998, an additional 5,100 responded to a supplemental telephone survey. A total of 11,441 Gulf War veterans responded (75%), and 9,476 non-deployed veterans responded (64%) (overall response rate of 70%).

The questionnaire included various symptoms, medical diagnoses, measures of functional impairment, and potential environmental exposures. Gulf War veterans reported many chronic medical conditions significantly more frequently than the controls, such as recurrent headaches, frequent diarrhea, and arthritis. However, there were no reported differences in the rates of several serious conditions, such as cancer, coronary heart disease, stroke, diabetes, or cirrhosis of the liver. In addition, Gulf War veterans reported an increased frequency of all 48 of the 48 symptoms on the survey, compared to the controls. Members of the Reserve or National Guard consistently reported higher rates of symptoms and medical conditions, than active-duty members did. Army veterans reported higher rates than veterans of the other services did.

50.8% of Gulf War veterans reported that they had visited a clinic or seen a physician during the past year, compared to 40.5% of non-deployed veterans. 7.8% of Gulf War veterans reported having been hospitalized overnight during the past year, compared with 6.4% of non-deployed veterans. Medical records were retrieved for a small proportion of veterans (784 records of clinic visits and 105 records of hospitalizations). To the extent that records were available, the self-reported reasons for clinic visits (e.g., headaches, rash) and reasons for hospitalizations (e.g., appendicitis) correlated well with the reasons documented in the written records.

Overall, the results of this survey indicate that the self-reported health of Gulf War veterans is not as good as the self-reported health of non-deployed veterans, as measured by functional impairment, health care utilization, symptoms, and medical conditions. These results are consistent with other large population-based studies of Gulf War veterans in Iowa, Canada, and the United Kingdom. (Iowa, 1997; Goss Gilroy, 1998; Unwin, et al, 1999) The final stage of this national VA survey includes a medical evaluation of 1,000 Gulf War veterans and their families and 1,000 non-deployed veterans and their families, which will be completed in 2001.

2. Doebbeling, BN, Clarke, WR, Watson, D, Torner, JC, Woolson, RF, Voelker, MD, Barrett, DH, and Schwartz, DA. Is there a Persian Gulf War syndrome? Evidence from a large population-based survey of veterans and

nondeployed controls. *American Journal of Medicine* 2000; 108(9):695-704. **(HHS-1)** In 1995-96, a randomly selected sample of Iowa military personnel was surveyed using a telephone interview. (Iowa, 1997) A total of 1,896 Gulf War veterans and 1,799 non-deployed veterans participated (76% response rate). The Gulf War veterans came from 889 different units that had been widely distributed during the war, which reflected a broad range of geographic and environmental exposures. The objective of this study was to look for evidence of a novel illness that was unique to Gulf War veterans, and that was not seen in a comparable military population. (Doebbeling, et al, 2000) Gulf War veterans reported significantly higher rates of 123 of 137 (90%) symptoms during the past year, compared to the controls. These symptoms were related to all organ systems. The authors concluded that the increased prevalence of nearly every symptom among Gulf War veterans is “difficult to explain pathophysiologically as a single condition.”

A statistical technique, factor analysis, was used to identify patterns of symptoms. This technique was used separately with the symptoms of the Gulf War veterans and with the symptoms of the controls, to determine if the patterns were unique. Factor analysis identified three patterns of symptoms that correlated with each other, among the Gulf War veterans. The three patterns included: 1) joint stiffness, myalgia, polyarthralgia, numbness or tingling, headaches, and nausea; 2) feeling nervous, worrying, feeling distant or cut-off, depression, and anhedonia; and 3) anxiety attacks, a racing, pounding or skipping heart, attacks of chest pain or pressure, and attacks of sweating.

However, these three patterns were highly replicable in the controls, that is, the patterns were almost identical (convergent correlations of 0.95 to 0.98). The authors concluded that the identification of the same patterns of symptoms among both groups is “not consistent with the existence of a unique Gulf War syndrome;” and the results should “help alleviate concern about an unexplained ‘mystery illness.’ ”

3. Knoke, JD, Smith, TC, Gray, GC, Kaiser, KS, and Hawksworth, AW. Factor analysis of self-reported symptoms: does it identify a Gulf War syndrome? *American Journal of Epidemiology* 2000; 152(4):379-388. **(DoD-1A)**

In 1994-95, an evaluation was performed of 98 symptoms reported by 524 Gulf War veterans and 935 non-deployed veterans, who were members of 14 Seabee commands, and who had remained on active-duty from 1991 until the time of the study. (Gray, et al, 1999a) A questionnaire assessed postwar symptoms and environmental exposures during the war, and it screened for chronic fatigue syndrome, post-traumatic stress disorder, and psychological symptoms (Hopkins Symptom Checklist). The objective of this study was to investigate the usefulness of a statistical technique, factor analysis, in characterizing a Gulf War syndrome. (Knoke, et al, 2000)

Factor analysis applied to the symptoms of Gulf War veterans yielded five patterns of symptoms. These were: three patterns of psychological symptoms that derived from the Hopkins Symptom Checklist; one pattern that suggested clinical depression; and one pattern that contained various physical symptoms that are often reported by Gulf War veterans. Factor analysis applied to non-deployed veterans yielded the same five patterns of symptoms. However, Gulf War veterans reported these patterns of symptoms with greater frequencies than the non-deployed veterans did. The authors concluded that “the symptoms and illnesses of Gulf War veterans closely reflect the symptoms and illnesses reported by non-deployed veterans; Gulf War veterans simply report more of the same symptoms and illnesses.” The authors concluded that factor analysis did not identify a unique Gulf War syndrome.

Some of the earliest Gulf War veterans who reported postwar morbidity were members of a Navy Reserve unit, the Naval Mobile Construction Battalion 24 (24th Seabees). In 1994, 249 members of this unit participated in a survey (41% response). Factor analysis was used to evaluate the symptoms, which yielded six patterns of symptoms. The authors of this study interpreted these six patterns to be “unique Gulf War syndromes.” (Haley, et al, 1997a) A major strength of the active-duty Seabee population included in the 2000 study is that they had served in the same tasks (construction work) and at the same sites as the symptomatic Reserve members in the 24th Seabees. (Gray, et al, 1999a; Knoke, et al, 2000) Four of the five symptom patterns in the 2000 study, found in both Gulf War veterans and non-deployed veterans, resembled four of the six symptom

patterns in the 1997 Haley study. The authors of the 2000 study stated that the conclusion of the 1997 Haley study regarding unique syndromes “was premature and would not have been reached had a corresponding analysis on an appropriate control group been performed.”

Four major studies have been published that used factor analysis to identify patterns of symptoms. The health of thousands of Gulf War veterans has been evaluated in these four studies, involving the US Air Force; the US Navy; the US Army, Navy, and Air Force combined, and all three armed services in the United Kingdom, combined. (Fukuda, et al, 1998; Knoke, et al, 2000; Doebbeling, et al, 2000; Ismail, et al, 1999) In each of these studies, the patterns of symptoms reported by Gulf War veterans were similar to the patterns reported by non-deployed veterans. The results of these four studies are consistent with the conclusion of a recent Institute of Medicine report, which was, “Thus far, there is insufficient evidence to classify veterans’ symptoms as a new syndrome. . . All Gulf War veterans do not experience the same array of symptoms. Thus, the nature of the symptoms suffered by many Gulf War veterans does not point to an obvious diagnosis, etiology, or standard treatment.” (Institute of Medicine, 2000)

4. Bell, NS, Amoroso, PJ, Williams, JO, Yore, MM, Engel, CC, Senier, L, DeMattos, AC, and Wegman, DH. Demographic, physical, and mental health factors associated with deployment of U.S. Army soldiers to the Persian Gulf. *Military Medicine* 2000; 165(10):762-772. **(DoD-73)**

The objective of this study was to describe the prewar demographic, occupational and physical health status of active duty Army soldiers who deployed to the Persian Gulf and to compare these with the same characteristics of soldiers on active duty who did not deploy. (Bell, et al, 2000) Differences in demographic variables, health behaviors, risk-taking behaviors, and mental or physical health could influence a soldier’s postwar health status. Such factors could also influence the chance of selection for deployment. This study expands on previous studies, by examining a broader range of prewar health status measures for all Army soldiers on active duty during the war, followed over a longer prewar period. A total of 675,626 active duty Army soldiers were followed from 1980, or

upon entry into the Army if they joined after 1980, to the beginning of the Gulf War. About 38% of these soldiers were deployed to the Gulf War between August 1, 1990 and June 14, 1991.

The Total Army Injury and Health Outcomes Database were used to describe the study population's demographic, health, and behavioral characteristics. In comparison to soldiers who did not deploy, Gulf War veterans were more likely to have the following characteristics: male, fewer than 5 years of time in service, younger than 25 years of age, black, single, high school education, fewer dependents, and junior enlisted rank. Deployed soldiers were more likely to be in certain military occupational specialties: infantry/gun crews, mechanical repair, or crafts workers (e.g., plumbers, metal workers). Deployed soldiers were more likely to have received hazardous duty pay before July 1990. Compared to non-deployed soldiers, deployed soldiers received this hazardous duty pay more frequently for parachuting or for potential exposure to hostile fire before July 1990.

Rates of hospitalizations in military hospitals were evaluated from 1980 to August 1, 1990, for all causes and all injuries. After adjustment for demographic and occupational factors, deployed soldiers were at slightly, but significantly, decreased risk of hospitalization for all causes, particularly in the three years before the war. This implies that the prewar health status of deployed soldiers was as good as or better than the prewar health status of non-deployed veterans. For most years between 1980 and 1990, the risk of hospitalization for injuries was higher among the deployed soldiers, even after control of potential confounders. This could imply a greater frequency of risk-taking behavior. In addition, male gender, young age, less education, single marital status, less time in service, and receipt of two or more types of hazardous duty pay during one pay period were all significant predictors of prewar hospitalization for injuries. The authors concluded that "postwar excess injury risk may be explained in part by a propensity for greater risk-taking, which was evident before and persisted throughout the war."

5. Nisenbaum, R, Barrett, DH, Reyes, M, and Reeves, WC. Deployment stressors and a chronic multisymptom illness among Gulf War

veterans. *Journal of Nervous and Mental Disease* 2000; 188(5):259-266. **(HHS-2)**

The Centers for Disease and Control Prevention performed a survey of four Air Force units in 1995 to compare symptoms and risk factors among 1,155 Gulf War veterans and 2,520 non-deployed veterans. (Fukuda, et al, 1998) A working case definition of a chronic multisymptom illness was developed, which included 1 or more chronic symptoms from at least 2 of 3 categories (fatigue, mood and cognition symptoms, and musculoskeletal symptoms). The prevalence of mild-to-moderate cases and severe cases among Gulf War veterans was 39% and 6%, respectively, compared with 14% and 0.7% among non-deployed veterans. The objective of this analysis was to determine the association between the chronic multisymptom illness and self-reported stressors during the war, among 1,002 Gulf War veterans with complete data. (Nisenbaum, et al, 2000)

Increasing age, female gender, non-white race, current smoking, and enlisted rank were significantly associated with illness. Severe illness and mild-to-moderate illness were significantly associated with self-reports of pyridostigmine bromide (PB) use; insect repellent use on a regular basis; and the belief that chemical or biological weapons (CBW) were used against them. The authors categorized these risk factors as chemical stressors (PB and insect repellent) and emotional stressors (belief in use of CBW). Severe illness was also associated with injuries during the war that required medical attention. The authors categorized injuries as physical stressors.

The authors suggested that these chemical, emotional, and physical stressors might have triggered physiological and psychological stress responses, thereby impacting the health of some veterans. They cautioned, however, that the self-reports of exposures could be subject to recall bias. In particular, the reports could be strongly influenced by extensive media coverage or by psychological states, such as PTSD, which were not controlled in the analysis.

6. Ismail, K, Blatchley, N, Hotopf, M, Hull, L, Palmer, I, Unwin, C, David, A, and Wessely, S. Occupational risk factors for ill health in Gulf veterans of the United Kingdom. *Journal of Epidemiology and Community Health* 2000; 54(11):834-838. **(DoD-39)**

In 1997-98, a mailed survey was conducted among a randomly selected sample of 3,297 British servicemen, who had deployed to the Gulf War (70% response rate). (Unwin, et al, 1999) The objective of this particular analysis was to examine whether certain military and deployment factors were associated with increased reporting of ill health in Gulf War veterans, after adjustment for potential sociodemographic confounders. (Ismail, et al, 2000) Because there is no general consensus on the definition of ill health in Gulf War veterans, the authors used two physical health status measures and two mental health status measures. Physical ill health was measured as fatigue, using the Chalder Fatigue Questionnaire, and as a multisymptom illness, based on the Centers for Disease Control and Prevention working case definition. (Fukuda, et al, 1998) Psychological ill health was measured as psychological distress, using the General Health Questionnaire-12, and as a measure of post-traumatic stress reaction.

There was a significant relationship between decreasing military rank and all four health outcomes. Privates were about two to three times more likely to report ill health than officers were. Rank may be considered as a proxy indicator for socioeconomic status, which is associated with both physical and psychological morbidity in civilian populations. At the time of the survey, 57% of the Gulf War veterans had left the armed forces. Veterans who had been discharged were about two times more likely to report all four health outcomes. Gulf War veterans who were divorced or separated were about two times more likely than married veterans to report psychological distress or post-traumatic stress reaction, which is similar to associations seen in civilian populations. There was a highly significant linear trend between smoking and all four health outcomes.

The authors hypothesized that Royal Army personnel might have been in closer geographical proximity to some of the environmental exposures implicated during the war, than Royal Navy or Royal Air Force personnel. Nonetheless, Army personnel reported the same levels of health problems as Navy and Air Force personnel. Combat troops, such as the infantry, reported the same levels of health problems as support troops, such as engineering or medical personnel. One possible

explanation is that the ground war only lasted four days, whereas chemical and biological weapons were a real threat for several months and beyond the immediate geographical frontline.

7. Hotopf, M, David, A, Hull, L, Ismail, K, Unwin, C, and Wessely, S. Role of vaccinations as risk factors for ill health in veterans of the Gulf War: cross-sectional study. *British Medical Journal* 2000; 320(7246):1363-1367. **(DoD-39)**

In 1997-98, a mailed survey was conducted among a randomly selected sample of 3,284 British servicemen, who had deployed to the Gulf War (70% response rate). (Unwin, et al, 1999) The objective of this particular analysis was to explore the relationship between ill health after the Gulf War and vaccines received before or during the conflict. (Hotopf, et al, 2000) Because recall bias can be a problem, this study only used data from veterans who reported that they still had their vaccine records (n=923; 28% of responders). The associations of vaccinations with six health outcomes were evaluated. These were: fatigue, using the Chalder Fatigue Questionnaire; multisymptom illness, based on the Centers for Disease Control and Prevention working case definition (Fukuda, et al, 1998); psychological distress, using the General Health Questionnaire-12; a measure of post-traumatic stress reaction; health perception, using the SF-36; and physical functioning, using the SF-36.

Multiple vaccines (defined as 5 or more vaccines) received before deployments were associated with only one of the six health outcomes (post-traumatic stress reaction). In contrast, five of the six outcomes were associated with multiple vaccines received during deployment (all but post-traumatic stress reaction). The strongest association was with the CDC multisymptom illness (odds ratio of 5.0). In addition, the associations were evaluated between multiple vaccinations and three atopic conditions (asthma, hay fever, and eczema or psoriasis). There were no significant associations between vaccines, before or during deployment, and these atopic conditions. Anthrax vaccination was not associated with the CDC multisymptom illness, whether given before or during deployment.

The pattern of vaccines given before deployment was different from the pattern given during deployment, with more "routine" vaccines and

fewer biological warfare vaccines given before deployment. In addition, there were probably reasons why some veterans received vaccines during the war rather than before it, including, veterans who received vaccines during deployment tended to have been deployed earlier; and Army personnel were more likely to receive multiple vaccines during deployment than Navy or Air Force personnel. The authors concluded that multiple vaccines in themselves do not seem to be harmful, in that the combination of multiple vaccines before deployment seemed safe. However, multiple vaccines, combined with the “stress” of deployment, might be associated with ill health. The authors recommended that “every effort should be made to maintain routine vaccinations during peacetime;” or at least, “early vaccination with as long a gap as possible before the actual stress of deployment would be prudent.”

This study has raised a number of methodological concerns, in particular, that the restricted sample of 923 veterans who kept their vaccine records might be biased in some way. (Shaheen, 2000; Bolton, et al, 2001) For example, symptomatic veterans who kept their vaccine records might have discerned the study hypothesis, and therefore over-reported the vaccines they received. The authors are continuing their investigation, using a case-control design comparing healthy and ill Gulf War veterans, and relying on Ministry of Defence medical records to validate vaccine use. (Hotopf, et al, 2001)

8. Steele, L. Prevalence and patterns of Gulf War illness in Kansas veterans: association of symptoms with characteristics of person, place, and time of military service. *American Journal of Epidemiology* 2000; 152(10):992-1002. **(Not Federally funded; funded by state of Kansas)**

The objective of this study was to describe the prevalence and risk factors for health problems in 1,548 Gulf War veterans, in comparison with 482 non-deployed veterans. (Steele, 2000) Telephone interviews were conducted in 1998, achieving a 65% participation rate. Veterans currently living in Kansas in 1998 were eligible if they had served on active-duty some time between August 1990 and July 1991; and if they were separated or retired from the military or currently serving in the Reserve. Note that this sampling design lead to a skewed sample that contained 55% Reserve/National Guard, which is

more than three times the proportion that served during the war (17% Reserve/National Guard). In other studies, Reserve/National Guard troops have invariably reported more symptoms than active-duty troops. (Iowa, 1997; Sharkansky, et al, 2000; Kang, et al, 2000)

47% of Gulf War veterans stated their health was worse in 1998 than in 1990, compared to 19% of non-deployed veterans. Gulf War veterans reported significantly higher rates of 10 of 21 medical conditions that were diagnosed or treated by a physician, such as depression, arthritis, migraine headache, or PTSD. Gulf War veterans reported significantly higher rates of all 37 of 37 symptoms. Notably, there were no reported differences in the rates of hospitalizations (1991 to 1998) or rates of application for VA disability benefits (1991 to 1998).

