Appendix C

Summary of Progress in Response to the 21 Research Questions Highlighted in the 1996 *Working Plan for Research on Gulf War Veterans' Illnesses*

SUMMARY OF PROGRESS IN RESPONSE TO
21 RESEARCH QUESTIONS HIGHLIGHTED IN THE 1996
A WORKING PLAN FOR RESEARCH ON GULF WAR VETERANS' ILLNESSES
(JUNE 2001)

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EXECUTIVE SUMMARY

In 1996, the Research Working Group identified 21 major research questions, related to illnesses in Gulf War veterans. These questions were published in *A Working Plan for Research on Persian Gulf Veterans' Illnesses, First Revision*. (PGVCB, 1996) The comprehensive Gulf War research portfolio has addressed each of these 21 questions, and relevant results have been published. The purpose of this report is to outline the progress made in answering these questions.

First, the list of 21 questions is provided. The 21 questions are grouped into categories, such as symptoms and general health status, brain and nervous system function, and reproductive health. A chapter is provided for each category, which includes the research questions, the number of Federally-funded projects, a summary assessment of the results of the studies to date, and a list of major relevant publications. Each chapter is summarized in one or two paragraphs in this Executive Summary. The final section of the report is a bibliography.

I. Symptoms and General Health Status: Gulf War veterans have consistently reported increased rates of self-reported symptoms related to a wide variety of organ systems, compared to non-deployed veterans. The reported prevalence of symptoms has been increased, in virtually all the published studies to date. Five large studies have shown that Gulf War veterans do not suffer from a unique, previously-unrecognized "Gulf War Syndrome." In all five studies, the patterns of symptoms reported by Gulf War veterans were similar to the patterns reported by non-deployed veterans.

There are very few differences in the rates and causes of hospitalizations among Gulf War veterans and non-deployed veterans. Other than hospitalization data, there is little published evidence about the rates of medical diagnoses, therefore several ongoing studies are designed to evaluate objective medical diagnoses. In addition, follow-up studies are a high priority to monitor whether the health of Gulf War veterans is improving or getting worse, therefore five studies are following approximately 18,000 veterans over time. Two studies have evaluated their cohorts four times, and the other three studies have evaluated their cohorts two times.

II. Brain and Nervous System Function: Neurological examinations have been performed in several populations of Gulf War veterans. These studies have consistently shown that Gulf War veterans do not generally demonstrate objective evidence of neurological diseases. Three large population-based studies are using neurological evaluations to detect central nervous system and peripheral nervous system abnormalities, which will be completed in 2001. Eight studies are performing neuroimaging in Gulf War veterans and non-deployed veterans, including conventional magnetic resonance imaging (MRI), functional MRI, magnetic resonance spectroscopy, and single-photo emission computed tomography.

Studies of several populations of Gulf War veterans and non-deployed veterans have demonstrated consistent results on neuropsychological testing. Self-reports of memory and concentration problems were usually more frequent among the groups of Gulf War veterans than among the control subjects. However, on objective testing, performance was the same on most neuropsychological tests in Gulf War veterans and control subjects. In a small proportion of tests, Gulf War veterans performed significantly more poorly than controls. After adjustment for

PTSD or other psychological distress, the differences on the tests between the two groups diminished or disappeared.

Many studies have demonstrated that the majority of Gulf War veterans have reported high levels of stressful experiences during the war. In several studies, ill Gulf War veterans have consistently reported more combat stressors than healthy Gulf War veterans, such as deaths among unit members. In many studies, Gulf War veterans have been diagnosed with significantly higher rates of posttraumatic stress disorder (PTSD) and major depression than non-deployed veterans. These higher rates have been demonstrated in several different populations of Gulf War veterans, through structured psychiatric interviews, as well as through self-administered questionnaires. In two large cohorts, Gulf War veterans diagnosed with PTSD or depression reported physical symptoms in many organ systems at higher rates than non-deployed veterans or healthy Gulf War veterans.

III. Mortality: Mortality rates in both Gulf War veterans and non-deployed veterans are about 40% of the mortality rates in the general US population, which means that veterans are much healthier. In both the US and the UK, Gulf War veterans have had a significantly higher mortality rate due to unintentional injuries, mostly motor vehicle injuries, compared to non-deployed veterans. This is the only difference in mortality rates, to date. The follow-up mortality studies in the US and UK will continue indefinitely. The rates of cancer diagnosis have been very low in Gulf War veterans, and they have been similar to or lower than the rates in non-deployed veterans.

IV. Reproductive Health: Two very large studies based on medical records have demonstrated that the rates of birth defects in the offspring of Gulf War veterans and non-deployed veterans were the same. Several ongoing studies are evaluating birth defects and other aspects of reproductive health.

V. Infectious Diseases: Four studies have shown that the rates of infectious diseases have been low in Gulf War veterans, and significantly lower than the rates in non-deployed veterans. Two studies have demonstrated no differences in the rates of infection with *Mycoplasma fermentans* in Gulf War veterans, compared to non-deployed veterans, either before or after the war. The Antibiotic Treatment Trial is a multi-site clinical trial designed to determine whether long-term treatment with doxycycline leads to improvement in *Mycoplasma*-positive Gulf War veterans, and it will be completed in late 2001.

VI. Immune Function: If there were increased rates of serious infectious diseases or autoimmune diseases in Gulf War veterans, this could be an indicator of altered immune function or host defense. The evidence to date has shown that Gulf War veterans have the same or significantly lower rates of these diseases, compared to non-deployed veterans.

VI. Oil Well Fire Smoke: The most visible source of possible contamination to which US troops were exposed during the Gulf War was the smoke from more than 600 burning oil wells. Air monitoring studies showed the smoke concentrations were intense in some geographical locations, but few troops were in those locations, or the troops in those locations were only exposed for brief periods (hours to days). A series of health risk assessments have been performed, and the overall risk of long-term adverse effects from exposure to the oil well fires has been assessed to be minimal.

The rates of self-reported pulmonary symptoms and diagnoses have been higher in Gulf War veterans than non-deployed veterans in some studies, however, the rates have been similar in other studies. Five ongoing studies involve clinical evaluations, including pulmonary function tests. When these studies are completed in 2001, they will clarify whether GWV have increased rates of objective pulmonary diagnoses.

VIII. Chemical Weapons: US soldiers definitely destroyed many, but not all, of the chemical rockets at Khamisiyah, Iraq, on March 10, 1991. DoD assessed that some US troops were likely exposed to very low levels of sarin and cyclosarin from the demolitions. No service members have reported symptoms related to nerve agent exposure at that time. This is the only known event during the Gulf War that may have exposed large numbers of troops to chemical warfare agents, even at low concentrations. It is possible, but indeterminate, that 75 or fewer Special Operations Forces personnel who were in Iraq may have been exposed to low levels of nerve agent on three possible dates in February 1991, due to the bombing of Muhammadiyat, Iraq. Other than the Khamisiyah and Muhammadiyat incidents, the only possible, documented chemical weapon exposure during the war was the incident of indeterminate mustard agent exposure of one soldier on March 1, 1991.

There are 6 research projects that focus on the possible long-term effects of exposures due to the demolitions at Khamisiyah, three completed studies and three that will be completed in 2001. One study demonstrated no differences in the rates or causes of hospitalizations among veterans who may have had low-level exposure due to Khamisiyah, compared to veterans who had no exposure. A second study showed no differences in the rates or causes of mortality among veterans with possible low-level exposure, compared veterans with no exposure. The third study showed no differences on sensitive neurological and neurophysiological tests among veterans with possible low-level exposure, compared to veterans with no exposure.

IX. Interactions of Exposures (Including Pyridostigmine Bromide and Pesticides): Several studies have been published recently that focused on the potential health effects of pyridostigmine bromide (PB) and pesticides, alone or in combination. The key research question is whether PB can cross the blood-brain barrier (BBB). Several studies have evaluated whether other chemicals, such as pesticides, or stressful stimuli, such as heat stress, can increase the permeability of the BBB, and can therefore enhance penetration of PB into the brain. All these recent studies have reached the same conclusion, that other chemicals or stressful stimuli do not increase the permeability of the BBB to PB, and that PB does not penetrate the brain, even at lethal levels. If PB does not cross the BBB, it is very unlikely to cause changes in brain function.

X. Environmental Toxicology (Including Depleted Uranium, Biological Warfare Agents, and Vaccines): Because of the scientific evidence to date, and the low radioactivity of natural and depleted uranium, no radiological health hazard is expected from inhalation, dermal, or oral exposure to natural or depleted uranium. While depleted uranium (DU) could theoretically cause heavy metal toxicity at very high levels, in particular kidney dysfunction, no Gulf War veterans experienced intakes high enough to cause adverse health effects. The available scientific and medical evidence to date does not support concerns that DU has caused or is causing illnesses in Gulf War veterans. A total of 104 individuals were exposed to DU in friendly fire incidents, some of whom have retained metallic fragments. While there has been no clinical evidence of

illness associated with DU exposure to date, the veterans involved in friendly fire incidents will remain under medical surveillance indefinitely.

There is no evidence that Iraq used biological warfare agents during the Gulf War. In particular, there were no cases of anthrax or botulism among US troops.

During the Gulf War, several "routine" vaccines were administered to service members, such as influenza and tetanus vaccines, as well as vaccines against biological warfare agents. The very low numbers of reported casualties from infectious diseases were partially due to the effectiveness of the vaccines given to service members before and during deployment. About 150,000 service members received the anthrax vaccine. There is inadequate evidence to determine if this vaccine can cause long-term adverse effects, because studies of this vaccine have not used active surveillance to systematically evaluate long-term health outcomes. DoD and CDC have several ongoing studies to evaluate the potential long-term effects of the anthrax vaccine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

I. SYMPTOMS AND GENERAL HEALTH STATUS

Relevant Questions from 1996: 1, 9

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?

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

Number of Federally-funded projects with this primary or secondary focus area
(1994 to December 31, 2000): 76

I.A. Prevalence of symptoms and illnesses in Gulf War veterans (GWV), compared to an appropriate control population (1996 Question 1)

1. Several conclusions can be drawn about symptoms and illnesses among GWV, compared to non-deployed veterans (NDV). GWV consistently report increased frequencies of symptoms, compared to NDV, related to a wide variety of organ systems. For example, large population-based studies in the US, UK, and Canada have shown increased rates of self-reported illnesses in GWV, including chronic fatigue, memory problems, posttraumatic stress disorder, musculoskeletal problems, and asthma. (Iowa Persian Gulf Study Group, 1997; Kang, et al, 2000; Goss Gilroy, 1998; Unwin, et al; 1999; Cherry, et al, 2001a) Other large studies that were not population-based have also shown the same pattern of increased symptom reporting in GWV, compared to NDV. (Pierce, 1997; Fukuda, et al, 1998; Gray, et al, 1999a; Wolfe, et al, 1999b; Steele, 2000)

2. In many published studies, GWV have reported increased frequencies of almost all symptoms included in the questionnaires. For example in the Iowa study, GWV reported significantly higher rates of 123 of 137 symptoms (90%) during the past year, compared to NDV. (Iowa, 1997) These symptoms were related to all organ systems. The authors concluded that the increased prevalence in GWV of nearly every symptom is "difficult to explain pathophysiologically as a single condition." Similar patterns of symptom reporting were found in many other studies. (Kang, et al, 2000; Unwin, et al, 1999; Cherry, et al, 2001a; Gray, et al, 1999a; Steele, 2000)

3. There have been two major publications about hospitalizations in GWV and NDV. (Gray, et al, 1996; Gray, et al, 2000) The 2000 study extended the follow-up period of the 1996 study. The rates and causes of hospitalizations in all 697,000 GWV were compared to the rates in an equal number of NDV. Hospitalizations for fractures and soft-tissue injuries were more frequent in GWV in military hospitals nationwide and in civilian hospitals in the state of California. Hospitalizations for respiratory system and digestive system diagnoses were more frequent in GWV in VA hospitals nationwide. There were no differences in rates of hospitalizations for other diagnoses among GWV and NDV. (Gray, et al, 2000)

4. Without a clinical evaluation, it is impossible to determine whether symptoms can be explained with a medical diagnosis. (Roy, et al, 1998) Two studies in Portland, Oregon and East Orange, New Jersey have highlighted the necessity of caution in the interpretation of surveys, if they are used as the sole source of health data. (McCauley, et al, 1999a; Pollet, et al, 1998; Lange, et al, 1999) For example, in the Portland study, only 4% of the self-reported skin problems and only 20% of the self-reported gastrointestinal symptoms were confirmed during the clinical exam, yet remained unexplained. Several large studies include comprehensive evaluations to provide medical verification of self-reported symptoms and illnesses, including the VA National Survey, and studies in Portland, New Jersey, Pennsylvania, Iowa, and the UK. (McCauley, et al, 1999a; Storzbach, et al, 2000; Pollet, et al, 1998; Lange, et al, 1999; Fukuda, et al, 1998; Doebbeling, et al, 2001; Barrash, et al, 2001b; Wessely, 2001; David, et al, 2001)