The author proposed a Kansas case definition of “Gulf War Illness” as the report of chronic symptoms in 3 or more of 6 domains (fatigue/sleep problems; pain symptoms; neurologic/cognitive/mood symptoms; gastrointestinal symptoms; respiratory symptoms; skin symptoms). This Kansas case definition was reported by 34% of Gulf War veterans and 8% of non-deployed veterans. The prevalence of this Kansas case definition was significantly associated with female gender, lower household incomes, lower education, enlisted status, and service in the Army. The prevalence of the CDC working case definition of multisymptom illness was also evaluated. (Fukuda, et al, 1998) This CDC case definition was reported by 47% of Gulf War veterans and 20% of non-deployed veterans. These data clearly indicate that Gulf War veterans and non-deployed veterans reported similar patterns of symptoms, although Gulf War veterans reported higher rates.

This study has substantial limitations, in particular, all the health data and most of the military data were self-reported. The author pointed out that “The considerable amount of media attention given to issues surrounding Gulf War-related health problems may have generated an increased awareness of symptoms among Gulf War veterans and an increased willingness to report them.” For example, 70 of the 482 veterans, whose military records did not document that they had deployed, provided a history of Gulf War service. The self-reported

deployment information of 50 of these veterans could not be verified, and their data was excluded in the analysis.

9. Smith, TC, Gray, GC, and Knoke, JD. Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 2000; 151(11):1053-1059. **(DoD-1B)**

The objective of this study was to examine the association of Gulf War service with three diseases: systemic lupus erythematosus (SLE), amyotrophic lateral sclerosis (ALS; also called Lou Gehrig's disease), and fibromyalgia (FM). All regular, active-duty personnel were included, who were on active duty during the period of August 8, 1990 to July 31, 1991. This included 551,841 service members who were deployed to the Gulf War and 1,478,704 service members who were not deployed. All military hospitalization data were evaluated for the three specific diseases, during the six-year follow-up period of August 1, 1991 to July 31, 1997.

During the six-year follow-up period, 36 Gulf War veterans and 160 non-deployed veterans were diagnosed with SLE. Gulf War service was not associated with a diagnosis of SLE (relative risk = 0.94). Other factors were significantly associated with a diagnosis of SLE: female sex (relative risk = 12.12); black race (relative risk = 3.61); and increasing age (relative risk = 1.04).

During the six-year follow-up period, 6 Gulf War veterans and 12 non-deployed veterans were diagnosed with ALS. Gulf War service was not associated with a diagnosis of ALS (relative risk = 1.66). One factor that was significantly associated with a diagnosis of ALS was increasing age. It is noteworthy that in 2000, the VA and DoD initiated an evaluation of the rates of ALS in Gulf War and non-deployed veterans, which will include data from VA, DoD, and civilian sources.

During the six-year follow-up period, 239 Gulf War veterans and 621 non-deployed veterans were diagnosed with FM. Gulf War service was significantly associated with a diagnosis of FM (relative risk = 1.23). Other factors were also significantly associated with a diagnosis of FM: female sex (relative risk = 3.28); increasing age (relative risk = 1.05); and hospitalization for any

diagnosis other than FM, during the 12 months prior to the war (relative risk = 1.63). Comprehensive Clinical Evaluation Program (CCEP) participation was a strong independent risk factor for FM. In particular, CCEP participants had 26.4 times the risk of being hospitalized for FM, compared with non-participants. It is important to note that symptoms of FM are being evaluated in three large Gulf War populations. These include questionnaires and physical examinations in the VA National Survey, Iowa study, and Portland study.

B. Brain and Nervous System Function

Overview:

Seven studies were published that focused on brain and nervous system function. These publications presented the results of studies conducted at five Federally funded research centers in Portland, Oregon, Boston, New Orleans, East Orange, New Jersey, and Washington, DC. Six of these studies included several hundred to several thousand individuals. Four of these publications relied upon neurological and/or psychiatric evaluations, rather than relying solely on self-administered surveys. (Storzbach, et al, 2000; Storzbach, et al, 2001; Fiedler, et al, 2000; Engel, et al, 2000)

The Portland Environmental Hazards Research Center performed a population-based case-control study of 2,022 Gulf War veterans. In this analysis, 241 Gulf War veterans who reported unexplained symptoms, which could not be diagnosed after a thorough evaluation, were compared with 113 healthy Gulf War veterans (controls). (Storzbach, et al, 2000) 87% of the cases had unexplained cognitive or psychological symptoms, 38% had unexplained musculoskeletal symptoms, and 42% had unexplained fatigue. There were 12 psychological tests and 6 neurobehavioral tests. Cases differed significantly from controls on all psychological test scales, in the direction of increased distress. There were significant differences on tests of posttraumatic stress disorder, psychiatric symptoms, and personality measures. Almost all psychological measures had effect sizes that were large. Case performance on all neurobehavioral tests was deficient compared to the controls. However, the deficiencies were statistically significant in only 2 of the 6 tests. All neurobehavioral tests had

effect sizes that were small. The results of the neurobehavioral tests did not support a distribution-wide deficit in ill veterans. (Storzbach, et al, 2001) The performance of about 90% of the cases was similar to the controls. In contrast, about 10% of the cases performed significantly worse than the controls on almost all the neurobehavioral tests.

Ill Gulf War veterans consistently reported more combat stressors than healthy Gulf War veterans, such as deaths of unit members. This has been demonstrated in several different groups of ill veterans. These have included veterans with posttraumatic stress disorder (PTSD) (King et al, 2000; Benotsch, et al, 2000; Engel, 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 evaluation (Storzbach, et al, 2000).

In two large longitudinal studies in Boston and New Orleans, Gulf War veterans were evaluated soon after returning from the war, and again 1 to 2 years later. (King, et al, 2000; Benotsch, et al, 2000) In both cohorts, the number of reported PTSD symptoms increased significantly from Time 1 to Time 2, rather than ameliorating over time. In the Boston cohort, the number of reported depression symptoms increased significantly from Time 1 to Time 2. (King, et al, 2000) Also, in the Boston cohort, the number of reported combat stressors increased significantly from Time 1 to Time 2.

Three studies evaluated the relationship between psychological symptoms and different types of strategies for coping with combat-related stress. (Sharkansky, et al, 2000; Benotsch, et al, 2000; Fiedler, et al 2000) In other studies, efforts to deal directly with the stressor (problem-focused or approach-based coping) tended to be associated with better outcomes, compared to attempts to alleviate the emotional distress associated with the stressor or efforts to avoid the stressor (emotion-focused or avoidance-based coping).

A subgroup of 1,058 members of the Boston cohort were selected at Time 1 because they had identified a combat-related experience as their most stressful event during the Gulf War (e.g., deaths of unit members). (Sharkansky, et al, 2000) At Time 1, increased PTSD symptoms were predicted by the number of combat-related stressors, female gender, younger age,

Reserve/National Guard status, enlisted status and by proportionately greater reliance on avoidance-based coping strategies during the war. At Time 2, PTSD symptoms were predicted by PTSD symptoms at Time 1, combat exposure, Reserve/National Guard status, and intervening stressors (such as divorce or loss of a home due to a disaster, between Time 1 and Time 2). At Time 1, depression symptoms were predicted by combat exposure, female gender, and greater reliance on avoidance-based coping strategies during the war. At Time 2, depression symptoms were predicted by combat exposure, intervening stressors, and greater reliance on avoidance-based coping strategies during the war.

In the New Orleans cohort, problem solving as a positive coping strategy decreased significantly from Time 1 to Time 2, while the disadvantageous strategy of avoidance-based coping increased significantly over time. (Benotsch, et al, 2000) Both avoidance-based coping at Time 1 and decreased family cohesion at Time 1 significantly predicted PTSD symptoms at Time 2. These relationships between coping, family cohesion, and PTSD remained significant, after controlling for emotional distress at Time 1, reported number of war zone stressors, and enlisted status.

The New Jersey Environmental Hazards Research Center performed a study to compare several risk factors among 58 Gulf War veterans, who met clinical criteria for chronic fatigue syndrome (CFS), with 45 healthy Gulf War veterans. (Fiedler, et al, 2000) Veterans with CFS reported significantly more negative life events during the 6 months following the war. Veterans with CFS reported more avoidance-based coping strategies. The authors concluded that Gulf War veterans with medically unexplained fatigue could be significantly differentiated from healthy veterans, on the basis of stressors both during and since the war (e.g., combat stressors, negative life events); personality traits (e.g., neuroticism, the tendency to experience negative, distressing emotions); and avoidance-based coping strategies.

The relationship of the diagnosis of PTSD to physical symptoms was evaluated, after controlling for the possible effects of medical diagnoses and reported environmental exposures. (Engel, et al, 2000) Symptoms and diagnoses were based on the medical records of 21,232

participants in the DoD Comprehensive Clinical Evaluation Program. Physical symptoms were determined using a 16-item checklist. Veterans diagnosed with PTSD were more likely to report each of the 16 physical symptoms. 5.2% of veterans were diagnosed with PTSD, who reported a mean of 6.7 physical symptoms. 31.4% of veterans were diagnosed with other psychological conditions, who reported a mean of 5.3 physical symptoms. 63.4% of veterans were diagnosed with non-psychological conditions, who reported a mean of 3.1 physical symptoms. The positive association between PTSD and the number of physical symptoms remained almost unchanged, even after controlling for the potentially confounding effects of other psychological diagnoses, medical diagnoses, and reported environmental exposures. The authors recommended that “Clinicians should carefully consider PTSD when evaluating Gulf War veterans with vague, multiple, or medically-unexplained physical symptoms.”

Brain and Nervous System Function- Individual Studies:

1. Storzbach, D, Campbell, KA, Binder, LM, McCauley, L, Anger, WK, Rohlman, DS, and Kovera, CA. Psychological differences between veterans with and without Gulf War unexplained symptoms. *Psychosomatic Medicine* 2000; 62(5):726-735. (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 (controls). (McCauley, et al, 1999) Cases and controls were selected from respondents to a questionnaire, which was mailed to a random sample of 2,022 Gulf War veterans who lived in Oregon or Washington. Questions focused on chronic fatigue, psychological/cognitive symptoms, and musculoskeletal symptoms. 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. Potential cases were excluded from the study if they had explainable diagnoses, or exclusionary

diagnoses, or if they denied having case symptoms at the time of clinical evaluation.

The objective of this particular analysis was to compare measures of psychological and neurobehavioral functioning between 241 Gulf War veterans with unexplained symptoms and 113 healthy Gulf War veterans. (Storzbach, et al, 2000) 87% of the cases had unexplained cognitive or psychological symptoms, 38% had unexplained musculoskeletal symptoms, and 42% had unexplained fatigue. 48% had 2 or more symptom types. There were 12 psychological tests and 6 neurobehavioral tests, which provided objective measures of memory, concentration, complex cognitive processing, and response speed.

Cases were significantly different from controls on all psychological test scales, in the direction of increased distress. There were significant differences on tests of posttraumatic stress disorder, psychiatric symptoms, and personality measures. Almost all psychological measures had effect sizes that were large. There were also significant differences on all SF-36 scales of self-rated physical health, mental health, and health-related function. Cases reported significantly greater exposure to combat stressors. Case performance on all neurobehavioral tests was deficient compared to the controls. However, the deficiencies were statistically significant in only 2 of the 6 tests (2 tests of memory, attention, and response speed). All neurobehavioral tests had effect sizes that were small.

All statistically significant psychological and neurobehavioral variables were entered as candidate variables into a logistic regression analysis, with case disposition as the dependent variable (case vs. control). Four psychological variables and no neurobehavioral variables entered into the model. The four tests were: the Hs scale of the MMPI-2, a measure of somatic symptoms associated with psychological distress; the Mississippi PTSD scale, a measure of symptoms associated with wartime posttraumatic stress; the SCIS, a measure of subjective experience of cognitive impairment; and the SF-36 General Health, a measure of perceived health. The model successfully classified 86% of the subjects overall (89% of the cases and 80% of the controls). The authors concluded that “The high degree of accurate classification based on psychological tests

highlights the relative prominence of the psychological measures, suggesting that they discriminate veterans with health symptoms from those without symptoms and should be retained as part of future batteries used to assess Gulf war veterans.”

2. Storzbach, D, Rohlman, DS, Anger, WK, Binder, LM, and Campbell, KA. Neurobehavioral deficits in Persian Gulf veterans: additional evidence from a population-based study. *Environmental Research* 2001; 85(1):1-13. (VA-6)

The Portland Environmental Hazards Research Center performed a population-based case-control study. (McCauley, et al, 1999; Anger, et al, 1999; Storzbach, et al, 2000) The objective of this particular analysis was to compare measures of psychological and neurobehavioral functioning between 239 Gulf War veterans with unexplained symptoms and 112 healthy Gulf War veterans. (Storzbach, et al, 2001) There were 12 psychological tests and 6 neurobehavioral tests, which provided objective measures of memory, concentration, complex cognitive processing, and response speed.

There was a definite bimodal distribution on one of the neurobehavioral tests, the latency time on the Oregon Dual Task Procedure (ODTP), a test of motivation, attention, and memory. (Storzbach, et al, 2001) Subjects were divided into three groups: 30 individuals who were slow on this test (“slow ODTP,” including 27 cases and 3 controls); 212 “other cases;” and 109 controls. Both subgroups of slow ODTP and other cases had significantly higher levels of abnormal results on the psychological tests than the controls. The performance of the other cases was similar to the controls on the neurobehavioral tests, whereas, the slow ODTP subgroup performed significantly worse than the controls on almost all of the neurobehavioral tests.

On the Armed Forces Qualifying Test, which each recruit must take, there were no differences between the other cases and the controls. In contrast, the subgroup of slow ODTP had significantly lower scores on this test than the controls. This raises the possibility that the neurobehavioral performance of the slow ODTP is attributable to pre-Gulf War ability. In addition, a significantly higher percentage of slow ODTP reported seeking medical treatment

during the Gulf War (73%), than the other cases (54%) or the controls (28%). The authors suggested that this difference in seeking medical attention might mean that the slow ODTP group could have been from the “unhealthy end” of the Gulf War population at the time of their deployment.

The authors pointed out that deficits on neurobehavioral tests are not markers of brain dysfunction. Cognitive abnormalities are nonspecific and associated with various conditions, including somatoform disorders and PTSD. The authors concluded that their results did not support a distribution-wide neurobehavioral deficit in ill veterans. If a distribution-wide deficit had been demonstrated, it would have important implications for the understanding of Gulf War veterans with unexplained illnesses. Instead, it appeared that a small proportion of quite symptomatic veterans, who responded very slowly on a recognition memory test, also demonstrated deficits on other tests of response speed, memory and attention.

3. King, DW, King, LA, Erickson, DJ, Huang, MT, Sharkansky, EJ, and Wolfe, J. Posttraumatic stress disorder and retrospectively reported stressor exposure: A longitudinal prediction model. *Journal of Abnormal Psychology* 2000; 109(4):624-633. (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. (Wolfe, et al 1996) 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 (Time 2), four years (Time 3), and six 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. At Time 2, 2,313 subjects participated, which was 78% of the original cohort.

The objective of this particular analysis was to use longitudinal data to evaluate risk factors for posttraumatic stress disorder (PTSD) over time. (King, et al, 2000) Comparisons were made at Time 1 and Time 2, focusing on responses on the Mississippi Scale for Combat-Related PTSD, a well-validated survey instrument. The Lauffer

Combat Exposure Scale, a validated questionnaire, was used to measure combat stressor exposure. It was supplemented by additional questions intended to represent events unique to the Gulf War, for a total of 31 combat stressors. This analysis examined the association between PTSD and retrospective self-reports of exposure to highly stressful events. In particular, it focused on the question: To what extent does PTSD symptom severity alter later reports of stressor exposure?

Mean scores on both the reported stressor measure and the PTSD scale increased between Time 1 and Time 2. On the reported stressor measure, only 9% of the subjects responded completely consistently at Time 1 and Time 2. The mean number of changes was 3 out of 31 questions. The number of no-to-yes changes was two times the number of yes-to-no changes, which means that persons who initially disavowed a particular exposure later endorsed that event. Some questions changed by as much as 30% over time. This is puzzling, since some of these exposures were serious, dramatic, and distressing events, such as “Did you see Americans or other troops killed or wounded?”

The number of changes in the stressor measure had a significant, although small, association with the severity of PTSD symptoms at both Time 1 and Time 2. One possible explanation is that increased reporting as a function of PTSD symptoms might be related to efforts to explain distress in terms of prior war experiences; veterans experiencing psychological problems might seek justification by increasing their endorsement of possible causal events. However, there was little evidence that the severity of Time 1 PTSD symptoms significantly influenced reporting of stressor exposure at Time 2. Stressor exposures reported at Time 2 were primarily related to stressor exposures reported at Time 1. The authors concluded that “changes in reporting past events over time should not necessarily be a source of undue alarm that Time 1 PTSD symptom severity accounts for those changes.”