5. Several large studies have demonstrated a significant association between demographic, lifestyle, and occupational risk factors and increased reporting of symptoms among GWV. Demographic and lifestyle factors consistently associated with increased symptoms include increasing age, female gender, lower education, and cigarette smoking. Occupational factors consistently associated with increased symptoms include Reserve/National Guard vs. active-duty status; enlisted vs. officer status; and Army vs. the other military branches. (Iowa, 1997; Kang, et al, 2000; Steele, 2000; Fukuda, et al, 1998; Nisenbaum, et al, 2000; Unwin, et al, 1999; Ismail, et al, 2000; Cherry, et al, 2001a; Wolfe, et al, 1998; Sharkansky, et al, 2000)

6. Follow-up studies are a high priority to monitor whether the health of GWV is improving or getting worse over time. Five studies in Boston, New Orleans, New Jersey, Iowa, and the United Kingdom are following approximately 18,000 veterans. The Boston and New Orleans studies have evaluated their cohorts four times, and the other three studies have evaluated their cohorts two times.

7. The results of longitudinal studies have been published for Time 1 and Time 2 for the Boston and New Orleans cohorts. In both groups, GWV were evaluated soon after returning from the war and again 1 to 2 years later. (Wolfe, et al, 1996; Wolfe, et al, 1999a; King, et al, 2000; Sutker, et al, 1995; Brailey, et al, 1998; 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 also increased over time.

8. In summary, Gulf War veterans have consistently reported increased rates of symptoms, compared to non-deployed veterans. The self-reported prevalence of symptoms related to a wide variety of organ systems has been increased, in virtually all the published studies to date. However, there are very few differences in the rates and causes of hospitalizations among GWV and NDV. Other than the hospitalization data, there is little published evidence about the rates of medical diagnoses in GWV and NDV. Several ongoing studies are designed to evaluate objective medical diagnoses. Follow-up studies are a high priority to monitor whether the health of GWV is improving or getting worse, therefore five studies are following approximately 18,000 veterans over time. Two studies have evaluated their cohorts four times, and three studies have evaluated their cohorts twice.

I.B. Prevalence of symptom complexes in GWV, compared to an appropriate control group (1996 Question 9)

1. Several studies have evaluated the rates in GWV of three poorly-understood syndromes that are defined on the basis of patterns of symptoms. These are chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia. GWV reported increased rates of symptoms of CFS and MCS, compared to NDV. (Iowa, 1997; Black, et al, 2000; Goss Gilroy, 1998; Unwin, et al, 1999; Reid, et al, 2001; Proctor, et al, 2001) Ill GWV reported increased rates of symptoms of CFS and MCS, compared to healthy GWV. (Kipen, et al, 1999) GWV with CFS or MCS reported significantly higher rates of psychiatric disorders than control populations, a finding that has previously been reported in civilian populations with CFS or MCS. (Pollet, et al, 1998; Lange, et al, 1999; Lange, et al, 2001; Black, et al, 1999; Black, et al, 2000; Reid, et al, 2001; Proctor, et al, 2001) GWV also reported higher rates of symptoms of fibromyalgia (FM) than NDV. (Iowa, 1997; Goss Gilroy, 1998; Smith, et al, 2000) Several studies are ongoing, which include thorough medical evaluations of veterans with symptoms of CFS, MCS, and FM. These include the VA National Survey, and studies in New Jersey, Portland, Iowa, and the UK. (Pollet, et al, 1998; Lange, et al, 1999; Lange, et al, 2001; McCauley, et al, 1999a; Storzbach, et al, 2000)

2. Several large studies have shown that GWV do not suffer from a unique, previously unrecognized "Gulf War syndrome." Five controlled studies have been published, that used a statistical technique, factor analysis, to identify patterns of symptoms. Thousands of GWV and NDV have been evaluated in these studies, involving the US Air Force; the US Navy; the US Army, Navy, and Air Force combined; and all three services in Great Britain combined, in two independent studies. (Fukuda, et al, 1998; Knoke, et al, 2000; Doebbeling, et al, 2000; Ismail, et al, 1999; Cherry, et al, 2001a) In all five studies, the patterns of symptoms reported by GWV were similar to the patterns reported by NDV. In general, GWV reported higher rates of the patterns of symptoms than NDV. However, sometimes, the NDV reported higher rates of some of the patterns of symptoms than the GWV. (Knoke, et al, 2000; Cherry, et al, 2001a) These five studies did not replicate the results of one small study, in which factor analysis yielded six patterns of symptoms. (Haley, et al, 1997a) The authors of the small study interpreted the six patterns to be "unique Gulf War syndromes;" however, the study did not include a control group of NDV with comparable symptoms.

3. These five large studies are consistent with the conclusion of an Institute of Medicine report: "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." (IOM, 2000)

I.C. Major Relevant Publications-Source of Funding, by Project Number (See bibliography for complete citations.)

- DoD-1: Gray, et al, 1996; Gray, et al, 1999a; Gray, et al, 2000; Knoke, et al, 2000; Smith, et al, 2000

- DoD-39: Unwin, et al; 1999; Ismail, et al, 1999; Ismail, et al, 2000; Reid, et al, 2001; Wessely, 2001; David, et al, 2001

- DoD-45: Pierce, 1997
- DoD-58: Doebbeling, et al, 2001; Barrash, et al, 2001b
- Funded by DoD (no project number): Roy, et al, 1998
- HHS-1: Iowa Persian Gulf Study Group, 1997; Black, et al, 1999; Black, et al, 2000; Doebbeling, et al, 2000
- HHS-2: Fukuda, et al, 1998; Nisenbaum, et al, 2000
- VA-2: Kang, et al, 2000
- VA-4: Wolfe, et al, 1999b; Proctor, et al, 2001
- VA-5: Pollet, et al, 1998; Kipen, et al, 1999; Lange, et al, 1999; Lange, et al, 2001
- VA-6: McCauley, et al, 1999a; Storzbach, et al, 2000
- VA-7: Wolfe, et al, 1996; Wolfe, et al, 1998; Wolfe, et al, 1999a; King, et al, 2000; Sharkansky, et al, 2000
- VA-12: Sutker, et al, 1995; Brailey, et al, 1998; Benotsch, et al, 2000
- Funded by VA (no project number): Institute of Medicine, 2000
- Funded by State of Kansas: Steele, 2000
- Funded by the Perot Foundation: Haley, et al, 1997a
- Funded by Canadian Department of National Defence: Goss Gilroy, 1998
- Funded by UK Medical Research Council: Cherry, et al, 2001a

II. BRAIN AND NERVOUS SYSTEM FUNCTION

Relevant Questions from 1996: 8, 16, 18

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

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

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

Number of Federally-funded projects with this primary or secondary focus area (1994 to December 31, 2000): 75

II.A. Prevalence of psychophysiological stressors reported by GWV, compared to an appropriate control population (1996 Question 8)

1. In 1999, a comprehensive review was published on the potential effects of stressors on health in GWV. (Marshall, et al, 1999) It summarized studies published through the end of 1997, including 55 studies that measured veterans' exposure to stressors through in-theater psychiatric evaluations or surveys conducted in-theater or following the war; and 60 studies that focused on the link between stressors and health problems reported by GWV. This section on psychophysiological stressors and the next section on psychological diagnoses will begin with the conclusions of the Marshall review, and then highlight the results of additional studies published in 1998-2001. Another comprehensive review of the potential effects of stressors on the health of GWV, which complements the 1999 Marshall review, was published in 1996. (Ursano and Norwood, 1996)

2. Deployment to the GW exposed both combatants and non-combatants to a wide range of stressors as reported by veterans. (Marshall, et al, 1999) Exposure to more intense stressors, such as actual combat, was limited. However, during the six-month build-up phase, many GWV experienced prolonged anticipation of the risk of serious injury or death due to impending air and ground assaults, as well as to possible chemical or biological warfare and SCUD missile attacks. Although exposures were not perceived as stressful by all GWV, a high proportion reported experiencing high levels of stress resulting from multiple circumstances. These findings were consistent among many studies and over time (i.e., 2 to 3 years after the war). Certain groups consistently reported higher exposures to stressors: reserve/National Guard personnel, enlisted personnel, and female veterans.

3. Many studies in 1998-2001 have evaluated reports of combat stressors and other stressful experiences in GWV. (Gray, et al, 1999a; McCauley, 1999b; Storzbach, et al, 2000; Unwin, et al, 1999; Nisenbaum, et al, 2000; Wolfe, et al, 1998; Wolfe, et al, 1999a; King, et al, 2000; Sharkansky, et al, 2000; Benotsch, et al, 2000; Fiedler, et al, 2000; Engel, et al, 2000; Cherry,

et al, 2001a; Cherry, et al, 2001b) The results of these studies are quite consistent with previous publications. (Marshall, et al, 1999)

4. Ill GWV have consistently reported more combat stressors than healthy GWV, such as deaths among unit members. This has been demonstrated in several different groups of ill GWV. These have included veterans with posttraumatic stress disorder (Wolfe, et al, 1998; Wolfe, et al, 1999a; Wagner, et al, 2000; King, et al, 2000; Sharkansky, et al, 2000; Benotsch, et al, 2000; Engel, et al, 2000); veterans with major depression and other psychological conditions (Engel, et al, 1999; Sharkansky, et al, 2000); veterans with chronic fatigue syndrome (Fiedler, et al, 2000); and veterans with chronic unexplained symptoms that could not be diagnosed after a thorough evaluation (Storzbach, et al, 2000)

5. In summary, many studies have demonstrated that the majority of Gulf War veterans have reported high levels of stressful experiences during the war. In several studies, ill Gulf War veterans have consistently reported more combat stressors than healthy GWV, such as deaths among unit members.

II.B. Prevalence of psychological symptoms and diagnoses in GWV, compared to a appropriate control group (1996 Question 18)

1. In 1999, 15 studies were reviewed on the relationship between stressor exposure and symptoms of posttraumatic stress disorder (PTSD) among GWV. (Marshall, et al, 1999) Each of the 15 studies demonstrated a positive correlation. The correlations between stress and PTSD symptoms were stronger in persons exposed to very high stress levels, such as actual combat, a SCUD missile attack, or graves registration (mortuary) duties. Ten studies were reviewed that evaluated the relationship between stressor exposure and other mental health problems in GWV, such as major depression or anxiety. (Marshall, et al, 1999) Most of these 10 studies demonstrated a correlation between stressor exposure and psychological distress.

2. Many studies in 1998-2001 have evaluated the rates of symptoms of PTSD in GWV and NDV. (Goss Gilroy, 1998; Gray, et al, 1999a; Unwin, et al, 1999; Dlugosz, et al, 1999; Lange, et al, 1999; Benotsch, et al, 2000; Wolfe, et al, 1999a; Wolfe, et al, 1999b; Wagner, et al, 2000; King, et al, 2000; Sharkansky, et al, 2000) In several studies, GWV were at increased risk for PTSD, in comparison with control populations. The results of these studies are quite consistent with previous publications. (Marshall, et al, 1999)

3. In 1998-2001, three studies used structured psychiatric interviews to evaluate major depression. GWV were at increased risk for depression, compared to control populations. (Fukuda, et al, 1998; Lange, et al, 1999; Wolfe, et al, 1999b) GWV were at increased risk for hospitalization for alcohol-related disorders, compared to NDV, in a very large study of all DoD hospitalizations through September 1993. (Dlugosz, et al, 1999)

4. In several studies, psychiatric diagnoses were made by clinicians through structured diagnostic interviews, not just through self-administered surveys. (Fukuda, et al, 1998; McCauley, et al, 1999a; Dlugosz, et al, 1999; Proctor, et al, 1998; Wolfe, et al, 1999b; Proctor, et al, 2001; White, et al, 2001; Vasterling, et al, 1997; Vasterling, et al, 1998; Pollet, et al, 1998; Lange, et al, 1999; Fiedler, et al, 2000; Lange, et al, 2001; Engel, 2000) The

studies in Boston, and New Orleans are ongoing. (Proctor, et al, 1998; Wolfe, et al, 1999b; Proctor, et al, 2001; White, et al, 2001; Vasterling, et al, 1997; Vasterling, et al, 1998)