4. Sharkansky, EJ, King, DW, King, LA, Wolfe, J, Erickson, DJ, and Stokes, LR. Coping with Gulf War combat stress: mediating and moderating effects. *Journal of Abnormal Psychology* 2000; 109(2):188-197. (VA-7)

The Boston Environmental Hazards Research Center has been performing a prospective study of 2,949 Army veterans since their return from the Gulf War in 1991. (Wolfe, et al, 1996; King, et al, 2000) The objective of this particular analysis was to evaluate the relationship between psychological symptoms at Time 1 and Time 2 and different types of strategies for coping with combat-related stress. (Sharkansky, et al, 2000) The hypothesis was that greater reliance on avoidance-based coping would be associated with worse outcomes (higher levels of symptoms of PTSD and depression). Coping is defined as conscious efforts to manage internal or external stressors that the individual perceives as exceeding existing resources. In previous studies, efforts to deal directly with the stressor (problem-focused or approach-based coping) tended to be associated with better outcomes, compared to attempts to alleviate the emotional distress associated with the stressor or efforts to avoid the stressor (emotion-focused or avoidance-based coping).

1,058 subjects (36% of the total cohort at Time 1) were selected for this analysis. These subjects were selected because they had identified a combat-related experience as their most stressful event during the Gulf War (for example, a SCUD missile attack or deaths of unit members). They were asked to identify which of 48 possible coping strategies they used to deal with the most stressful event. PTSD and depression symptoms were assessed with two validated questionnaires, the Mississippi Scale for Combat-Related PTSD and the Brief Symptom Inventory.

At Time 1, increased PTSD symptoms were predicted by combat exposure (number of combat-related stressors), female gender, younger age, Reserve/National Guard status, and enlisted status. PTSD symptoms at Time 1 were also predicted by proportionately greater reliance on avoidance-based coping strategies during the war. At Time 2, PTSD symptoms were predicted by PTSD symptoms at Time 1, combat exposure, Reserve/National Guard status, and intervening stressors (such as divorce or loss of a home due to a disaster, between Time 1 and Time 2). PTSD symptoms at Time 2 were not predicted by coping strategies during the war. At Time 1, depression symptoms were predicted by combat exposure, female gender, and proportionately greater reliance on avoidance-based coping strategies during the war. At Time 2, depression symptoms were predicted by

combat exposure, intervening stressors, and proportionately greater reliance on avoidance-based coping strategies during the war.

The authors concluded: “These data suggest that soldiers who actively attempt to cope with combat-related stress by analyzing and making efforts to solve the problem, seeking guidance and support from others, and positively reappraising the situation fared better initially and in the long run than those who coped by avoiding thinking about the situation, getting involved with distracting activities, letting off emotional steam, or resigning themselves to the situation.” They stated their data suggested “the potential value of training military personnel in more active methods of coping with war zone stress to aid in the prevention of some combat-related disorders.”

5. Benotsch, EG, Brailey, K, Vasterling, JJ, Uddo, M, Constans, JI, and Sutker, PB. War zone stress, personal and environmental resources, and PTSD symptoms in Gulf War veterans: a longitudinal perspective. *Journal of Abnormal Psychology* 2000; 109(2):205-213. **(VA-12)**

The New Orleans Veterans Affairs Medical Center has been following 348 Gulf War veterans since 1991, including 180 members of the Louisiana National Guard and 168 members of the Army, Marine, Air Force, or Navy Reserve. (Sutker, et al, 1995; Brailey, et al, 1998) The initial assessments occurred an average of 14 months after the end of hostilities (Time 1). Follow-up assessments occurred an average of 13 months later (Time 2). The assessments were identical at both time points. The 348 participants available for retesting were from an original sample of 828 (42% response at Time 2). Attrition was due to reservists having left the military, having been transferred to another unit, or being absent from drill exercises on the scheduled retest date. Although there did not appear to be important psychological differences between the participants who were retested and those who were lost to follow-up, the authors acknowledged the high rate of attrition as a limitation.

The objective of this particular analysis was to examine the relationships of resources and PTSD symptoms at two time points, including personal resources (personality hardiness and coping styles), environmental resources (social support

and family relationships), emotional distress, and potentially protective demographic variables (age and rank). (Benotsch, et al, 2000) Forty-two percent of participants reported experiencing at least one potentially traumatizing event during the war, such as encountering casualties. Probable diagnoses of PTSD were based on the PTSD Checklist, and psychological distress was assessed with the Brief Symptom Inventory (BSI), in particular, anxiety, depression, and hostility. PTSD symptoms increased significantly from Time 1 to Time 2. 39 veterans (11%) scored high enough for a probable PTSD diagnosis at Time 2. Veterans identified as having PTSD at Time 2 reported significantly greater war zone stress than veterans without PTSD.

The positive personal resources of hardiness, commitment, and control decreased significantly from Time 1 to Time 2. Problem solving as a positive coping strategy decreased significantly over time, while the disadvantageous strategy of avoidance-based coping increased significantly over time. There were no significant decreases in the environmental resources of family or other social support. Both avoidance-based coping and decreased family cohesion at Time 1 significantly predicted PTSD symptoms at Time 2. These relationships remained significant after controlling for emotional distress on the BSI at Time 1, perceived stressfulness of the war zone, and enlisted vs. officer status.

The authors concluded that “Troops returning from a war zone may be faced with the dual challenge of simultaneously accommodating to increasing emotional distress and decreasing personal resources.” For example, PTSD symptoms are likely to disrupt social relationships, and the loss of such support limits the subsequent available options to manage new sources of stress, leading, in turn, to increased emotional distress. The authors cautioned that the original directionality of cause and effect between PTSD and resources could not be determined conclusively, because of a lack of pre-war information on coping strategies, social support, and psychopathology.

6. Fiedler, N, Lange, G, Tiersky, L, DeLuca, J, Policastro, T, Kelly-McNeil, K, McWilliams, R, Korn, L, and Natelson, B. Stressors, personality traits, and coping of Gulf War veterans with chronic fatigue. *Journal of Psychosomatic Research* 2000; 48(6):525-535. **(VA-5)**

The New Jersey Environmental Hazards Research Center performed a study of veterans who were enrolled in the VA Persian Gulf Registry. (Kipen, et al, 1999; Lange, et al, 1999) The objective of this study was to compare several risk factors among Gulf War veterans, who met clinical criteria for chronic fatigue syndrome (CFS), with healthy Gulf War veterans. (Fiedler, et al, 2000) Fifty-eight veterans who reported severe fatigue and forty-five healthy veterans were selected from 1,161 veterans who were enrolled in the VA Persian Gulf Registry, and who had participated in a large mailed questionnaire in 1995-1996. This particular analysis evaluated several risk factors, including the occurrence of self-reported war-related and non-war-related stressors, personality variables, and coping styles.

These 103 veterans underwent an intensive medical history, physical exam, and blood tests. To assess Axis I psychiatric disorders according to DSM-III-R criteria, trained personnel administered a computerized standardized diagnostic interview. The 58 CFS cases were divided into two groups: 35 veterans with Axis I psychiatric illnesses within the past 12 months (CFS/psychiatric illness), and 23 veterans with no Axis I illnesses since the war (CFS/no psychiatric illness). The healthy veterans had no Axis I psychiatric illnesses since the war. Both CFS groups reported significantly more combat exposures than the healthy controls.

There were no differences among the three groups for non-war-related negative life events during the 6 months before the war or during the war. Both CFS groups reported significantly more negative life events during the 6 months following the war. Both CFS groups reported more avoidance-based coping strategies, with the CFS/psychiatric illness group reporting the highest levels of these strategies. The CFS/psychiatric illness group reported the most significant levels of negative affective state ("neuroticism," the tendency to experience negative, distressing emotions), as well as having the most difficulty in clearly identifying and communicating this distress accurately (highest level of "alexithymia"). The authors suggested that these personality attributes likely contributed to their difficulty in coping with adverse life events since the war.

The authors concluded that Gulf War veterans with medically unexplained fatigue could be significantly differentiated from healthy veterans on the basis of stressors both during and since the war (e.g., combat stressors, negative life events); personality traits (e.g., neuroticism, alexithymia); and avoidance-based coping strategies. They cautioned, however, that these results were restricted to Gulf War veterans with CFS who were willing to undergo extensive evaluation, and therefore, these results could not be generalized to all Gulf War veterans with unexplained symptoms.

7. Engel, CC, Liu, X, McCarthy, BD, Miller, RF, and Ursano, R. Relationship of physical symptoms to posttraumatic stress disorder among veterans seeking care for Gulf War related health conditions. *Psychosomatic Medicine* 2000; 62(6):739-745. **(Funded by DoD)**

The objective of this study was to test the relationship of the diagnosis of PTSD to physical symptoms, after controlling for the possible effects of medical diagnoses and reported environmental exposures. (Engel, et al, 2000) Symptoms and diagnoses were based on the medical records of 21,232 participants in the DoD Comprehensive Clinical Evaluation Program. Physical symptoms were determined using a 16-item checklist. The mean number of symptoms was 4.0. 16% of veterans reported no symptoms, while 9% reported 10 or more symptoms. Veterans diagnosed with PTSD were more likely to report each of the 16 physical symptoms. This was even true for symptoms that have no apparent relationship to the neurophysiology of PTSD, such as bleeding gums. The symptoms most frequently reported by patients with PTSD were fatigue, sleep disturbance, joint pain, memory loss, headache, depressed mood, and difficulty concentrating.

5.2% of veterans were diagnosed with PTSD, who reported a mean of 6.7 physical symptoms. 31.4% of veterans were diagnosed with other psychological conditions, who reported a mean of 5.3 physical symptoms. 63.4% of veterans were diagnosed with non-psychological conditions, who reported a mean of 3.1 physical symptoms. 7.6% of the latter group were diagnosed as healthy, who reported a mean of 1.2 physical symptoms. In addition, veterans diagnosed with PTSD reported significantly increased numbers of combat stressors,

compared to veterans diagnosed with other psychological conditions or non-psychological conditions.

A second symptom count was also evaluated, after exclusion of 5 symptoms that potentially overlap with symptoms of PTSD and other psychological disorders (depressed mood, difficulty concentrating, memory loss, sleep disturbance, and fatigue). The same order was maintained, with PTSD patients reporting the most symptoms, even after exclusion of the 5 neuropsychiatric symptoms. The authors commented that “The relationship between PTSD and different physical symptoms is remarkably consistent, irrespective of whether a given symptom overlaps with the diagnostic criteria for PTSD.”

A model was developed to predict the number of physical symptoms, including PTSD diagnoses, other psychological diagnoses, medical diagnoses, and reported environmental exposures. The positive association between PTSD and the number of physical symptoms remained almost unchanged, even after controlling for the potentially confounding effects of other diagnoses and environmental exposures. The authors cautioned that, because physical symptoms and psychological distress were assessed at the same time, it could not be determined whether distress caused amplified estimates of physical symptom severity or whether physical symptoms caused psychological distress. They recommended that “Clinicians should carefully consider PTSD when evaluating Gulf War veterans with vague, multiple, or medically-unexplained physical symptoms.”

C. Diagnosis

Overview:

Two published studies in 2000 focused on the diagnosis of infectious diseases. (Lo, et al 2000; Specht, et al, 2000) The objectives of the first study were to compare the prevalence of antibodies to *Mycoplasma fermentans* among ill and healthy Gulf War veterans, and to determine the rates of seroconversion for this organism, based on specimens obtained before and after the war. (Lo, et al, 2000) The objective of the second study was to identify infectious diseases that are endemic to the Persian Gulf region,

through review of pathology specimens obtained from Gulf War veterans. (Specht, et al, 2000)

Diagnosis-Individual Studies:

1. Lo, SC, Levin, L, Ribas, J, Chung, R, Wang, RY, Wear, D, and Shih, JW. Lack of serological evidence for *Mycoplasma fermentans* infection in army Gulf War veterans: A large-scale case-control study. *Epidemiology and Infection* 2000; 125(3):609-619. **(DoD-47)**

The objectives of this study were to compare the prevalence of antibodies to *Mycoplasma fermentans* among ill and healthy Gulf War veterans, and to determine the rates of seroconversion for this organism, based on specimens obtained before and after the war. (Lo, et al, 2000) There has been some speculation that the increased rate of symptom reporting in Gulf War veterans might be due to a previously undetected infectious organism. Some scientists and veterans have proposed occult infection with *Mycoplasma fermentans* as a possible cause.

The cases were 718 Army Gulf War veterans with chronic illnesses, which were often disabling, who had been evaluated in Phase II of the DoD Comprehensive Clinical Evaluation Program (CCEP). The controls were 2,233 Gulf War veterans who were randomly selected from Army veterans who had not enrolled in the CCEP. Cases were matched on age, gender, length of time deployed to the Gulf War, and length of time between the pre-war and post-war specimen collections. Despite the matching procedure, cases were significantly more likely to be non-white, married, and senior enlisted rank. These demographic differences were not associated with antibody status.

Before the war, 34 out of 718 cases (4.8%) and 116 out of 2,233 controls (5.2%) tested positive for antibodies to *Mycoplasma fermentans*. There were no differences in the rates of seroconversion, which means a negative result on the first antibody test, and a positive result on a later antibody test. 1.1% of cases and 1.2% of controls seroconverted. Based on a large sample size, these results provide no evidence that infection with *Mycoplasma fermentans* was associated with the development of chronic illnesses in the cases. The authors concluded that such infection is unlikely to play an

important role in the disease process of chronic illnesses in Gulf War veterans.

The results of this study of Army Gulf War veterans are quite consistent with the results of a similar study of Navy Gulf War veterans. The Navy study compared the rates of antibodies to *Mycoplasma fermentans* between Gulf War veterans and non-deployed veterans. (Gray, et al, 1999b) Antibodies to *Mycoplasma* were present both before the war and after the war. The prevalence of antibodies was similar in Gulf War veterans and non-deployed veterans. Also, antibodies to *Mycoplasma* were not associated with postwar symptoms in either Gulf War veterans or non-deployed veterans.

2. Specht, CS, Lewin-Smith, MR, Kalasinsky, VF, Peterson, MR, and Mullick, FG. The surgical pathology and cytopathology of US Persian Gulf War military veterans: Identification of diseases endemic to the theater of operations. *Archives of Pathology and Laboratory Medicine* 2000; 124(9):1299-1301. **(Funded by DoD and VA)**

The objective of this study was to identify infectious diseases that are endemic to the Persian Gulf region, through review of pathology specimens obtained from Gulf War veterans. (Specht, et al, 2000) The Kuwait Registry was established at the Armed Forces Institute of Pathology to act as a repository for surgical pathology and cytopathology specimens, which were contributed from Veterans Affairs medical centers and military medical treatment facilities. These specimens were collected as part of routine screening or as part of workups for any presenting medical complaints.

Registry diagnoses from 1992 to December 1997 were reviewed to identify infectious diseases endemic to the Persian Gulf region. This long list of infections included leishmaniasis, malaria, hepatitis A, B, and C, anthrax, and several others. Most of these endemic infectious diseases produce acute medical illnesses that do not require biopsy or surgery, or do not leave long-term specific cellular changes. The only endemic diseases that would be detectable in pathology specimens would be associated with an etiologic agent that persists within the patient for a long time or associated with a persistent cellular abnormality.

Specimens were available from 2,852 Gulf War veterans. One patient in the Registry was diagnosed with hepatitis B (prevalence of 0.04%) and 15 patients were diagnosed with hepatitis C (prevalence of 0.58%). The prevalence of these two diseases in the Registry was well below the prevalence in the general US population. It is unknown whether these cases of hepatitis were contracted before, during, or after the war. No other endemic diseases were identified in the Registry specimens. Nearly all of the 32 cases of leishmaniasis among Gulf War veterans were diagnosed before the Registry started in 1992, so the Registry did not identify any of those cases.

D. Reproductive Health

Overview:

Two published studies focused on reproductive health among Gulf War veterans. (Araneta, et al, 2000; Frommelt, et al, 2000) The objective of the first study was to determine the prevalence of major congenital abnormalities among infants of Gulf War veterans and non-deployed veterans in Hawaii, a state that conducts statewide, population-based surveillance for birth defects. (Araneta, et al, 2000) The objective of the second study was to evaluate the rates of cervical cytology abnormalities among female Gulf War veterans and non-deployed veterans, using the results of Pap smears. (Frommelt, et al, 2000)

Reproductive Health-Individual Studies:

1. Araneta, MR, Destiche, DA, Schlangen, KM, Merz, RD, Forrester, MB, and Gray, GC. Birth defects prevalence among infants of Persian Gulf War veterans born in Hawaii, 1989-1993. *Teratology* 2000; 62(4):195-204. **(DoD-1G)**

The objective of this study was to determine the prevalence of major congenital abnormalities among infants of Gulf War veterans and non-deployed veterans in Hawaii, a state that conducts statewide, population-based surveillance for birth defects. (Araneta, et al, 2000) The personal identifiers of 684,645 Gulf War veterans (GWV) and 1,587,102 non-deployed veterans (NDV) were matched against birth certificate records of 99,545 live births in Hawaii between 1989 and 1993, to identify births to military personnel. 17,182 infants were identified who were born to military parents (22% GWV and 78% NDV). Notably, 19% of

all infants born in Hawaii were born to military parents. GWV infants were less likely to have a mother in the military (5% GWV vs. 17% NDV). GWV infants were much more likely to have a parent who served in the Marine Corps (41% GWV vs. 9% NDV). There were no differences in infants born to GWV and NDV in rates of low birth weight or prematurity.

Live births were matched to records in the Hawaii Birth Defects Program. 367 infants were identified with one or more of 48 major birth defects (2% of live births). The prevalence of the 48 birth defects was similar for GWV and NDV in the prewar period (January 1, 1989 to December 31, 1990); and for the postwar period (January 1, 1991 to December 31, 1993). The prevalence of birth defects was similar among GWV before and after the war. For both GWV and NDV, the most common types of birth defects were in the genitourinary system (hypospadias and epispadias). 202 women were GWV who gave birth in 1989 to 1993. 37 of these infants were conceived before the war and 165 of these infants were conceived during or after the war. Of these 165 infants, 6 were born with birth defects.

Only one previous, large study had a similar purpose; that is, to evaluate birth defects among Gulf War veterans. This earlier study had the limitation that it included only births in military hospitals. (Cowan, et al, 1997) The 2000 study has a number of strengths, in particular, the inclusion of births in both military and civilian hospitals. (Araneta, et al, 2000) It included parents who were currently in the Reserve or National Guard, and it included live births to parents who had separated from the military (40% of the GWV and 46% of the NDV, by the end of 1993). It included birth defects diagnosed through the first 12 months of life. The authors are continuing their investigation using the same methods in 5 additional states that perform active case surveillance for birth defects--Arizona, Arkansas, California, Georgia, and Iowa.

2. Frommelt, RA, Peterson, MR, and O'Leary, TJ. A comparison of cervical pathology between United States Air Force women who did and did not serve in the Persian Gulf War. *Annals of Epidemiology* 2000; 10(5):285-292. **(Funded by DoD)**

The objective of this study was to evaluate the rates of cervical cytology abnormalities among

female Gulf War veterans and non-deployed veterans, using the results of Pap smears. (Frommelt, et al, 2000) More than 48,000 women deployed to the Gulf War, more than any other war in US history. Concerns about an increased frequency of abnormal Pap smears among women Gulf War veterans had been raised because of a 1995 survey of 525 female Air Force veterans. (Pierce, 1997) In 1995, Gulf War veterans reported a rate of 10.4% abnormal tests vs. 4.9% among non-deployed veterans.

Pap smears were collected as part of routine medical care at 28 military treatment facilities in 20 states and Japan, and forwarded to the Armed Forces Institute of Pathology. Pap smears were evaluated from 6,715 women on active-duty in the Air Force in 1994 (1,446 Gulf War and 5,269 non-deployed). Pap smears were also evaluated from a minority of these same women in 1995 and 1996. For the 3 years of data, there were no differences in the rates of abnormal Pap smears between the two groups of women. In 1994, 11.9% of the Pap smears in the Gulf War veterans were classified as "other than within normal limits," as were 10.9% in the non-deployed veterans (not significant).

The percentage of self-reported abnormal results among Gulf War veterans in the 1997 study was similar to the findings here (10.4% vs. 11.9%). (Pierce, 1997) In contrast, the percentage of self-reported abnormal results among the non-deployed veterans in the 1997 study was about half the findings here (4.9% vs. 10.9%). The authors stated that a possible explanation for the results of the 1997 study is that the non-deployed veterans failed to recall an abnormal Pap smear that did not require additional treatment, rather than a real increase in abnormal Pap smears among Gulf War veterans. The authors concluded that "Overall, the data provide little support for the hypothesis that a difference exists between Gulf War veterans and non-deployed veterans with respect to abnormal cervical cytology." (Frommelt, et al, 2000)

E. Mortality

Macfarlane, GJ, Thomas, E, and Cherry, N. Mortality among UK Gulf War veterans. *Lancet* 2000; 356(9223):17-21. **(Funded by UK Medical Research Council)**

One published study in 2000 focused on mortality in Gulf War veterans. The objective of

this study was to document the mortality experience of all 53,462 British Gulf War veterans and a matched comparison group of 53,462 non-deployed veterans in the eight years since the war. (Macfarlane, et al, 2000) The comparison group was matched on age, sex, rank, and service. Individuals were identified on central registers of the UK Office for National Statistics, and information on death among subjects was obtained, including cause of death. Follow-up started on April 1, 1991, and continued to March 31, 1999. Person-years at risk were calculated until the earliest of: date of death, date of permanent emigration from the UK, or March 31, 1999.

Vital status was determined for 97.2% of the Gulf War veterans and 95.7% of non-deployed veterans. The cohorts were 98% male and 72% were 30 years or younger on January 1, 1991. There were 395 deaths among the Gulf War veterans (0.7%) and 378 deaths among the non-deployed veterans (0.7%). Mortality due to disease-related causes was slightly lower in the Gulf War veterans (mortality rate ratio [MRR] = 0.87; 95% C.I., 0.67-1.11). There were 53 cancer deaths among the Gulf War veterans and 48 cancer deaths among the controls. There was no excess of any particular type of cancer.

Mortality due to “external” causes was slightly higher in the Gulf War veterans (MRR = 1.18; 95% C.I., 0.98-1.42). This higher mortality rate due to “external” causes was mainly due to accidents, and there were no differences in the rates of suicide or homicide. The higher mortality rate due to “external” causes in the UK is consistent with the results of a mortality study in US Gulf War veterans. (Kang and Bullman, 1996) Both the UK and US mortality studies will continue indefinitely.

F. Depleted Uranium

McDiarmid, MA, Engelhardt, SM, and Oliver, M. Urinary uranium concentrations in an enlarged Gulf War veteran cohort. *Health Physics* 2001; 80(3):270-273. **(Funded by VA and DoD)**

One published study focused on the effects of depleted uranium in Gulf War veterans. (McDiarmid, et al, 2001) In 1993, the Baltimore Veterans Affairs Medical Center began a prospective study of Gulf War veterans who had been wounded in friendly fire incidents, to

quantify body burdens of uranium over time and to detect any adverse health effects from this exposure. (Hooper, et al, 1999; McDiarmid, et al, 2000) The VA and DoD were concerned that embedded depleted uranium (DU) fragments could dissolve over time, potentially leading to toxic effects in the kidneys and other organs. Because of concern expressed by many veterans about possible DU exposure, VA and DoD initiated a national effort in August 1998 to offer a DU medical evaluation to any concerned Gulf War veteran, including urinary uranium testing. The objective of this particular study was to describe the results of the first 169 veterans who volunteered for this expanded program in August 1998 to December 1999. (McDiarmid, et al, 2001)

169 veterans submitted 24-hour urine samples for determination of urinary uranium concentration and questionnaires describing their potential exposures to DU during the Gulf War. 44 of these individuals were still on active-duty and 125 had been discharged. DU exposure was determined from 30 questions, such as inspection or repair activities in damaged Abrams tanks or Bradley vehicles with possible DU contamination, or clean-up activities after a fire at Doha, Kuwait, which included possible DU contamination.

The urinary uranium concentrations ranged from 0.001 to 0.432 micrograms uranium per gram creatinine (median of 0.010). The cut point of elevated uranium concentration was selected as 0.050 micrograms uranium per gram creatinine, based on the upper limit of normal in the general population. Twelve individuals exceeded this cut point on the first urine test. Six of these 12 were retested; and 3 were still in the elevated range and 3 were in the low range. Of the 3 individuals with repeat elevated results, one person probably had retained DU metal fragments from a friendly fire incident. The sources of the elevated results in the other 2 persons were unknown. In fact, one of them was not even a Gulf War veteran.

The authors concluded that in 2000, elevated urinary uranium levels were unlikely to be observed, except for those veterans with retained DU metal fragments. This is consistent with their previous results in the medical surveillance of veterans involved in friendly fire incidents. (Hooper, et al, 1999; McDiarmid, et al, 2000) The authors concluded, “There is little likelihood

that the possible but transient exposure to DU during the Gulf War will result in significant health issues now or in the future. . . Those with normal uranium values now are unlikely to develop any uranium-related toxicity in the future regardless of what their DU exposure may have been during the Gulf War.”

G. Chemical Weapons

Overview:

Three published studies in 2000 focused on the effects of sarin in laboratory animals. (Spruit, et al, 2000; Khan, et al, 2000; Jones, et al, 2000) None of the results of these studies can be directly extrapolated to health effects in humans, because of the high doses used and the routes of exposure (injection, in most of the studies). The first study investigated the toxicokinetics of two stereoisomers of sarin in guinea pigs. (Spruit, et al, 2000) The second study evaluated the short-term effects of sarin on several enzymes and acetylcholine receptors in Sprague-Dawley rats. (Khan, et al, 2000) The third study evaluated the effects on enzymes and permeability of the blood-brain barrier, 90 days after a single dose of sarin in Sprague-Dawley rats. (Jones, et al, 2000)

Chemical Weapons-Individual Studies:

1. Spruit, HE, Langenberg, JP, Trap HC, van der Wiel, HJ, Helmich, RB, van Helden, HP, and Benschop, HP. Intravenous and inhalation toxicokinetics of sarin stereoisomers in atropinized guinea pigs. *Toxicology and Applied Pharmacology* 2000; 169(3):249-254. **(DoD-55)**

The objective of this study was to investigate the toxicokinetics of two stereoisomers of sarin (- and +). (Spruit, et al, 2000) The - isomer causes toxic effects, while the + isomer is relatively nontoxic. Anesthetized, atropinized, and restrained guinea pigs were exposed to air concentrations of sarin for 8 minutes, which corresponded to 0.4 and 0.8 of the LCt50 (lethal air concentration in 50% of the animals). To serve as a reference for the respiratory exposures, another set of experiments was performed with an intravenous dose corresponding to 0.8 of the LD50 (lethal intravenous (IV) dose in 50% of the animals). Blood specimens were taken for analysis of sarin level and blood acetylcholinesterase level

(AChE). In all experiments, the blood concentrations of the non-toxic isomer of sarin (+) were below the detection limit. In both the IV and respiratory experiments, the toxicokinetics of the toxic isomer of sarin (-) showed a significant non-linearity with dose. During the respiratory experiments, the blood AChE levels decreased rapidly during the exposure period. At a dose of 0.4 and 0.8 of the LCt50, the AChE decreased to about 70% and 15% of control activity, respectively.

2. Khan, WA, Dechkovskaia, AM, Herrick, EA, Jones, KH, and Abou-Donia, MB. Acute sarin exposure causes differential regulation of choline acetyltransferase, acetylcholinesterase, and acetylcholine receptors in the central nervous system of the rat. *Toxicological Sciences* 2000; 57(1):112-120. **(DoD-72)**

The objective of this study was to evaluate the short-term effects of sarin on several enzymes and acetylcholine receptors concurrently, because of the central role of the cholinergic system in the manifestation of toxic symptoms of sarin. (Khan, et al, 2000) Previous studies have shown that changes in acetylcholine-related metabolism are the key regulators of central nervous system toxicity of sarin and other organophosphate chemicals. The acute effects of intramuscular injections of sarin were studied in male Sprague-Dawley rats. The rats were treated with injections of either 1 x LD50 (lethal dose in 50% of the animals) and sacrificed at several different time points, up to 20 hours after treatment; or they were treated with smaller doses of sarin (0.01, 0.1 or 0.5 x LD50) and sacrificed 15 hours after treatment. Plasma butyrylcholinesterase levels (BChE) and brain acetylcholinesterase levels (AChE) were inhibited 45-50%, 30 minutes after the LD50 dose. BChE in the plasma and AChE in various brain regions remained inhibited for up to 20 hours after a single LD50 dose. No inhibition in plasma BChE was observed 20 hours after treatment with doses lower than the LD50 dose. Another enzyme, choline acetyltransferase (ChAT) is considered a specific marker of cholinergic innervation in the brain, because it catalyzes the final step in the biosynthesis of acetylcholine. ChAT activity was increased in various brain regions 6 hours after LD50 treatment, and this elevated enzyme activity persisted up to 20 hours after treatment. Overall, sarin caused significant inhibition of brain region-specific AChE and activation of ChAT.

The elevated activity of ChAT in the brain may enhance the availability of acetylcholine above and beyond that caused by inhibition of AChE alone. This combination of effects on enzymes could lead to overstimulation of the receptors for acetylcholine in the brain.

3. Jones, KH, Dechkovskaia, AM, Herrick, EA, Abdel-Rahman, AA, Kahn, WA, Abou-Donia, MB. Subchronic effects following a single sarin exposure on blood-brain and blood-testes barrier permeability, acetylcholinesterase, and acetylcholine receptors in the central nervous system of rat: a dose-response study. *Journal of Toxicology and Environmental Health* 2000; 61(8);695-707. **(DoD-72)**

The objective of this study was to evaluate the effects after 90 days of a single intramuscular dose of sarin in male Sprague-Dawley rats. (Jones, et al, 2000) The animals were treated once with various doses of sarin (0.01, 0.1, 0.5, or 1 x LD50-lethal dose in 50% of the animals), and then sacrificed 90 days later. The blood-brain permeability was measured in various brain regions at 90 days. The brainstem showed a significant decrease in the permeability of the blood-brain barrier (BBB), at the 1 x LD50 dose. There were no changes in the permeability of the BBB at any dose in the other brain regions. Plasma butyrylcholinesterase (BChE) activity was at control levels at 90 days, reflecting recovery of the enzyme activity from its initial inhibition. At the 1 x LD50 dose, acetylcholinesterase activity (AChE) in the brain cortex remained inhibited at 90 days, whereas AChE activity in the brainstem showed an increase. These results suggest that BBB changes in the brainstem and inhibition of AChE in the cortex are persistent as long as 90 days after a single 1 x LD50 dose of sarin. Even though the rats had recovered from all the acute clinical effects, there were persistent changes in the brain that could play a role in neuropathological conditions, long after a single, high-dose sarin exposure.

H. Pyridostigmine Bromide

Li, L, Gunasekar, PG, Borowitz, JL, and Isom, GE. Muscarinic receptor-mediated pyridostigmine-induced neuronal apoptosis. *NeuroToxicology* 2000; 21(4):541-552. **(DoD-59)**

One published study in 2000 focused on the effects of pyridostigmine bromide (PB) alone. (Li, et al, 2000) The objective of this study was to evaluate the potential of PB to produce cell death in the brains of male Sprague-Dawley rats. Rats were injected (intraperitoneally) with one of four doses of PB twice daily for 4 days.

Apoptosis, which is a sequential process of programmed cell death, was evaluated by special histological studies of the brains. Apoptotic brain cell death was noted in the cerebral cortex of some rats, at all 4 doses, and at the highest dose, it was also noted in the striatum and hippocampus of some rats. These cell death processes were blocked by pretreatment with atropine 30 minutes before PB injection. The results of these experiments in rats cannot be directly extrapolated to humans because of the very high doses of PB, and because the route of administration was injection directly into the abdomen. PB did not cause a significant decrease in brain cholinesterase activity, which implies that PB did not cross the blood-brain barrier. The authors stated that the mechanism could possibly be due to either central or peripheral action. The possibility of peripheral action has been suggested by other studies. (Van Haaren, et al, 1999, 2000; Chaney, et al, 1999, 2000)

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

Overview:

Five published laboratory studies in 2000 focused on the effects of pyridostigmine bromide in combination with stress. (Grauer, et al, 2000; Sinton, et al, 2000; Servatius, et al, 2000; Somani, et al, 2000; Verma-Ahuja, et al, 2000)

Four published laboratory studies focused on the effects of pyridostigmine bromide (PB), in combination with other chemicals (DEET or permethrin). (Hoy, et al, 2000a; Hoy, et al, 2000b; van Haaren, et al, 2000; Chaney, et al, 2000)

Stress alone has been shown to induce significant changes in blood-brain barrier (BBB) permeability in young rats and mice, but little or no change 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 CNS. These studies have been conducted primarily in young, immature animals. (Ben-Nathan, et al, 1989; Dvorska, et al, 1992; Sharma, et al, 1991; Sharma, et al, 1992; Sharma, et al, 1995; Wijsman and Shivers, 1993) 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)

Several studies have recently evaluated whether stress can increase BBB permeability, and can therefore enhance penetration of PB into the brain. These have included several species and strains of animals: 3 different strains of mice (Telang, et al, 1999; Chaney, et al, 1999; Grauer, et al, 2000); guinea pigs (Lallement, et al, 1998); and 3 strains of rats (Sinton, et al, 2000; Chaney, et al, 2000). These studies have included several types of acute stressors: forced swimming stress (Telang, et al, 1999; Grauer, et al, 2000; Sinton, et al, 2000); heat stress (Lallement, et al, 1998; Sinton, et al, 2000); severe cold stress (Grauer, et al, 2000); restraint stress (Sinton, et al, 2000); and chemical stress (coadministration of high doses of DEET) (Chaney, et al, 1999; Chaney, et al, 2000).

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 lethal doses. For example, Sinton, et al, 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, Haley, et al, 2000) This conclusion is particularly noteworthy because it is contradictory to a report by one of the authors. He had 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, 1997b)

These recent findings about PB and stress are consistent with the conclusion of a recent White House report on illnesses in Gulf War veterans, as follows: “Several more recent studies have failed to reproduce this finding [of Friedman’s study in 1996] using a variety of species, a variety of stressful stimuli, and extremely high doses of PB. If PB does not cross the BBB, it is very unlikely to cause changes in brain function.” (White House, 2000)

Interactions of Exposures-Individual Studies:

Interactions of PB in Combination with Stress-Individual Studies:

1. Grauer, E, Alkalai, D, Kapon, J, Cohen, G, and Raveh, L. Stress does not enable pyridostigmine to inhibit brain cholinesterase after parenteral administration. *Toxicology and Applied Pharmacology* 2000; 164(3):301-304. **(Not Federally funded; Israeli study)**

The objective of the Grauer study was to determine the effects in mice of pyridostigmine bromide (PB), with or without stress. (Grauer, et al, 2000) PB was injected at a dose that was equivalent to about 0.1% of the LD50. Two strains of adult mice were used, including CD-1 and FVB/n, the same strain used in Friedman’s study. (Friedman, et al, 1996) There was no inhibition of brain AChE due to mild stress (swimming) or severe stress (standing in ice water). No change in brain AChE activity was detected in any of the groups treated with PB, with or without stress. Even with variations in gender, strain of mouse, and type of stressor, the authors concluded that they could not replicate Friedman’s findings that suggested that PB could affect brain AChE following stress.