5. Two large studies that analyzed data from the Comprehensive Clinical Evaluation Program demonstrated that, with increasing thoroughness of clinical evaluation, the proportion of GWV with undiagnosed symptoms decreased, and the proportion of GWV diagnosed with psychological conditions, such as major depression, increased significantly. (Roy, et al, 1999; Engel, et al, 1999) Three large population-based studies are utilizing structured psychiatric interviews-the VA National Survey and studies in Iowa and the United Kingdom. (Doebbeling, et al, 2001; Barrash, et al, 2001b; Wessely, 2001; David, et al, 2001; Ismail, et al, 2001)

6. Historically after exposure to stressful events, several psychological and physical symptoms have been observed frequently, including depression, anxiety, fatigue, impaired memory and concentration, headaches, back and neck aches, gastrointestinal complaints, and breathing difficulty. (Marshall, et al, 1999) All these symptoms are frequently reported by GWV, suggesting to some researchers that stressful experiences may be one of the underlying risk factors for their illnesses. (Marshall, et al, 1999)

7. In two large cohorts, the clinical diagnoses of PTSD and/or major depression were associated with an increased rate of reported physical symptoms in GWV, in nearly every organ system. (Wolfe, et al, 1998; Proctor, et al, 1998; Wolfe, et al, 1999b; Wagner, et al, 2000; Engel, et al, 2000) GWV reported more physical symptoms than NDV; and GWV with PTSD and/or major depression reported more physical symptoms than GWV without these diagnoses. (Wolfe, 1999b; Engel, et al, 2000)

8. In two large longitudinal studies in Boston and New Orleans, GWV were evaluated soon after returning from the war and again 1 to 2 years later. (Wolfe, et al, 1996; Wolfe, et al, 1999a; King, et al, 2000; Sutker, et al, 1995; Brailey, et al, 1998; 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 also increased over time.

9. Long-term follow-up evaluations of physical and psychological symptoms are continuing in five studies that include about 18,000 GWV and NDV, in Boston, New Orleans, New Jersey, Iowa, and the United Kingdom. This research will provide a better understanding of the mind/body connection of stress and how stress may have placed GWV at increased risk for adverse health outcomes, ultimately leading to improved treatment and prevention strategies in the future.

10. In summary, in many studies, Gulf War veterans have been diagnosed with significantly higher rates of posttraumatic stress disorder (PTSD) and major depression than non-deployed veterans. These higher rates have been demonstrated in several different populations of Gulf War veterans, through structured psychiatric interviews, as well as through self-administered questionnaires. In two large cohorts, Gulf War veterans diagnosed with PTSD or depression reported physical symptoms in many organ systems at higher rates than non-deployed veterans or healthy Gulf War veterans.

II.C. Prevalence of organic neuropsychological and neurological deficits in GWV, compared to an appropriate control group (1996 Question 16)

II.C.1. Prevalence of neuropsychological deficits in GWV, compared to an appropriate control group

1. A population-based study in Portland, Oregon focused on standardized psychological and neuropsychological evaluations in 241 GWV who reported unexplained symptoms, which could not be diagnosed after a thorough medical evaluation, and 113 healthy Gulf War veterans. (Anger, et al, 1999; Binder, et al, 1999; Storzbach, et al, 2000; Storzbach, et al, 2001) 87% of the cases had unexplained cognitive or psychological symptoms, 38% had unexplained musculoskeletal symptoms, and 42% had unexplained fatigue. Cases differed significantly from controls on all 12 psychological test scales, in the direction of increased distress. Almost all psychological measures had effect sizes that were large. Case performance on all 6 neuropsychological tests was deficient compared to the controls, however, the deficiencies were significant in only 2 of the 6 tests. All neuropsychological tests had effect sizes that were small. The results of the neuropsychological tests did not support a distribution-wide deficit in ill veterans, because the performance of 90% of the cases was similar to the controls. In contrast, 10% of the cases performed significantly worse than the controls on almost all the neuropsychological tests. The authors concluded that cognitive impairment should not be diagnosed, based solely on subjective complaints, and that objective cognitive testing is necessary.

2. In 1994-95, scientists at the Boston VAMC and New Orleans VAMC performed neuropsychological testing on 193 GWV and 47 control subjects. (White, et al, 2001) 142 GWV were part of the Fort Devens cohort, and 51 GWV were part of the New Orleans cohort. These two cohorts had been evaluated two times before, in 1991 (Time 1), and about one to two years later (Time 2). In 1994, the GWV were selected to produce an equal representation of veterans reporting higher vs. lower physical numbers of symptoms at Time 2. The control subjects were deployed to Germany during the Gulf War. 15 neuropsychological tests were used, which involved 7 functional domains. These 15 tests yielded 52 neuropsychological outcome measures. (White, et al, 2001) There were no significant differences between GWV and controls on education, alcohol use, and on estimated pre-morbid IQ. The GWV were significantly younger and reported significantly higher levels of psychological symptoms, than the controls. After adjusting for age, education, and gender, GWV performed more poorly than the controls on several specific neuropsychological tests. However, after adjusting for multiple statistical comparisons, only the differences in mood complaints (the POMS test) remained significant. The POMS (Profile of Mood States) contained five subscales (fatigue, anger, depression, anxiety, and confusion), all of which showed large effect sizes. Similarly, only adverse mood effects were significant, if the neuropsychological outcome measures were controlled for PTSD, psychological diagnosis, or other variables known to affect the tests.

3. In 1995-96, 100 GWV who met symptom criteria for chronic fatigue syndrome (CFS) and 47 healthy GWV underwent thorough physical exams, psychiatric evaluations, and neuropsychological tests at the East Orange, New Jersey VAMC. (Pollet, et al, 1998; Lange, et al, 1999) After medical exclusions, 48 GWV with CFS and 39 healthy GWV participated in 15 neuropsychological tests, which involved 5 major domains of cognition. (Lange, et al,

2001) There were no differences between the cases and controls on age, gender, race, alcohol use, and estimated pre-morbid IQ. There were significant differences on 4 of the 15 tests, before controlling for psychiatric illnesses. 67% of the CFS cases and 13% of the controls had Axis I psychiatric disorders, most frequently, major depression, PTSD, and anxiety disorders. After controlling for psychiatric illnesses, there were significant differences on only 2 neuropsychological tests. These tests related to response speed and mental flexibility. The authors concluded: "Since major depression or anxiety disorders can affect cognitive function, a thorough psychiatric assessment is important when evaluating Gulf veterans neuropsychologically."