2. Sinton, CM, Fitch, TE, Petty, F, and Haley, RW. Stressful manipulations that elevate corticosterone reduce blood-brain barrier permeability to pyridostigmine in the rat. *Toxicology and Applied Pharmacology* 2000; 165(1):99-105. **(Not Federally funded; funded by the Perot Foundation)**

The objective of Sinton study was to determine the effects of stress on the permeability to PB in the brains of two strains of adult male rats, Long-Evans and Wistar. (Sinton, et al, 2000) Three main types of stress were used: a forced swim stress, a restraint stress, and a combination of swim and restraint. In addition, a smaller number of rats were subjected to heat stress. Rats were injected intraperitoneally with one of five doses of PB; the three highest doses caused severe signs of toxicity. Both the dosage of PB and the effects of each type of stress were significantly associated with decreased brain AChE levels. However, stress reduced the penetration of PB across the BBB. The authors 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.” This conclusion is particularly noteworthy because it is contradictory to a report by one of the authors. He had 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, 1997)

3. Servatius, RJ, Ottenweller, JE, Guo, W, Beldowicz, D, Guanping, Z, and Natelson, BH. Effects of inescapable stress and treatment with pyridostigmine bromide on plasma butyrylcholinesterase and the acoustic startle response in rats. *Physiology and Behavior* 2000; 69(3):239-246. **(VA-49)**

The objectives of the Servatius study were 1) to determine whether exposure to inescapable stress decreased plasma butyrylcholinesterase (BuChE) levels in male Sprague-Dawley rats; and 2) to determine whether concurrent exposure to stress and PB would produce persistent neurobehavioral changes in rats. (Servatius, et al, 2000) A supine restraint protocol was chosen to evaluate the effects of inescapable stress. Exposure to supine restraint alone induced a persistent decrease in plasma BuChE levels. However, the combination of stress plus PB did

not cause further decreases in BuChE levels. Exposure to restraint stress caused an exaggerated startle response, evident on the last day of stress (Day 7) and for an additional 24 hours. This exaggerated response did not persist at 8, 15, or 22 days after cessation of stress. PB also caused an exaggerated startle response over the same time period, but to a lesser degree. However, treatment with PB appeared to antagonize the effects of stress on startle response (stress plus PB had less effect than stress alone). Two major strengths of this study included the use of oral PB doses that were relevant to those used by humans, and the follow-up period of 22 days after the cessation of treatment with stress or PB, which demonstrated reversibility of the effects on startle response.

4. Somani, SM, Husain, K, Asha, T, and Helfert, R. Interactive and delayed effects of pyridostigmine and physical stress on biochemical and histological changes in peripheral tissues of mice. *Journal of Applied Toxicology* 2000; 20(4):327-334. **(DoD-62)**

The objective of the Somani study was to investigate the effects of PB and treadmill exercise on cholinesterase activity and histology of peripheral tissues in male, adult NIH Swiss mice. (Somani, et al, 2000) There were four groups of mice: sedentary controls; exercise training for 10 weeks; PB during weeks 5 and 6, but no exercise training; and exercise training for 10 weeks, plus PB during weeks 5 and 6. The oral dose of PB in the mice was chosen to correspond to the dose (1.2 mg per kg body weight) and duration (2 weeks) that veterans used during the Gulf War. Each group of mice was sacrificed at 10 weeks, at which time blood and muscle chemistries and histological studies were performed. Overall, there were no significant chemistry changes due to exercise alone or PB alone. There were only a few significant changes in blood and muscle chemistries related to the combination of exercise plus PB. There were no obvious histological abnormalities in the triceps muscle among the four groups.

5. Verma-Ahuja, S, Husain, K, Verhulst, S, Espinosa, JA, and Somani, SM. Delayed effects of pyridostigmine and exercise training on acetylcholinesterase and muscle tension in mouse lower extremity. *Archives of Toxicology* 2000; 74(9):539-546. **(DoD-62)**

The objective of the Verma-Ahuja study was to investigate the effects of PB and treadmill exercise on muscle tension and acetylcholinesterase activity in male, adult NIH Swiss mice. (Verma-Ahuja, et al, 2000) There were four groups of mice: sedentary controls; exercise training for 10 weeks; PB during weeks 5 and 6, but no exercise training; and exercise training for 10 weeks, plus PB during weeks 5 and 6. Each group of mice was sacrificed at 10 weeks, at which time muscle tension studies and blood and muscle chemistries were performed. There were no differences in triceps muscle levels of AChE among the controls, the exercise alone group, and the PB alone group. The exercise plus PB group demonstrated a significant decrease in AChE levels in triceps muscle (79% of control levels; $p < 0.01$). Muscle tension was measured in the lower extremity by flexing the foot and stimulation of the peroneal nerve. There was a significant increase in muscle tension in the exercise plus PB group, compared to the control and exercise alone groups. The authors do not discuss the relevance of a daily, strenuous treadmill test in mice to sedentary or exercising humans. There was no follow-up after cessation of the treadmill exercise to determine if the changes in muscle tension or blood and muscle chemistries were prolonged, which is relevant to the possible effects in humans.

Interactions of PB in Combination with Other Chemicals-Individual Studies:

1. Hoy, JB, Cornell, JA, Karlix, JL, Schmidt, CJ, Tebbett, IR, and van Haaren, F. Interactions of pyridostigmine bromide, DEET, and permethrin alter locomotor behavior of rats. *Veterinary and Human Toxicology* 2000a; 42(2):65-71. **(DoD-37)**

The objective of the first Hoy study was to determine if there were interactions of various combinations of PB, DEET and permethrin on the locomotor behavior of male and female Sprague-Dawley rats. (Hoy, et al, 2000a) Various doses of PB and DEET were given by gavage, and various doses of permethrin were injected. The routes of exposures for DEET (oral) and permethrin (injection) in the rats caused higher doses than could have been absorbed in a few hours of dermal exposure in soldiers. The three chemicals were tested singly and in various combinations to determine the effects on the rate of locomotion in a one square

meter open-field arena, during a two-hour period. Single drug effects were very limited with the doses tested. In particular, PB caused no effects at 10 mg per kg of body weight. Two-drug administrations at half the single-drug doses resulted in significant interactions in male rats only. Female rats did not show any significant interactions. In male rats, the combinations of permethrin plus PB or permethrin plus DEET caused a significantly decreased speed of locomotion. There was no follow-up to determine if the behavioral changes due to the chemical combinations were prolonged, which is relevant to the possible effects in humans.

2. Hoy, JB, Cornell, JA, Karlix, JL, Tebbett, IR, and van Haaren, F. Repeated coadministrations of pyridostigmine bromide, DEET, and permethrin alter locomotor behavior of rats. *Veterinary and Human Toxicology* 2000b; 42(2):72-76. **(DoD-37)**

The objective of the second Hoy study was to determine the effects of repeated administrations of PB, DEET and permethrin, alone and in combination, on the locomotor behavior of male and female Sprague-Dawley rats. (Hoy, et al, 2000b) Various doses of PB and DEET were given by gavage, and various doses of permethrin were injected. The three chemicals were tested singly and in various combinations to determine the effects on the rate of locomotion in a one square meter open-field arena. Twenty-four hours after the last of 7 daily drug administrations, locomotor behavior was quantified by video camera for one hour. Single-drug administrations caused no significant effects compared to controls. Both male and female rats given DEET plus PB had a significantly slower locomotion rate. Males given DEET plus permethrin had a significantly faster locomotion rate. Three-drug administration (at one-third the single-drug doses) caused no significant effects. There was no follow-up to determine if the behavioral changes due to the chemical combinations were prolonged, which is relevant to the possible effects in humans.

3. van Haaren, F, Cody, B, Hoy, JB, Karlix, JL, Schmidt, CJ, Tebbett, IR, and Wielbo, D. The effects of pyridostigmine bromide and permethrin, alone or in combination, on response acquisition in male and female rats. *Pharmacology Biochemistry and Behavior* 2000; 66(4):739-746. **(DoD-37)**

The objective of the van Haaren study was to investigate the effects of PB and permethrin, alone or in combination, on the acquisition of a learned response in male and female Sprague-Dawley rats. (van Haaren, et al, 2000) The rats were treated with PB or distilled water by gavage for 7 days. Half of the rats also received an intraperitoneal injection of permethrin, at one of two doses, before they were placed in an experiment, in which they could earn food pellets by pressing a lever in a learning chamber. Permethrin alone had no effect on acquisition of the learned response. PB caused delayed acquisition of the learned response in male and female rats, and decreased the number of reinforced responses. Permethrin levels were higher in rats that were treated with PB; however, the combination of PB plus permethrin did not cause a decrement in learning, compared to the rats treated with PB alone. There were no measurements of brain levels of PB, permethrin, or acetylcholinesterase; therefore, it is unknown whether these chemicals crossed the blood-brain barrier. There was no follow-up to determine if the behavioral changes due to the chemicals were prolonged, which is relevant to the possible effects in humans.

4. Chaney, LA, Wineman, RW, Rockhold, RW, and Hume, AS. Acute effects of an insect repellent, N,N-Diethyl-m-toluamide, on

cholinesterase inhibition induced by pyridostigmine bromide in rats. *Toxicology and Applied Pharmacology* 2000; 165(2):107-114. **(Not Federally funded)**

The objective of the Chaney study was to investigate changes in acetylcholinesterase (AChE) levels in the brain and periphery (diaphragm, heart, and blood) after injection of PB and/or DEET in male Sprague-Dawley rats. (Chaney, et al, 2000) The intent was to determine if the combination caused inhibition of brain AChE. Several animals receiving the highest PB alone dose experienced seizures and died shortly after dosing. Combinations of PB and DEET, at all PB doses, caused seizures and death in some animals. PB alone did not alter brain AChE levels, even at doses that caused lethality. DEET alone had no effects on peripheral or brain AChE levels. PB plus DEET caused a significant decrease of brain AChE at only the highest PB dose (60% of the control levels). This study demonstrates that doses of PB alone and PB plus DEET, that were high enough to cause seizures and lethality, did not cause an effect on brain AChE in most animals. This means that even these high doses did not cause increased permeability of the blood-brain barrier. Because these massive doses caused seizures and death within minutes, the results of this study cannot be directly extrapolated to humans.

III. RESEARCH FUNDING TRENDS

A. Overview

Appendix A provides details of the Gulf War Veterans' Illnesses Research Database. It was last updated during the second quarter of Fiscal Year 2001 (through March 31, 2001). Research projects are grouped according to the Department that is responsible for the conduct or sponsorship of the research.

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 can approximately 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 other 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 disease risk factors.

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 medical records reviews.

In addition to the research on Gulf War veterans' illnesses, the RWG 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 RWG 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 Gulf War Veterans' Illnesses Research Database 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 40 years.

The Gulf War Veterans' Research Database only contains research that is Federally sponsored. 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 RWG attempts to stay abreast of all research relevant to Gulf War veterans' illnesses. The RWG accomplishes this by monitoring the peer reviewed published scientific literature, attending scientific meetings, and even using newspaper reports and personal accounts of researchers.

Regardless of the source of support for particular research projects, the RWG will ensure that all research, which has been published in peer reviewed scientific literature, will be used in formal assessments of the nature and causes of Gulf War veterans' illnesses. A number of projects that were not Federally funded have been reviewed in Section II. Research Results of this *Annual Report to Congress*.

A formal assessment of the nature and causes of illnesses in Gulf War veterans has been included in this *Annual Report to Congress* in Appendix C. In 1996, the RWG 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 provides 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 1994-2001 (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 are sponsored by VA, DoD, or HHS. From 1994 through 2000, the Departments have sponsored 193 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 planned DoD Broad Agency Announcement (BAA) for 2001.

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 FY00, and a projection of funding into FY01. Currently, the Federal Government is projecting cumulative expenditures of \$173.6 million for research from FY94 through FY01. As of September 30, 2000, 100 projects were completed. As of March 31, 2001, an additional 16 projects were completed, and 77 projects were ongoing (40% of total of 193 projects).

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

Department	FY'94	FY'95	FY'96	FY'97	FY'98	FY'99	FY'00	FY'94-00	FY'01
DoD	\$ 6.2	\$11.0	\$11.7	\$28.9	\$12.6	\$23.2	\$16.3	\$109.8	\$10.6
VA	\$ 1.2	\$ 2.3	\$ 3.9	\$ 2.8	\$ 4.8	\$ 9.1	\$12.1	\$ 36.1	\$ 7.9
HHS	\$ 0.0	\$ 2.5	\$ 1.6	\$ 0.0	\$ 1.6	\$ 1.6	\$ 1.6	\$ 9.0	\$ 0.2
Total	\$ 7.4	\$15.8	\$17.2	\$31.7	\$19.0	\$33.9	\$30.0	\$154.9	\$18.7

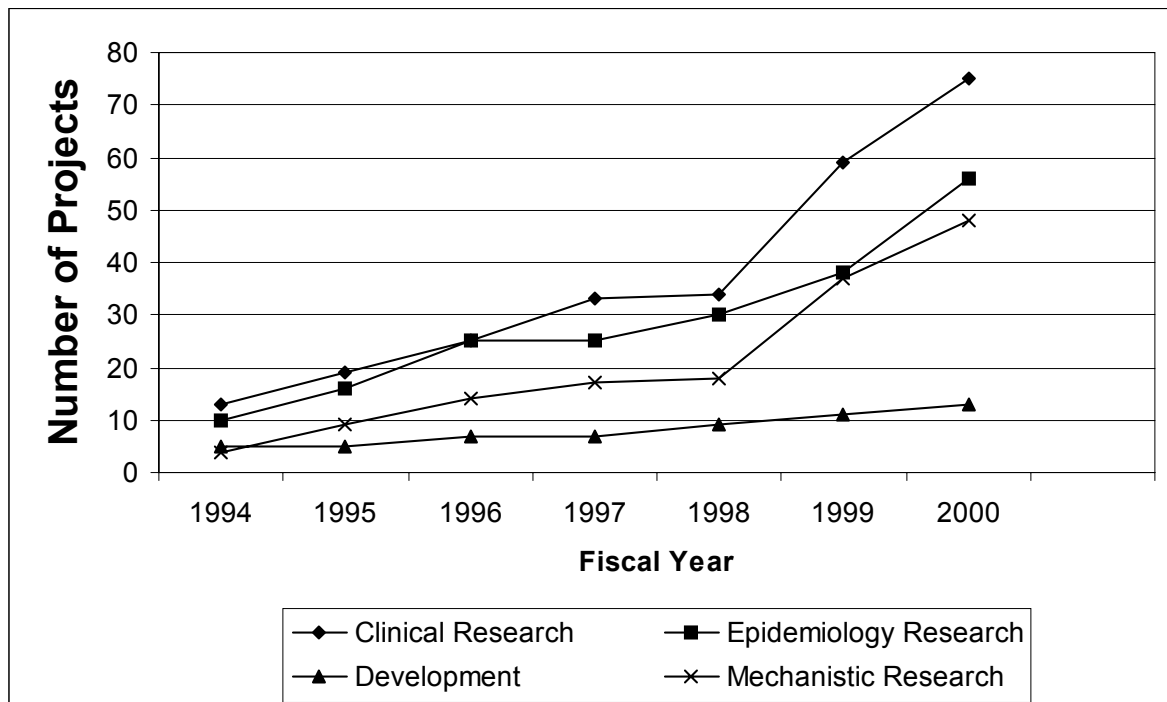
Table III-1. does not include funds to cover operational costs for administration, infrastructure, etc. For example, the VA research appropriation does not pay for clinician/investigator salaries. In addition, Table III.1. does not include funding for activities performed by members of the RWG (salaries, travel, etc.). The FY'01 funds are estimated, and they do not include funds for anticipated or future solicitations.

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

<i>Fiscal Year</i>	<i>New</i>	<i>Completed</i>
1992-1994	61	3
1995	21	8
1996	16	4
1997	35	10
1998	17	15
1999	29	22
2000	14	38

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

Figure III-1. Cumulative number of research projects by research type (1994-2000).



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. **Figure III-1** illustrates the number of projects of each research type for each year since FY94. 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. In particular, the numbers of clinical and mechanistic research projects have increased more rapidly over time.

The distribution of projects across different research focus areas is illustrated in **Figure III-2**. Projects for each focus area are categorized, based on which of the focus areas 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-2 in two ways. For each focus area, a black bar represents the total number of projects for which that focus area is listed as being primary. A clear bar represents the total number of projects for which the focus area is listed as being 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-2**, the overall emphasis of research has been greatest in the focus areas of the Brain and Nervous System and in Symptoms and General Health. 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 many of the potential exposures in the Gulf were to neurotoxins.

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. Of note is a relatively greater increase over the years of research on chemical interactions, chemical warfare agents and pyridostigmine bromide. These increases are an outgrowth of increased concern over the health risks posed to veterans by exposures to multiple toxic agents at low levels.

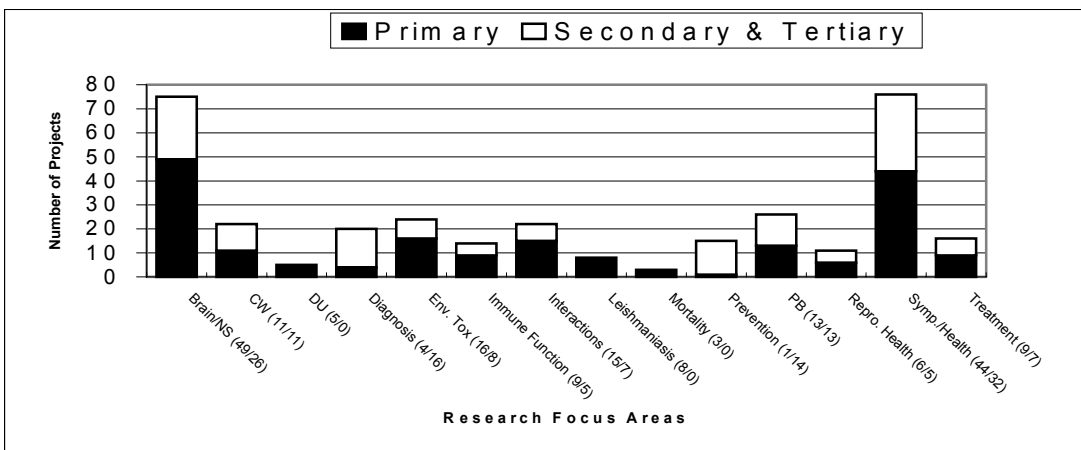


Figure III-2. Number of projects in each research focus area. Closed bars represent the number of projects with the focus area as primary; open bars represent the number of projects with the focus area being either secondary or tertiary. The first number within the parenthesis represents the number of projects with a primary research focus area. The second number represents the number of projects with a secondary or tertiary research focus area

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 2000 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 RWG (PGVCB, 1995b; PGVCB, 1996b).

IV.A. NEW RESEARCH PROJECTS

IV. A. 1. New Research Projects Funded by the 2000 DoD Broad Agency Announcements

In 1998, DoD established new funding for programmed research. The purpose of this program element funding is to address Gulf War veterans' illnesses issues, which may also be of concern in future deployments. These include issues identified in both the research plans of the PGVCB and the Presidential Review Directive 5. (PGVCB, 1995b; PGVCB, 1996b; NSTC, 1998) This planned funding is approximately \$20 million per year for fiscal year 1999 through fiscal year 2002, and \$5 million per year thereafter. This funding makes it possible to organize multi-year research and improves the ability to respond to new research needs based on discoveries in the currently funded programs. The program is guided by a tri-service DoD panel and coordinated with the RWG.

The overall objective of this effort is to enhance Force Health Protection in future deployments, through research specifically targeted to solving problems that emerged from service in the Gulf War. Specific research areas include:

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;
4. epidemiological studies to continue long-term follow-up of Gulf War veterans and to improve health status monitoring in future deployments; and
5. improved and accelerated research on leishmaniasis prevention, diagnosis, and treatment.

In coordination with the RWG, DoD developed a new research initiative for Fiscal Year 2000. Under this initiative, DoD solicited new research proposals for studies consistent with current concepts of Force Health Protection. There were four Broad Agency Announcements (BAAs), each with a deadline of July 26, 2000.

The specific requests focused on the following four areas of research interest:

1. Epidemiological Investigations of Deployment Health Monitoring Methods

The purpose of these epidemiological studies is to fill critical knowledge gaps for monitoring soldier health during deployments. Threats to health during deployments might include psychological stress, toxic chemical exposures, environmental stressors, and infectious agents. The focus is on physiologically based methods to assess deployment health consequences, through a demonstrated change in health. Projects are required to have a strong biological basis (i.e., objective measurements instead of subjective/questionnaire assessments). Studies are specifically sought in four topic areas:

- a. psychological health status, including establishment of mental health baselines of military populations;
- b. practical methods for large-scale studies to assess changes in male and female reproductive fertility;
- c. clinical illness associated with high frequency of deployments or perceived stress of deployments; and
- d. coping strategies used by military personnel to alleviate symptoms associated with Gulf War

deployment (e.g., alcohol or complementary and alternative medicine).

2. Deployment Stress Health and Performance Consequences

These studies focus on the effects of psychological stress on cognitive and physiological consequences. Studies should quantify the association between clinical health outcomes or militarily-relevant performance measures and various types of stress, which might be typically encountered in military field deployments (e.g., isolation, family separation, anxiety, inadequate sleep). The studies should explore biological stress measures, which may be useful predictors of health and performance decrements.

3. Biochemical and Physiological Markers to Assess Toxic Chemical Exposures and Health Effects in Deployed Military Personnel

These studies focus on applied physiologically based methods and techniques for assessment of toxic chemical exposures in deployed military personnel. The research should improve current methods and techniques or identify and develop new, readily applied, methods and techniques. Specifically, studies must identify and develop biological markers of exposure that enhance environmental monitoring or provide markers of effect related to exposures of individual service members. Methods and techniques should be applicable to risk assessment or health surveillance of toxic chemicals and chemical mixtures that are a concern in military deployments. Specific chemicals of interest include petrochemical products (including JP8 fuel), insecticides, insect repellents, and Chemical Agent Resistant Coating (CARC).

4. Toxicity of Militarily Relevant Heavy Metals

These studies focus on biological effects of heavy metals currently used or contemplated for use in armor and as armor penetrators. These include tungsten and tungsten alloys, depleted uranium, depleted uranium and titanium alloys, and oxidation products of these metals and their alloys. Inclusion of positive (e.g. lead) and negative (e.g. tantalum) controls should be considered in study designs. Outcomes of special interest include identification of mechanisms of injury to pulmonary, hepatic, renal, and nervous systems from particulate and

solubilized forms; and localized soft tissue responses produced by embedded fragments (distinguishing foreign body, radiation, toxicological, and acute phase responses). Exposures should be based on realistic scenarios, and should consider current pharmacokinetic and pharmacodynamic knowledge of the metal or alloy under study. Epidemiological studies could be included based on exposure models.

A total of 62 proposals were submitted in response to these 4 BAAs. These proposals were scientifically peer reviewed by the American Institute of Biological Sciences. Highly meritorious proposals were chosen for funding by DoD program review and then were referred to the RWG for secondary review, based on interagency programmatic relevance. This review process is detailed in Section V. Research Management.

In early 2001, funding decisions were made and DoD undertook contract negotiations with principal investigators. The scope of work and funding level for each project should be finalized by the end of 2001, at which time the list of the newly funded projects will be announced.

IV.B. 2000 UPDATE OF KEY RESEARCH PROJECTS AND INITIATIVES

Three research initiatives are described in this section:

- one ongoing Institute of Medicine project;
- one completed White House report; and
- the 2001 Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research.

IV.B.1. Institute of Medicine Study of Health Effects Associated with Exposures during the Gulf War

In 1997, VA followed the recommendation of the Presidential Advisory Committee on Gulf War Veterans' Illnesses to contract for an assessment with an independent scientific organization, such as the National Academy of Sciences (NAS). (PAC, 1997) In its *Special Report*, the PAC recommended that the VA contract for a periodic review
“of the available scientific evidence regarding associations between illnesses

and Gulf War service. The object of such an analysis would be to determine statistical associations between service in the Gulf War and morbidity and mortality, while also considering whether a plausible biological mechanism exists, whether research results are capable of replication and of clinical significance, and whether the data withstand peer review.” (PAC, 1997)

Public Law 105-368 was enacted on October 21, 1998, and was titled the “Veterans Programs Enhancement Act of 1998.” It mandated that the VA contract with the NAS to perform a “review and evaluate the available scientific evidence regarding associations between illness and service in the Persian Gulf War.” The Public Law stated that the NAS review should:

- identify the biological, chemical, or other toxic agents, environmental or wartime hazards, or preventive medicines or vaccines to which members of the Armed Forces may have been exposed;
- identify the illnesses associated with the agents, hazards, or medicines or vaccines; and
- identify the illnesses (including diagnosed illnesses and undiagnosed illnesses) for which there is scientific evidence of a higher prevalence among populations of Gulf War veterans when compared with other appropriate populations of individuals.

On June 24, 1998, four months before the passage of the Public Law, VA contracted with the Institute of Medicine (IOM) of the NAS to carry out the assessment. The purpose of the IOM project is to review the scientific and medical literature regarding adverse health effects associated with exposures experienced during the Gulf War. Scientific evidence concerning the association of exposures and illness will be examined taking into account:

- the strength of the scientific evidence and the appropriateness of the methods used to identify associations;
- whether the evidence indicates the levels of exposure of the studied populations were comparable to the exposures of Gulf War veterans; and

- whether there exists a plausible biological mechanism or other evidence of a causal relationship between exposure to the risk factor or factors and the medical conditions.

Different types of research findings, e.g., animal toxicology data, occupational exposure data, and epidemiological data, need to be analyzed and integrated. The review will include recommendations for additional scientific studies to resolve areas of continued scientific uncertainty related to the health effects of Gulf War service.

The first phase of the study summarized the medical literature on pyridostigmine bromide, depleted uranium, sarin and cyclosarin, and the anthrax and botulinum toxoid vaccines. The two chemical warfare agents were selected because Gulf War veterans may have had low-level exposure to them as a result of the demolitions at Khamisiyah. Phase one was funded for 27 months at a cost of \$1.25 million. The IOM committee held their first meeting in January 1999 and they held six additional meetings through March 2000. The report on this first phase was published in September 2000, entitled *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, Vaccines*. The findings and research recommendations are summarized below.

During phase two, medical literature on pesticides and solvents used during the Gulf War is being reviewed. The cost of phase two is \$3.57 million. This second phase began when a newly constituted IOM committee held its first meeting in February 2001. The methodology of the review will be the same in the second phase as in the first phase. IOM plans to publish the second report about 18 months after the first meeting, in September 2002.

The third phase will consist of a series of updates of the literature and the associations, to be conducted every two years. These periodic reviews are consistent with the language of Public Law 105-368.

Findings and Recommendations of *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, Vaccines (IOM, 2000)*, and VA, DoD, and HHS Plans for Implementation of IOM Recommendations

Sarin:

- IOM Findings on potential long-term effects of sarin: IOM concluded that there was “limited or suggestive evidence” of an association between “exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects.” IOM concluded that there was “inadequate evidence” to determine whether an association does or does not exist between “sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent adverse long-term effects.”
- IOM Recommendations and Research Working Group Response (Note that all IOM research recommendations appear in italics.):
 1. *IOM: Long-term follow-up of populations exposed to sarin in the Matsumoto and Tokyo terrorist attacks.*
 - The RWG concurs with IOM’s recommendation that Japanese scientists should continue the long-term follow-up of populations exposed to sarin in the Matsumoto and Tokyo terrorist attacks. The RWG will keep apprised of the results of these studies.
 2. *IOM: Studies in experimental animals to investigate the long-term effects of an acute, short-term exposure to sarin at doses that do not cause overt cholinergic effects and minimal acetylcholinesterase inhibition.*
 - Since 1996, DoD has funded several studies of the long-term effects of short-term sarin exposure at doses that do not cause overt symptoms and cause only minimal acetylcholinesterase inhibition. Nine toxicology studies are focusing on the effects of sarin, alone or in combination. These combinations have

included PB, DEET, permethrin, chlorpyrifos, heat stress and/or exercise stress.

- In addition to the IOM recommendation on animal studies on sarin, the RWG is coordinating three epidemiological studies that are focusing on the health of veterans potentially exposed to low-level sarin due to the demolitions at Khamisiyah. The results of one of these projects were published in 1999 (project DoD-1B). (Gray, 1999c) The conclusion was there were no differences in rates of health problems among Gulf War veterans, who were potentially exposed to subclinical levels of sarin, compared to Gulf War veterans who were not exposed. The second Khamisiyah-related project is being performed by the Oregon Health Sciences University (DoD-63). The purpose is to compare neurological symptoms and results of neuropsychological tests between Gulf War veterans, who were potentially exposed to low levels of sarin, versus Gulf War veterans who were not exposed. The third Khamisiyah-related project is being performed by the Medical Follow-Up Agency of the IOM (DoD-69). The purpose is to compare mortality, hospitalizations, and symptoms between Gulf War veterans, who were potentially exposed to low levels of sarin, versus Gulf War veterans who were not exposed.
- In addition to the Khamisiyah studies, the RWG is coordinating a contract for MFUA to perform an epidemiologic study of the long-term effects of short-term exposure to nerve agents in human volunteers in experiments conducted at Aberdeen Proving Ground in the 1950s to 1970s (DoD-93).
- 3. *IOM: Research on genetic factors that may alter susceptibility to sarin toxicity.*
 - VA and DoD have funded a number of research projects on genetic factors that may alter the susceptibility to sarin and/or PB toxicity. These studies are described in detail in the section on PB below.

Pyridostigmine Bromide (PB):

- IOM Findings on potential long-term effects of PB: IOM concluded that there was “inadequate evidence” to determine whether an association does or does not exist between PB and long-term adverse health effects.
- IOM Recommendations and Research Working Group Response:

1. IOM: Research on chemical interactions between PB and other agents such as stressful stimuli, and certain insecticides.

- Since 1994, VA and DoD have funded 26 projects related to PB, alone or in combination with other chemicals or stressful stimuli. In particular, VA and DoD have funded 18 projects on the potential interactions between PB and other agents. Six of these projects have published results, focusing on the effects of PB in rodents, in combination with DEET, permethrin, swimming stress, restraint stress, or exercise stress (projects VA-49, DoD-10, DoD-37, DoD-62, DoD-65, DoD-75). One important and consistent result of recent studies is that stressful stimuli, such as swimming stress or restraint stress, do not cause an increase in the permeability of the blood-brain barrier, or cause PB to cross the blood-brain barrier into the brain. In 1996, the earliest research in this area was performed, which indicated increased permeability of the blood brain barrier to PB, due to swimming stress in a particular strain of mice. Several more recent studies have failed to replicate this finding using a variety of species, a variety of types of stressful stimuli, and extremely high doses of PB.

2. IOM: Research on differences in genetic susceptibility (e.g., genetic polymorphisms of butyrylcholinesterase or paraoxonase) that may contribute to increased risk of disease.

- VA and DoD have funded eight projects on genetic factors that may alter susceptibility to the effects of PB or

sarin, including polymorphisms of enzymes. Six projects in humans are evaluating the effects of genetic differences in polymorphisms of acetylcholinesterase, butyrylcholinesterase, and/or paraoxonase (projects VA-5, DoD-21, DoD-60, DoD-64, DoD-65, DoD-111). Two projects in rats are evaluating the effects of genetic differences in polymorphisms of acetylcholinesterase and butyrylcholinesterase (VA-5D, VA-49).

3. IOM: Epidemiological studies on the possible long-term health effects of PB.

- The RWG concurs with IOM that neurologists, who perform long-term follow-up of the course and treatment of myasthenia patients, should consider the possible long-term effects of PB. These patients take PB for many years. IOM concluded that PB has been used safely and effectively in thousands of myasthenia gravis patients since the 1950s. However, there has not been a systematic evaluation to determine if there are subtle long-term effects. The RWG plans to keep apprised of the results of such long-term studies of myasthenia gravis patients, and contacts have been instituted on this issue with the Myasthenia Gravis Foundation of America.

Vaccines:

- IOM Findings on the potential long-term effects of vaccines: IOM concluded that there was “inadequate evidence” to determine whether an association does or does not exist between anthrax vaccination, botulinum toxoid vaccination, or multiple vaccinations, and long-term adverse health effects.
- IOM Recommendations and Research Working Group Response:

1. IOM: Long-term systematic research to examine potential adverse effects of anthrax and botulinum toxoid vaccination in multiple species and strains of animals.

- The RWG concurs that long-term research is needed to examine potential adverse effects of anthrax and botulinum toxoid vaccination in experimental animals. Such research is underway in DoD laboratories, including more than 50 projects. Also, CDC has recently funded non-human primate studies of the health effects and efficacy of the anthrax vaccine.
 - In 2000, the CDC Anthrax Group began a collaborative effort with DoD to study the safety and effectiveness of vaccines used against biological agents, especially the anthrax vaccine. This effort includes addressing the risk factors for various reactions, including differences in rates between men and women; developing better measurements of vaccine effectiveness; reducing the number of injections in the series; and changing the route of administration from subcutaneous to intramuscular.
2. *IOM: Identification of cohorts of Gulf War veterans and Gulf War era veterans, for whom vaccination records exist, followed by careful studies of current symptoms, functional status, and disease status.*
- The CDC published a study of Air Force Gulf War veterans in 1998, which included measuring antibodies to anthrax and botulinum to determine which individuals had received the vaccines (HHS-2). (Fukuda, et al, 1998) The CDC found no relationship between the vaccinations and the development of a multisymptom illness (chronic symptoms of fatigue, cognitive and mood problems, and musculoskeletal pain).
 - The United Kingdom has also published a study in 2000 on a cohort of 923 Gulf War veterans for whom vaccination records exist (DoD-39). (Hotopf, et al, 2000) There was no association between having received the anthrax vaccine and the development of multisymptom illness, as defined by CDC.
3. *IOM: Long-term longitudinal studies of the participants in the Anthrax Vaccine Immunization Program that would actively monitor and systematically collect and analyze data about symptoms, functional status, and disease status.*
- In 1999, DoD funded a long-term longitudinal study of participants in the Anthrax Vaccine Immunization Program. The Naval Health Research Center has established DoD-wide surveillance of hospitalizations in military hospitals, linking these to data on anthrax vaccine recipients (project DoD-99). This active surveillance system ensures early detection of any associations between vaccinations and severe reactions that require hospitalizations. In addition, there are several ongoing projects that are following smaller groups of vaccine recipients to evaluate adverse effects.
 - IOM summarized several of these smaller completed and ongoing human studies, nearly all of which are unpublished. (IOM, 2000) IOM strongly urged the DoD investigators who are conducting these studies to submit their results to peer reviewed journals for publication. Additionally, IOM recently started a new two-year study on the safety and efficacy of the anthrax vaccine, funded by DoD. This new study will review some of the unpublished, non-peer reviewed information that was not previously available. CDC has also recently funded a two-year IOM study of the safety and efficacy of the anthrax vaccine.