4. Several studies have reported on neuropsychological exams in other groups of GWV:
   - 21 ill GWV and 38 healthy civilians in Pittsburgh (Goldstein, et al, 1996);
   - 49 members of an Army National Guard unit in Detroit (Axelrod and Milner, 1997; Sillanpaa, et al, 1997; Sillanpaa, et al, 1999); and
   - 19 GWV with PTSD and 24 GWV without PTSD in New Orleans (Vasterling, et al, 1997; Vasterling, et al, 1998).

   The results of these studies in Pittsburgh, Detroit, and New Orleans were generally consistent with the studies in Portland, Boston, and New Jersey. Self-reports of memory and concentration problems were more frequent among the groups of GWV than among the control subjects. However, on objective testing, performance was the same on most neuropsychological tests in GWV and control subjects. In a small proportion of tests, GWV performed significantly more poorly than controls. After adjustment for PTSD or other psychological distress, the differences on the tests between the GWV and the NDV diminished or disappeared.

5. Haley and colleagues interpreted the symptoms of 50 Gulf War veterans to indicate three different "unique Gulf War syndromes." (Haley, et al, 1997a; Haley, et al, 1997b; Hom, et al, 1997) 23 of the 50 cases were selected because they reported the most symptoms, including 5 individuals with "Syndrome 1," 13 individuals with "Syndrome 2," and 5 individuals with "Syndrome 3." Twenty healthy veterans were used as controls. A large, unknown number of neuropsychological tests was performed. There were no differences on the tests between the 5 cases with Syndrome 1, the 5 cases with Syndrome 3, and the 20 controls. The 13 cases with Syndrome 2 performed significantly worse than the 20 controls on most of the tests. (Haley, et al, 1997b) There was no adjustment made in the tests for pre-morbid IQ or major depression. Based on the results of some of the neuropsychological tests, the average pre-morbid IQ was probably lower in the 13 cases. (Hom, et al, 1997; White, et al, 2001) Depression was significantly more frequent in the cases (59%), than in the controls (17%). (Haley, et al, 2000) Pre-morbid IQ and depression have been shown to cause substantial confounding in other studies. (Binder, et al, 1999; Storzbach, et al, 2000; Storzbach, et al, 2001; White, et al, 2001).

6. Several large ongoing studies are using neuropsychological exams to evaluate cognitive function, including the VA National Survey, and studies in Boston, New Orleans, Iowa, and the UK. (White, 2001; Krengel, et al, 2001; Sullivan, et al, 2001; Doebbeling, et al, 2001; Barrash, et al, 2001a; Barrash, et al, 2001b; Wessely, 2001; David, et al, 2001)

7. In summary, studies of several populations of Gulf War veterans and non-deployed veterans have demonstrated consistent results on neuropsychological testing. Self-reports of memory and concentration problems were usually more frequent among the groups of Gulf War veterans than among the control subjects. However, on objective testing, performance was the same on most neuropsychological tests in Gulf War veterans and control subjects. In a small proportion of tests, Gulf War veterans performed significantly more poorly than controls. After adjustment for PTSD or other psychological distress, the differences on the tests between the two groups diminished or disappeared.

II.C.2. Prevalence of neurological deficits in GWV, compared to an appropriate control group

1. There have been two major publications about hospitalizations in GWV and NDV. (Gray, et al, 1996; Gray, et al, 2000) The 2000 study extended the follow-up period of the 1996 study. Hospitalizations in all 697,000 GWV were compared to an equal number of NDV. Data were used from three hospital systems: DoD hospitals nationwide, VA hospitals nationwide, and all hospitals in the state of California. In the DoD system, the rates of hospitalization for neurological diseases were low, and the same for GWV and NDV. In the VA and California systems, the rates of hospitalization for neurological diseases were low, and the rates were significantly lower in GWV, than for NDV.

2. Neurological diagnoses of patients in the Comprehensive Clinical Evaluation Program are relevant, because this is the largest group of GWV who have received systematic, thorough medical evaluations. (Joseph, 1997) Among the first 20,000 GWV in the CCEP, only 42 were diagnosed with peripheral neuropathy or polyneuropathy (0.2%). Over 800 GWV who had neuromuscular symptoms received neuropsychological evaluations. Approximately 300 of these 800 patients also received nerve conduction studies and electromyography. No common or distinctive anatomical, physiological or pathological abnormality was identified among these 800 GWV.

3. Four studies have reported the results of neurological examinations in GWV:
   - 65 ill GWV (Newmark and Clayton, 1995);
   - 14 ill GWV and 13 healthy controls (Jamal, et al, 1996);
   - 20 GWV veterans with severe symptoms of muscle fatigue, weakness, and/or muscle pain (Amato, et al, 1997b); and
   - 12 GWV with symptoms of peripheral neuropathy (Rivera-Zayas, et al, 2001).

   In addition, one larger population-based study has reported the results of neurological exams, which included 158 ill GWV and 67 healthy GWV. (McCauley, et al, 1999a) In each of these studies, objective neurological exams were usually within normal limits. There were usually no specific diagnoses of neurological disorders that could explain the veterans' symptoms. For example, these studies provided no evidence for clinically significant peripheral neuropathy.

4. In early 1995, the Centers for Disease Control and Prevention (CDC) performed a thorough case-control study of the Pennsylvania 193rd Air Force National Guard unit. (Fukuda, et al, 1998) The unit reportedly had a high prevalence of "mystery illness," according to a physician at the Lebanon, Pennsylvania VAMC. 490 members of this unit deployed to the

Gulf War, of which 158 participated in the CDC study. This included medical histories, physical exams, structured psychiatric interviews, and clinical lab tests. Of these 158 GWV, 8% complained of severe, chronic symptoms of fatigue, musculoskeletal pain, and/or problems with mood or cognition. 54% complained of mild-to-moderate symptoms, and 37% did not report these symptoms (controls). One major finding was "Physical examinations were most notable for the general paucity of abnormal findings." In particular, "Several minor abnormalities were found on lymph node, liver, spleen, or neurologic examination, but none was associated with cases." CDC concluded: "The illness was not associated with physical examination or clinical laboratory abnormalities." In contrast, the prevalence of current psychiatric illness was significantly higher among cases than controls (i.e., major depression, somatization disorder, panic disorder, and PTSD).

5. In one small 1995 study, Haley and colleagues interpreted the symptoms of 23 Gulf War veterans to be indicative of three, different "unique Gulf War syndromes." The authors hypothesized that these "syndromes" were due to "generalized injury to the nervous system." (Haley, et al, 1997a; Haley, et al, 1997b) As part of this study, six independent neurologists reviewed the clinical findings for each of the 23 ill veterans and 20 healthy controls in order to arrive at a consensus diagnosis. (Haley, et al, 1997b) These neurologists had not participated in the exams of these 43 subjects and they conducted their review blinded to case-control status. The neurologists concluded that the clinical and laboratory findings were nonspecific and they were not sufficient to diagnose any known neurological disease. On detailed neurological exams, about 66% of the 43 subjects had one or more neurological abnormalities (most frequently, reduced muscle strength in the lower extremities). However, the proportion of subjects with abnormalities was the same in the 23 ill veterans and the 20 healthy veterans.

   Haley and colleagues' interpretation about "generalized injury to the nervous system" has been seriously questioned, in light of the evaluations of the independent neurologists, who concluded that the 23 ill veterans did not demonstrate significant neurological pathology. (Amato, et al, 1997a; Albers and Berent, 2000) For example, the Institute of Medicine recently stated "The clinical data presented provide little evidence with which to conclude that these patients had a neuropathic process. . . The principal limitation of this nested case-control study is the lack of clinical validity of measures used to infer neurological damage." (IOM, 2000) In 1998, 22 of the 23 ill veterans and 18 of the 20 controls were re-evaluated. (Haley, et al, 2000) The neurological examinations of the ill veterans continued to demonstrate few or no abnormalities. The authors concluded that the cases had "generally not, up to now, progressed to the point of having objective neurologic signs."

6. In 1995, the 23 ill veterans and 19 of the 20 healthy controls underwent magnetic resonance imaging (MRI), before and after gadolinium administration. (Haley, et al, 1997b) The MRI scans were within normal limits in 22 of the ill veterans and 17 of the 19 controls. The authors concluded "No abnormalities that could explain the symptoms were identified on brain MRI interpreted by a neuroradiologist who was blinded to the subjects' case or control status." (Haley, et al, 2000) In 1995, single-photon emission computed tomography (SPECT) scans were also performed. Consensus interpretation of the SPECT scans by three experts in nuclear radiology demonstrated no abnormalities. (Haley, et al, 1997b) In 1998, magnetic resonance spectroscopy (MRS) was performed in 22 of the ill veterans and 18 of the controls. (Haley, et al, 2000) MRS is a new research technique in neuroimaging that has

been used to explore brain chemistry. When the ratio of certain brain chemicals is reduced, it is thought to reflect a non-specific, generalized reduction of functional neuronal mass. This ratio of chemicals was significantly lower in the right basal ganglia and in the pons of the 12 cases with "Syndrome 2," compared with the 18 controls, but not in the left ganglia. There were no differences in the ratio of chemicals between the 5 cases with "Syndrome 1," the 5 cases with "Syndrome 3," and the 18 controls. There was no explanation of how to interpret an abnormal result on MRS, in the context of a normal neurological exam, a normal MRI scan, and a normal SPECT scan.

7. Several studies are performing neuroimaging in groups of GWV and NDV, including conventional MRI, functional MRI, MRS, and SPECT scans. Two completed studies at the East Orange, New Jersey VAMC and the West Haven, Connecticut VAMC have not published results yet (VA-5B and DoD-40). Four studies are ongoing (HHS-5, DoD-86, DoD-90, DoD-101). In 2001, DoD plans to fund a large study of GWV and NDV using MRI and MRS at the San Francisco VAMC.

8. Some Gulf War veterans have expressed concern about the prevalence of amyotrophic lateral sclerosis (ALS), a serious neurological disease. The rates of ALS were determined for more than 551,000 GWV and 1,479,000 NDV, with follow-up through July 1997. (Smith, et al, 2000) All hospitalizations in military hospitals were included. The rates of ALS were not significantly different between GWV and NDV. In 2000, VA and DoD initiated an epidemiological study of the incidence of ALS, to determine more definitively if there is an increased rate in GWV, compared to NDV. Nationwide ascertainment of cases and comprehensive evaluation of ALS cases will be completed in 2001, using DoD, VA, and civilian data sources.

9. Three large population-based studies are using neurological evaluations to detect central nervous system and peripheral nervous system abnormalities, which will be competed in 2001. These include the VA National Survey, and studies in Iowa and the United Kingdom. (Doebbeling, et al, 2001; Barrash, et al, 2001a; Barrash, et al, 2001b; Wessely, 2001; David, et al, 2001; Ismail, et al, 2001)

10. In summary, neurological examinations have been performed in studies of several populations of Gulf War veterans. These studies have consistently shown that Gulf War veterans do not generally demonstrate objective evidence of neurological diseases. Three large population-based studies are using neurological evaluations to detect central nervous system and peripheral nervous system abnormalities, which will be completed in 2001. Eight studies are performing neuroimaging in GWV and NDV, including conventional magnetic resonance imaging (MRI), functional MRI, magnetic resonance spectroscopy, and single-photon emission computed tomography.

II.D. Major Relevant Publications-Source of Funding, by Project Number
(See bibliography for complete citations.)

- DoD-1: Gray, et al, 1996; Gray, et al, 1999a; Dlugosz, et al, 1999; Gray, et al, 2000; Smith, et al, 2000

- DoD-32: Krengel, et al, 2001; White, 2001

- DoD-39: Unwin, et al, 1999; Wessely, 2001; David, et al, 2001; Ismail, et al, 2001
- DoD-58: Doebbeling, et al, 2001; Barrash, et al, 2001a; Barrash, et al, 2001b
- DoD-65: Haley, et al, 2000
- Funded by DoD (no project number): Marshall, et al, 1999; Newmark and Clayton, 1995; Ursano and Norwood, 1996; Amato, et al, 1997a; Amato, et al, 1997b; Joseph, 1997; Roy, et al, 1999; Engel, et al, 1999; Engel, et al, 2000
- HHS-2: Fukuda, et al, 1998; Nisenbaum, et al 2000
- VA-4: Proctor, et al, 1998; Wolfe, et al, 1999b; Proctor, et al, 2001; White, et al, 2001; Sullivan, et al, 2001; White, 2001
- VA-5: Pollet, et al, 1998; Lange, et al, 1999; Fiedler, et al, 2000; Lange, et al, 2001
- VA-6: McCauley, 1999a; McCauley, 1999b; Anger, et al, 1999; Binder, et al, 1999; Storzbach, et al, 2000; Storzbach, et al, 2001
- VA-7: Wolfe, et al, 1996; Wolfe, et al, 1998; Wolfe, et al, 1999a; Wagner, et al, 2000; King, et al, 2000; Sharkansky, et al, 2000
- VA-9: White, et al, 2001
- VA-11: Vasterling, et al, 1997; Vasterling et al, 1998
- VA-12: Sutker, et al, 1995; Brailey, et al, 1998; Benotsch, et al, 2000
- VA-13: Goldstein, et al, 1996
- VA-50: Axelrod and Milner, 1997; Sillanpaa, et al, 1997; Sillanpaa, et al, 1999
- Funded by VA (no project number): IOM, 2000; Rivera-Zayas, et al, 2001
- Funded by Perot Foundation: Haley, et al, 1997a; Haley, et al, 1997b; Hom et al, 1997; Haley, et al, 2000
- Research in US, not federally funded: Albers and Berent, 2000
- Funded by Canadian Department of National Defence: Goss Gilroy, 1998
- Funded by UK Medical Research Council: Cherry, et al, 2001a; Cherry, et al, 2001b
- Funded privately in UK: Jamal, et al, 1996