Depleted Uranium (DU):

- IOM Findings on the potential long-term health effects of DU: IOM concluded that there is “limited or suggestive evidence” that there is no association between exposure to uranium and “lung cancer at cumulative internal dose levels lower than 200 millisieverts or 25 centigrays.” IOM also concluded that there is “limited or suggestive evidence” that there is no association between exposure to uranium and “clinically significant renal

dysfunction.” IOM concluded that there was “inadequate evidence” to determine whether an association does or does not exist for several other potential long-term health effects.

- IOM Recommendations and Research Working Group Response:

1. *IOM: Continued follow-up of the Baltimore cohort of Gulf War veterans with DU exposure. Long-term studies of the health of other Gulf War veterans at high risk for DU exposure (e.g. cleanup or radiation control units).*

- The RWG concurs with the long-term follow-up of the veterans in the Baltimore cohort, who were injured during friendly fire incidents. (Hooper, et al, 1999; McDiarmid, et al, 2000) This cohort was expanded in 1999, beyond the original 33 individuals. Approximately 100 veterans were involved in friendly fire incidents. OSAGWI has interviewed each of these individuals, and invited them to participate in the Baltimore program. (OSAGWI, 2000a) While the Baltimore researchers have seen no definitive evidence of adverse clinical outcomes associated with uranium exposure to date, the veterans who were involved in the friendly fire incidents will remain under continuing medical surveillance.
- In addition, since mid-1998, VA and DoD have offered a DU medical evaluation to hundreds of other veterans with potential DU exposure, such as those involved in cleanup operations or radiation control units. Individuals who performed these functions have been interviewed and invited to participate in the DU medical evaluation program. (OSAGWI, 2000a) To date, the published data have shown that only veterans who have retained metallic fragments have demonstrated persistently elevated urinary uranium levels. (McDiarmid, et al, 2001)

2. *IOM: Continued follow-up of the cohorts of uranium processing workers.*

- The RWG concurs that the long-term follow-up should continue of cohorts of uranium processing workers. Many of these studies involve employees of manufacturing facilities managed by the Department of Energy or its contractors. Because of the recent increase in interest in the employees of these facilities, ongoing surveillance is likely to intensify in the future. The RWG will keep apprised of the results of these studies.

3. *IOM: Additional studies of the effects of depleted uranium in animals.*

- DoD has funded five toxicology projects that are investigating the health effects of DU in experimental animals (DoD-7A, DoD-7B, DoD-121, DoD-122, DoD-123). In particular, since 1994, the Armed Forces Radiobiology Research Institute (AFRRI) has been investigating the health effects of embedded DU pellets on rats. IOM cited the results of several published AFRRI studies. (IOM, 2000) For example, there was no detectable kidney toxicity in rats embedded with DU pellets, even at very high concentrations of urinary uranium. Also, in 2000, DoD released a Broad Agency Announcement to fund additional studies of health effects of heavy metals in experimental animals, including DU. Outcomes of particular interest include effects on the lung, liver, kidney, and nervous systems; and localized soft tissue responses of embedded fragments. Awards for these projects will occur in 2001.

**IV.B.2. White House Report:
*Health Consequences of the Gulf War: An Ongoing Analysis***

In mid-2000, White House staff charged the MVHCB with coordinating and editing an interagency report, which would summarize the activities of the Federal Government to address illnesses in Gulf War veterans. This report was completed in December 2000, and it was entitled *Health Consequences of the Gulf War: An Ongoing Analysis*. (White House, 2000) The White House released this report officially on

January 16, 2001, and President Clinton signed the foreword. This report provides an overview of the background, clinical programs, research and investigations, compensation initiatives, outreach efforts, and lessons learned from the Federal efforts to understand the causes of the illnesses arising from the Gulf War.

The Military and Veterans Health Coordinating Board coordinated the planning and drafting of this document by staff of DoD, VA, and HHS. MVHCB staff edited the report and placed it on their Internet site, at <http://www.mvhcb.gov/>. The Office of the Special Assistant for Gulf War Illnesses funded the printing of 3,300 color copies of the report. It was distributed to all members of Congress, the White House, Veterans' Service Organizations, and Military Service Organizations.

The report includes a chapter on Research, which summarizes the findings, to date, on illnesses in Gulf War veterans. (White House, 2000) The major conclusions are:

- Military personnel who served in the Gulf War have had a significantly higher incidence of suffering one or more symptoms that include fatigue, memory loss, difficulty concentrating, pains in muscles and joints, and rashes.
- The symptoms range in severity from barely detectable to completely debilitating.
- Other symptoms are noted with reduced frequency, but still may be experienced more often by deployed than by non-deployed veterans.
- No single accepted diagnosis or group of diagnoses has been identified that describes and explains these symptoms.
- No single exposure, or set of exposures, has been shown conclusively to cause individual or combinations of symptoms.
- No diseases included in the international classification systems have been shown to be more frequent in the deployed or in non-deployed veterans with the exception of PTSD [posttraumatic stress disorder] symptoms.
- Deaths among deployed veterans are not higher in general than deaths among non-deployed veterans (through 1997).
- Deaths due to accidents are higher among veterans that deployed to the Gulf.

IV.B.3. 2001 Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research

The RWG organized and hosted an international meeting, entitled the “*2001 Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research.*” It was held on January 24-26, 2001, in Alexandria, Virginia. The purpose of the meeting was to bring Federally sponsored researchers on Gulf War veterans’ illnesses together in a common forum. This year’s conference emphasized the current state of the science and lessons learned. Speakers were encouraged to place their new findings within the context of the implications of the research that has already been completed.

This was the fifth such conference. The first was held in Washington, DC, at the Armed Forces Institute of Pathology in 1995; the second in Fort Detrick, Maryland, in 1997; and the third and fourth in Arlington, Virginia, in 1998 and 1999. Since 1995, the conference has grown from about 50 participants to almost 400 scientists, clinicians, government officials, and veterans. The 2001 Conference included scientists from Great Britain, Canada, Australia, France, the Netherlands, Denmark, and Israel.

The objectives of the Conference were to bring Federally sponsored researchers together in a common forum to:

- Provide an opportunity for researchers to present and exchange study results.
- Learn from recognized experts about overarching research areas as they relate to the etiology, diagnosis, and treatment of Gulf War veterans’ illnesses.
- Inform clinicians of current practices for the treatment of Gulf War veterans’ illnesses, and the latest research findings and their potential impact on clinical care.
- Provide an opportunity for veterans and veterans groups to learn about ongoing research and to interact directly with researchers, clinicians, and Government officials.
- Provide an opportunity to inform executive and legislative branches of the Government about research and clinical initiatives related to the Gulf War that should be considered for future deployments.

- Encourage communication, cooperation, and collaboration among researchers, clinicians, and veterans.
- Evaluate the implications of research on Gulf War veterans' illnesses: current state of the science and lessons learned.

Over the course of three days, the 2001 Conference was organized into three morning plenary sessions, two afternoon breakout sessions on specific research topics, and one evening poster session. In addition, there were two early morning and one afternoon clinical symposia addressing treatment and clinical management of Gulf War veterans' illnesses.

The plenary sessions were intended to be of broad appeal to a wide audience. Nationally and internationally recognized experts focused on four major themes: longitudinal follow-up studies of Gulf War veterans; alternate approaches to case definitions; results of

neuropsychological testing; and research on potential exposures during the Gulf War. During the breakout sessions and the poster session, researchers presented their research findings in a wide range of scientific areas, including epidemiology, toxicology, psychology, neurology, neuropsychology, treatment, force health protection, and prevention.

The *Proceedings* for this conference were published in early 2001. (MVHCB, 2001b) The *Proceedings* contain the texts of the presentations provided by each plenary speaker, summaries of each breakout session, and a complete set of abstracts for each presentation in the breakout sessions and poster session. The section of the *Proceedings*, which contains the texts of the plenary sessions, has been reprinted as Appendix B of this *Annual Report to Congress for 2000*.

V. RESEARCH MANAGEMENT

A. Overview

Research on Gulf War veterans' illnesses is a complex undertaking, involving a number of different approaches. The Federal research effort on this problem involves scientists in Federal, academic, and private institutions, both in the United States and abroad, conducting research sponsored by VA, DoD, and HHS. Each of these Departments has distinct, though complementary, capabilities and capacities for conducting and sponsoring research on Gulf War veterans' health issues. In addition, each Department has its own appropriation for extramural and intramural general biomedical research programs.

The biomedical research programs in VA, DoD, and HHS have well-established management structures for science policy formulation and the solicitation, scientific peer review, and funding of both extramural and intramural programs. Each Department's research management hierarchy for Gulf War veterans' illnesses research has been linked through an overall coordinated effort carried out by the Research Working Group (RWG) of the Military and Veterans Health Coordinating Board (MVHCB). As an operational policy, the RWG works through the management authority that each Department maintains over its intramural scientists, its scientific program managers who are responsible for extramural research, and its budgets. However, the RWG has no budget authority itself, which ensures greater objectivity. As a consequence, all funds for research flow through the funding agency or Department.

B. Oversight of Research

Each Department engaged in research on Gulf War veterans' illnesses endorses the need for both prospective and retrospective scientific peer review of research. Review and oversight of research have been important, because of the urgency of the health concerns of Gulf War veterans and their families, and the diverse nature of the reported illnesses. VA, DoD, HHS, and the Executive Office of the President have established multiple oversight mechanisms to capture the full spectrum of the overall effort. Some oversight mechanisms are broad-based,

encompassing all research issues, while others are more focused on individual research projects and programs.

Four of the most important oversight activities are briefly discussed below. Although each has had a broad mandate that has encompassed virtually all issues related to Gulf War veterans' illnesses, the discussion below will focus on their research oversight activities, findings, and recommendations.

1. Institute of Medicine/Medical Follow-up Agency: *Health Consequences of Service During the Persian Gulf War*

As directed by Public Law 102-585, VA and DoD jointly entered into a contract with the Medical Follow-Up Agency (MFUA) of the Institute of Medicine, National Academy of Sciences. The three-year IOM contract started on September 30, 1993. The IOM was mandated to review existing scientific, medical and other information on the health consequences of military service during the Gulf War. The IOM was also mandated to write a report that focused on the following:

- an assessment of the effectiveness of actions taken by the VA and DoD to collect and maintain information that is potentially useful for assessing the health consequences of military service in the Gulf War;
- recommendations on means of improving the collection and maintenance of such information; and
- recommendations on whether there is sound scientific basis for an epidemiological study or studies on the health consequences of service in the Gulf War, and the nature of such study or studies.

On January 4, 1995, the IOM issued a report, entitled *Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Action* (IOM, 1995). In general, the IOM panel endorsed previous findings of the Defense Science Board (DSB, 1994) and a National Institutes of Health Technology Assessment Workshop (NIH, 1994) that no single disease entity could be identified for the health complaints expressed by Gulf War veterans. The panel also strongly emphasized the importance of population-based studies, which are currently ongoing in a number of areas.

The final IOM report of September 1996 stands as a separate document from its initial January 1995 report. It is entitled *Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems*. (IOM, 1996) The IOM panel stated that it could find no scientific evidence to date demonstrating adverse health consequences associated with service in the Gulf War beyond the few documented cases of leishmaniasis, combat-related or injury-related mortality or morbidity, and increased risk of psychiatric sequelae of deployment. The panel went on to state that there is a strong likelihood that no single hypothesis could account for all illnesses reported by Gulf War veterans, whether or not they resulted from service in the Gulf War. Finally, the panel observed that after previous wars and conflicts, a proportion of military service personnel and veterans have had medical complaints of varying degrees of severity that are not explainable based on identifiable health hazards or physical illnesses. This observation echoes work by Hyams et al. (1996) tracing such a phenomenon back at least to the Civil War.

The IOM panel made the following research recommendations:

- Determine factors for possible response differences among active and non-active duty service members.
- Conduct mortality studies on Gulf War veterans out to at least 30 years.
- Determine the reason for excess deaths by external causes among Gulf War and other veterans.
- Continue and extend the Defense Medical Epidemiological Database.
- Refine geographical information systems (GIS) for troop locations and plan for future conflicts.
- Conduct reviews of the Total Exposure Assessment Methodology used to predict pollutant exposure in the Gulf War.
- Study gender issues when assessing health effects of deployment.
- Conduct studies on the consequences of assigning men and women to serve together.
- Complete and publish the Naval Health Research Center epidemiology studies.
- Complete and publish the VA National Survey of Persian Gulf Veterans.

- Complete evaluation of predictors of VA registry enrollment.
- Strengthen the epidemiologic capabilities of the armed forces.
- Submit all research (intra- and extramural) for peer review publication in a timely manner.

Each of these IOM recommendations has been implemented by VA, DoD, and HHS. The progress, to date, is summarized below, in Section VI. Research Priorities.

In accordance with P.L. 102-585, the agreement with IOM has been extended for the general purposes of providing core epidemiological support for research on military and veteran populations. This support provides a valuable infrastructure to carry out epidemiological research on Gulf War veterans' illnesses. The Medical Follow-up Agency of the IOM is currently conducting a number of related projects (DoD-69, DoD-93, DoD-116/VA-63, and DoD-117).

2. Executive Office of the President: Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC)

The President established the PAC by Executive Order on May 26, 1995. Between August 1995 and January 1997, the Committee met a total of 23 times either as a full Committee or in subcommittees. The 12 member committee was composed of scientists, health care professionals, veterans, and policy experts. The Committee was charged with reviewing and providing recommendations on the full range of activities relating to the government's response to Gulf War veterans' illnesses. In addition the Committee evaluated the available data on the nature of Gulf War veterans' illnesses and on potential health effects related to Gulf War risk factors.

The Committee released an interim report in February 1996 (PAC, 1996a). Although the Interim Report stated that VA, DoD, and HHS research programs were generally well-designed and should lead to meaningful answers to issues concerning Gulf War veterans-related health issues, it also had several recommendations. The Committee's recommendations covered issues such as peer review, coordination of agency research activities, the use of public advisory committees, and the availability of information

on troop exposures. The Committee made no findings about specific illnesses or risk factors in the Interim Report. In response to the Interim Report, the Departments developed a coordinated plan of action that responded to the Advisory Committee's interim recommendations.

The Final Report of the Committee was released in December 1996 (PAC, 1996b). The PAC came to the following conclusions:

- Many veterans have illnesses likely to be connected to service in the Gulf War.
- Current scientific evidence does not support a causal link between the symptoms and illnesses reported today by Gulf War veterans and exposures while in the Gulf to:

- Pesticides
- Chemical warfare agents
- Biological warfare agents
- Vaccines
- Pyridostigmine bromide
- Infectious diseases
- Depleted uranium
- Oil well fires and smoke
- Petroleum products

The Final Report also concluded that stress (known to affect the brain, immune system, cardiovascular system, and various hormonal responses) is likely to be an important contributing factor to Gulf War veterans' illnesses.

The Final Report made the following research recommendations:

- Require any new large-scale epidemiologic studies to have scientific and public advisory committees.
- Develop more accurate and reliable troop locator systems.
- Plan and conduct further research on low-level exposure to organophosphate chemical warfare nerve agents.
- Monitor Gulf War veterans for increased rates of cancer through mortality studies.
- Conduct research on the health status of individuals with embedded depleted uranium fragments.
- Collect and archive serum samples from U.S. service personnel when feasible.

- Conduct basic and clinical research on the physiologic effects of stress and stress-related disorders.
- The Research Working Group should consult more thoroughly with other Federal agencies.

Each of these PAC recommendations has been implemented by VA, DoD, and HHS. The progress, to date, is summarized below, in Section VI. Research Priorities.

Because of concern over the adequacy of investigations into reports of possible chemical and biological warfare exposure incidents during the Gulf War, and because of a need to follow up on recommendations from the Committee's Final Report, the President extended the Committee through October 1997. At that time the PAC issued a Special Report (PAC, 1997). In the Special Report the Committee did not alter its findings and conclusions with respect to potential causes of Gulf War veterans' illnesses. The Special Report did not contain any specific recommendations for research.

With respect to Federally funded research on Gulf War veterans' illnesses, the PAC concluded that the Government has been adequately and appropriately responding to its recommendations. (PAC, 1997) The PAC particularly commended the Government for its new initiatives targeted on health effects of low-level exposure to chemical warfare (CW) agents. As the PAC noted in its Final Report, "the amount of data from either human or animal research on low-level exposures [to CW agents] is minimal." However, in its Special Report, the PAC concluded that planned research on the health effects of low-level exposure might address any uncertainties and inconclusiveness identified in the Final Report.

The PAC approved of the government's targeted solicitations for research and the process used to make such awards. (PAC, 1997) However, the Committee expressed reservations about a perceived deficiency in processes for funding some research projects related to Gulf War veterans' illnesses. The Committee noted that "competition and external peer review of research proposals are essential to guarantee scientific merit, relevance, and level of priority generally." The Committee acknowledged that benefit can accrue from small-scale, short-term funding on a sole source basis for pilot projects

or to address narrow scientific questions. The Committee stated, though, that such approaches should be rare and that protocols still should be peer reviewed prior to funding, limited in the amount of funds released, and not subject to renewal without competition.

The RWG of the MVHCB will continue to endorse peer review and competition as the means of obtaining the best research products.

3. Senate Committee on Veterans' Affairs: *Report of the Special Investigation Unit on Gulf War Illnesses*

The Senate Committee on Veterans' Affairs undertook a year-long investigation in 1997, and published a comprehensive report in 1998. (SVAC, 1998) The Special Investigative Unit (SIU) examined the policies and actions of the U.S. government that have had an impact on the current health of Gulf War veterans.

Specific areas of concern were encompassed: the DoD's plans and policies; the intelligence community's role; health risks encountered by U.S. troops during the war; record keeping before, during, and after it; and the VA's accountability to and responsibilities for Gulf War veterans.

The major conclusions of the SVAC related to research were:

- While there does not appear to be any single "Gulf War Syndrome," there is a constellation of symptoms and illnesses whose cause or causes eludes explanation at this time.
- There is a great need to monitor those veterans who are ill, or who may become ill in the future, to assess whether they are getting better or worse and to define better the long-term effects they may experience.
- There is insufficient evidence to prove or disprove that there was an actual low-level exposure of any troops to chemical weapon nerve agents, or that any of the health effects some veterans are experiencing were caused by such exposure.
- In the inherently difficult area of military health, research that is conducted before illnesses occur, not after the fact, can help to assure prompt, effective medical treatment; to prevent adverse health effects in the first place; and to provide clear information to

veterans who may be adversely affected by such exposures.

The SVAC made the following research recommendations:

- DoD should fund research into the health effects of depleted uranium exposure.
- DoD should establish a program to improve the capacity for rapid and early detection of exposures that may affect troop health during and after deployments; for example, to develop technology to rapidly screen persons exposed to a wide range of chemical toxins, including chemical warfare agents.
- DoD and VA should monitor the treatment provided to ill Gulf War veterans on an ongoing basis, especially those with unexplained illnesses, to determine whether those veterans are getting better or worse over time.
- DoD and VA should implement methods to monitor the health status of Gulf War veterans over time to provide early detection of future illnesses that may emerge years later, such as higher rates of cancer.
- DoD and VA should establish a birth defects registry for military service members to gather statistics on possible reproductive health effects stemming from battlefield exposures.
- DoD and VA should evaluate treatment protocols that have been useful for persons in the general population who suffer from illnesses similar to Gulf War veterans' unexplained illnesses, and they should fund appropriate clinical programs and research in this area.
- DoD and VA should fund Gulf War health research only through an impartial, scientific peer review process, except in the case of the most serious circumstances.

Each of the SVAC recommendations has been implemented by DoD and VA. The progress, to date, is summarized below, in Section VI. Research Priorities.

4. Presidential Special Oversight Board: *Final Report of Special Oversight Board for Department of Defense Investigations of Gulf War Chemical and Biological Incidents*

The Presidential Special Oversight Board (PSOB) was established in June 1998 in

response to a recommendation of the Presidential Advisory Committee on Gulf War Veterans' Illnesses. (PAC, 1997) The *Final Report* of the PSOB was published on December 20, 2000. (PSOB, 2000)

The PSOB charter called for it to "provide advice and recommendations [and oversight] . . . of DoD investigations into possible detections of, and exposures to, chemical or biological warfare agents and environmental and other factors that may have contributed to Gulf War Illnesses . . . [and to provide an] overall evaluation of DoD's plan for and progress toward the implementation of the Presidential Advisory Committee's recommendations contained in its Special Report." (PSOB, 2000)

There were a limited number of research conclusions and recommendations in this report, which were scattered in the report, rather than clustered in a summary. (PSOB, 2000) Most of the report was not directly related to research, since most of the report focused on an evaluation of the work of the DoD Office of the Special Assistant for Gulf War Illnesses (OSAGWI).

The major conclusions related to research in the PSOB *Final Report* were:

- "After every deployment of troops for war, similar symptoms have occurred in returning service personnel. This 'post-war syndrome' has been attributed to the stresses of deployment. It has been described in various ways in every war since the Civil War. . . The Board concludes that it is highly likely that a proportion of Gulf War veterans suffering from the symptoms of undiagnosed illnesses fall into the generalized category of 'post-war syndrome' or post deployment illness. As with all previous wars, stressful deployments to a combat zone can create significant medical problems for returning troops." (pages 44-45)
- "Mental disorders clearly affect military readiness. These factors are the second leading cause of hospitalization, the leading cause of inpatient bed days, and the leading medical cause of attrition from the military service. Mental disorders are also the most important cause of medical and occupational morbidity among active duty US military personnel." (page 72)

- "The only known potential exposure of US personnel to chemical warfare agents remains the accidental low-level release of nerve agents during demolition operations at Khamisiyah, Iraq, in March 1991." (page ii)
- "Based on the current body of evidence in the medical literature on studies of humans accidentally exposed to organophosphate nerve agents and on controlled animal exposures to organophosphate nerve agents at levels causing no acute signs or symptoms, low-level exposures do not produce chronic illnesses. However, gaps exist in the scientific literature regarding the potential long-term health consequences of exposure to low concentrations of nerve agents that are initially asymptomatic." (pages 48-49)
- "The Board concludes that DU [depleted uranium] is unlikely to be the cause of either the unexplained illnesses among Gulf War veterans or the diagnosed illnesses found during CCEP and VA Registry evaluations." (page 51)
- "The Board concurs with both the RAND study on PB [pyridostigmine bromide] and the Institute of Medicine analysis that 'available evidence is of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association [of PB use with adverse health effects] in humans.'" (page 55)

In its *Final Report*, the PSOB made the following research recommendations:

- "The Board concludes that stress is likely a primary cause of illness in at least some Gulf War veterans; it is a likely secondary factor in potentiating other causes of undiagnosed illnesses among some Gulf War veterans. . . This issue requires continued research. The Board commends DoD for recognizing the role of stress in deployment and in combat and for developing and implementing programs to address this issue." (page iv)
- "The Board recommends that OSAGWI and the MVHCB closely monitor the

development and resourcing of DoD's research on the health effects of low-level CWA [chemical warfare agent] exposures and make recommendations as appropriate to ensure continued progress in this area." (page vii)

- "The Board strongly believes that efforts to fund non-peer reviewed research projects do not serve the best interest of the nation or of its Gulf War veterans. Researchers and clinicians who advocate 'alternative' diagnostic and treatment methods, as well as those proposing more conventional approaches, should be encouraged to respond to Requests for Proposal and Broad Agency Announcements with well-constructed proposals capable of passing vigorous and independent peer review." (page viii)
- "The Board believes that DoD should fully support the Millennium Cohort Study and that the service members selected to participate in the program should cooperate fully. This twenty-year research project will significantly enhance the Federal Government's and the medical community's understanding of the long-term health consequences of military service and facilitate improved clinical care and force health protection for members of the Armed Forces." (page ix)
- "The Board concurs with the Institute of Medicine recommendations for: '1) additional studies in experimental animals to investigate the specific effects of DU; and 2) long-term follow-up of veterans exposed [and potentially exposed] to DU, including . . . [those] involved in clean-up operations or radiation control units.'" (page 51)
- "Further study is clearly needed in this area [pyridostigmine bromide], since PB remains the only viable prophylactic agent for soman exposure, and DoD intends to continue its use in future conflicts." (page 55)
- "PRD-5 recommended DoD possess the capability to collect and assess data associated with anticipated exposures during deployments and to respond to newly identified threats. . . The Board believes that the complexity of accurate assessment tools and epidemiological standards have

inhibited progress in this area of environmental health research. The Board recommends that DoD develop and implement a system for applied toxicological research based on prioritized lists of environmental and occupational substances, as suggested in PRD-5." (page 74)

Each of the PSOB recommendations has been implemented by DoD and VA. The progress, to date, is summarized below, in Section VI. Research Priorities.

5. Other Oversight

In addition to the broad oversight that has been provided by the four committees cited above, there are several standing and special committees responsible for oversight on individual research projects and programs. The RWG also continues to encourage that all large epidemiological studies establish public advisory groups that include representation of Gulf War veterans. Additionally, valuable review and oversight has been provided by the House Committee on Veterans' Affairs, the House Committee on Government Reform, and the General Accounting Office.

C. Research Coordination

In 1993, VA, DoD, and HHS recognized the importance of a coordinated approach to research on Gulf War veterans' illnesses and formed the "Persian Gulf Interagency Research Coordinating Council." In January 1994, the Secretaries of VA, DoD, and HHS formed the Persian Gulf Veterans Coordinating Board. The Research Coordinating Council became the Research Working Group (RWG), operating under the auspices of the Coordinating Board. In 2000, the mission of the RWG broadened to include issues of Force Health Protection, as the PGVCB transitioned to become the MVHCB. (PGVCB, 2001) Membership on the RWG consists of senior research scientists and clinical managers from VA, DoD, and HHS.

The RWG includes various subcommittees that have been in existence over the past several years. The Planning Subcommittee for Annual Meetings of Federal Researchers has been responsible for organizing five meetings of Federally funded researchers. These meetings have provided an opportunity for researchers to

gather and share recent research results and to discuss research problems of mutual interest. The 2001 conference was an open meeting allowing for extensive interactions among researchers, clinicians, veterans, and other members of the public.

The RWG reevaluated its general functions in September 2000, when the PGVCB transitioned to the MVHCB. The consensus statement on general functions is:

- The Research Working Group will provide coordination of the interagency research strategy, related to deployment health and health risk communication initiatives, affecting military personnel, veterans, and their families. It will:
 1. Assess the state and direction of research to identify new ideas or new research approaches, to identify gaps in scientific knowledge, and to make recommendations regarding research priorities.
 2. Promote and encourage appropriate scientific review of research sponsored by the Federal government.
 3. Make recommendations concerning appropriate actions and responses to research findings.
 4. Provide a forum for information exchange about research initiatives and priorities among the Departments of Defense, Veterans Affairs, and Health and Human Services, and the national and international research community.

Programmatic Review of Extramural Research Proposals

An important function of the RWG is programmatic review of research proposals that have been competitively reviewed and recommendation to funding agencies. Figure V-1 illustrates the general approach the RWG has taken regarding extramural research (research funded by an agency, but carried out by organizations outside of the agency such as universities, private laboratories, or other independent organizations). The RWG works collectively with VA, DoD, and HHS to establish research needs and identify

agency-specific funding mechanisms to support that research. For a specific research funding activity, the responsible funding agency works in coordination with the RWG to develop a targeted solicitation for research.

Proposals that are submitted to the funding agency in response to a solicitation are scientifically peer reviewed using agency-specific peer review programs. For example, the Department of the Army in DoD uses a contract with the American Institute of Biological Sciences. Abstracts of peer reviewed proposals, summaries of the reviews of the peer reviewers, and the scientific merit scores assigned by the peer reviewers, are provided to a subcommittee of the RWG charged with providing secondary review of proposals for relevance. Relevance determinations are guided by interagency programmatic needs articulated through the RWG process and reflected in the *Working Plan for Research* (1996b). In its secondary review, the RWG may re-rank proposals based on relevance, but it will not recommend funding for any non-meritorious proposal, regardless of relevance or availability of funds. The RWG has no budget authority; therefore all final funding decisions about research are made by the individual agencies.

Though scientists within intramural research programs do not compete for their funding in the same way as non-federal extramural scientists, the RWG works with agencies to ensure that intramural programs and projects are adequately peer reviewed. The RWG will continue to work diligently to foster the highest standards of competition and peer review for all research on Gulf War veterans' illnesses.

Notable among the activities of the RWG are:

- Development, production, and dissemination of the 1995 *A Working Plan for Research on Persian Gulf Veterans' Illness* (PGVCB, 1995b), and its 1996 revision (PGVCB, 1996b).
- Production and dissemination of *Annual Reports to Congress* for 1994 through 2000 on results, status, and priorities of Federal research activities (PGVCB, 1995a; 1996a; 1997; 1998a; 1999a; 2001; MVHCB, 2001a).

- Secondary programmatic review of research proposals that have been competitively reviewed by funding agencies.
- Organization of five conferences of Federally funded researchers, including publication of three Proceedings (PGVCB, 1998b; PGVCB, 1999b; MVHCB, 2001b).
- Coordination and oversight of implementation of relevant recommendations of the Institute of Medicine, Presidential Advisory Committee, Senate Veterans Affairs' Committee, the Presidential Review Directive 5, and the Presidential Special Oversight Board (IOM, 1995, 1996; PAC, 1996a, 1996b, 1997; SVAC, 1998; NSTC, 1998; PSOB, 2000).
- Two national treatment trials (exercise/behavior trial and antibiotic treatment trial).
- Organization of an international symposium in 1997, in conjunction with the Society of Toxicology on the health effects of low-level exposure to chemical warfare nerve agents.
- Development of a strategy for research on the health effects of exposure to low-levels of chemical warfare nerve agents.
- Follow-up investigation of preliminary reports of positive experimental serological tests for leishmaniasis in Gulf War veterans.

VI. RESEARCH PRIORITIES

The Research Working Group has identified the three sets of research priorities in 1995, 1996, and 1998. (PGVCB, 1995b; 1996b; 1999a) Substantial progress has been made on each of these priorities, which is 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:

1. 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 and DoD-106). The results of the first phase of the British investigation have been published. (Unwin, et al, 1999; Ismail, et al, 1999; Ismail, et al, 2000; Hotopf, et al, 2000) The Canadian government has published a comprehensive study of the health of Canadian Gulf War veterans, compared to non-deployed veterans. (Goss Gilroy, et al, 1998) Denmark also participated in the Gulf War as a coalition partner, primarily in the postwar period after April 1991. American scientists are collaborating with researchers in Denmark on a study of neuropsychological function in Danish soldiers (project HHS-5).
2. Because the health status of Saudi Arabian soldiers has 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-102). 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 will be compared, as will rates and causes of hospitalizations and outpatient visits.
3. Eight projects include research objectives related to the prevalence of adverse

reproductive outcomes among Gulf War veterans and their spouses. Three of these projects have been completed (HHS-4, DoD-1C, DoD-1G), and their results have been published. (Penman and Tarver, 1996; Cowan, et al, 1997; Araneta, et al, 1997; Araneta, et al, 2000) Five of these projects were completed recently, but have not published results yet (VA-2, VA-47, DoD-1D, DoD-35, and DoD-44).

4. 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).
5. The long-term mortality of Gulf War veterans will be followed by the VA for many years (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 risk due to external causes (e.g., motor vehicle accidents) among Gulf War veterans. The British recently published a mortality study of Gulf War veterans and non-deployed veterans in the UK, and they demonstrated 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)
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; OSAGWI, 2000e) Only three sites that were bombed during the air war might have released chemical weapons-Muhammadiyah, 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 are summarized in Appendix C. of this *Annual Report to Congress for 2000*.

3. Three funded investigations are focusing 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). One of these studies (DoD-1B) is complete and published. (Gray, et al, 1999c) In addition to these three funded projects focusing on Khamisiyah, there are three related studies that are outgrowths of other projects, which evaluate mortality rates, clinical diagnoses, and self-reported symptoms (VA-1, DoD-94, and VA-4). The mortality study is complete and published. (Kang and Bullman, 2001)

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 2000. (Benotsch, et al, 2000; Engel, et al, 2000; Fiedler, et al, 2000; Ismail, et al, 2000; King, et al, 2000; Nisenbaum, et al, 2000; Sharkansky, et al, 2000; Storzbach, et al, 2000; Wagner, et al 2000)
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 is evaluating the risk factors for the significantly increased risk for unintentional injuries in Gulf War veterans (DoD-73). This project resulted in an important epidemiologic report in 2000. (Bell, et al, 2000)
3. Three 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 (VA-6D, VA-47, and DoD-49). Several studies related to sarin and mustard agent have been published.
4. Fifteen toxicological projects are focusing on the potential long-term health effects resulting from low-level, subclinical exposures to chemical agents. Nine of these projects are focusing on sarin. Seven

epidemiological research projects are focusing on the potential long-term health effects resulting from low-level, subclinical nerve agent exposures. Six projects are focusing on possible sarin exposures due to the demolitions at Khamisiyah. (DoD-1B, DoD-63, DoD-69, DoD-94, VA-1, and VA-4) One project is 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-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 Research Working Group 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 is provided in Appendix C of this *Annual Report to Congress for 2000*.

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 LEISHMANIASIS 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

During 1998, the RWG reevaluated the issue of research priorities. (PGVCB, 1999a) Key factors that guided the RWG 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 RWG determined 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 RWG established the development of treatment protocols for unexplained illnesses as a research priority. In 1999, VA and DoD began two major multi-site treatment trials. These are 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 is more than \$9.6 million and \$5.2 million, respectively. These treatment trials will be completed in 2002.

In addition, VA has funded an Institute of Medicine study to identify effective treatments for health problems in Gulf War veterans. This 18-month study started in 1999 and it was described in some detail in section IV.B.2. of the *Annual Report for 1999*. (PGVCB, 2001) This project will be published in 2001.

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

The RWG has 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 2000, there are five studies that include 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 presented at the 2001 Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research. (MVHCB, 2001b) The abstracts for these presentations are included in Appendix B.

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 RWG has endorsed future research aimed generally at disease prevention, and more specifically at prevention of stress-related symptoms and conditions. As a result of RWG recommendations in the past, the Federal investment focusing on the pathophysiology of stress-related illnesses has markedly increased. There are currently approximately 75 projects with a primary or secondary focus on the Brain and Nervous System. With this investment in better understanding of the pathophysiology of stress-related illnesses, it is also appropriate to initiate research that can take advantage of new findings and how they might lead to better 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) The RWG, 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 \$5 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 RWG. Specific research thrust areas in 1999 and 2000 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;
4. epidemiological studies to continue long-term follow-up of Gulf War veterans and to improve health status monitoring in future deployments; and
5. improved and accelerated research on leishmaniasis prevention, diagnosis, and treatment.

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