III. MORTALITY

Relevant Questions from 1996: 20, 21

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?

Number of Federally-funded projects with this primary or secondary focus area (1994 to December 31, 2000): 3

III.A. Rates and causes of mortality in GWV, compared to an appropriate control population (1996 Question 21)

1. Two studies evaluated the rates and causes of death among American GWV during the period of August 1990 to July 1991. (Helmkamp, 1994; Writer, et al, 1996) In 1996, a study was published on the mortality rates of 622,000 Gulf War veterans and 746,000 NDV, with follow-up through September 1993. (Kang and Bullman, 1996) There was small, but significant, increase in mortality due to all causes in GWV (relative risk of 1.09). This excess was mainly due to unintentional injuries, mostly motor vehicle fatalities. The risk of unintentional injuries was 1.25 times higher in male GWV and 1.83 times higher in female GWV. The risk of death from diseases (natural causes) was lower in GWV than NDV (relative risk of 0.88).

2. This mortality study has been updated with the same cohorts of GWV and NDV, with follow-up through December 1997. (Kang and Bullman, 2001) Overall mortality rates in GWV and NDV were similar (relative risk in GWV of 0.95). There continues to be a small, significant increase in motor vehicle fatalities in GWV (1.19 times higher in male GWV and 1.63 times higher in female GWV). The risk of death from diseases (natural causes) continues to be lower in GWV (relative risk of 0.83). No disease categories were significantly increased in GWV, such as cardiovascular diseases, cancer, or respiratory diseases. Among GWV and NDV, the overall mortality rates were 41% and 42% of the age-adjusted mortality rates in the general U.S. population, respectively. This means that American GWV and NDV are much healthier than persons of the same age in the general U.S. population.

3. The mortality experience of all 53,462 British GWV was compared with an equal number of British NDV, with follow-up through March 1999. (Macfarlane, et al, 2000) Overall mortality rates in GWV (0.7%) and NDV (0.7%) were similar. Mortality due to "external" causes was slightly higher in GWV (relative risk of 1.18), mostly due to motor vehicle fatalities. The risk of death from diseases (natural causes) was lower in GWV (relative risk of 0.87). The results of the American and British mortality studies are very similar, and both studies will continue indefinitely.

4. There have been two major publications about hospitalizations in GWV and NDV. (Gray, et al, 1996; Gray, et al, 2000) The 2000 study extended the follow-up period of the 1996 study. The rates and causes of hospitalizations in all 697,000 GWV were compared to the rates in an equal number of NDV. Hospitalizations for fractures and soft-tissue injuries were significantly more frequent in GWV in military hospitals nationwide and in civilian hospitals in the state of California. There were no differences in rates of hospitalizations for injuries in VA hospitals nationwide. (Gray, et al, 2000) These hospitalization data are consistent with the increased rates of motor vehicle fatalities in GWV. One ongoing project is evaluating the risk factors responsible for the observed increase in motor vehicle fatalities in GWV (Project DoD-102). Another ongoing project is evaluating the risk factors for the significantly increased risk of unintentional injuries in GWV (Project DoD-73). (Bell, et al, 2000)

5. In summary, the mortality rates in both Gulf War veterans and non-deployed veterans are about 40% of the mortality rates in the general US population, which means that veterans are much healthier. In both the US and the UK, Gulf War veterans have had a significantly higher mortality rate due to unintentional injuries, mostly motor vehicle injuries, compared to non-deployed veterans. This is the only difference in mortality rates, to date. The follow-up mortality studies in the US and UK will continue indefinitely.

III.B. Rates and types of cancer in GWV, compared to an appropriate control group (1996 Question 20)

1. Mortality rates due to cancer are very low in American GWV and NDV. Cancer deaths have occurred in 477 male GWV and 860 male NDV (relative risk of 0.90). Cancer deaths have occurred in 49 female GWV and 103 female NDV (relative risk of 1.11). There were no increases in any specific type of cancer among GWV. (Kang and Bullman, 2001)

2. Mortality rates due to cancer are also very low in British GWV and NDV. There have been 53 cancer deaths among GWV and 48 cancer deaths among NDV. There were no increases in any specific type of cancer among GWV. (Macfarlane, et al, 2000)

3. There have been two major publications about hospitalizations in GWV and NDV. (Gray, et al, 1996; Gray, et al, 2000) The 2000 study extended the follow-up period of the 1996 study. Hospitalizations in all 697,000 GWV were compared to an equal number of NDV. Data were used from three hospital systems: DoD hospitals nationwide, VA hospitals nationwide, and all hospitals in the state of California. In the DoD system, the rates of hospitalization for cancer were low, and the same for GWV and NDV. In the VA and California systems, the rates of hospitalization for cancer were low, and the rates were significantly lower in GWV, than for NDV.

4. Diagnoses of cancer in participants in the Comprehensive Clinical Evaluation Program are relevant, because this is the largest group of GWV who have received systematic, thorough medical evaluations. (Joseph, 1997) Among the first 20,000 GWV in the CCEP, only 61 individuals were diagnosed with cancer (0.3%). These included 22 cases of lymphoma or leukemia, 9 cases of skin cancer, and 30 cases of other types of cancer.

5. In summary, the rates of cancer diagnosis have been very low in Gulf War veterans, and they have been similar to or lower than the rates in non-deployed veterans.

III.C. Major Relevant Publications-Source of Funding, by Project Number
(See bibliography for complete citations.)

- DoD-1: Gray, et al, 1996; Gray, et al, 2000
- DoD-15: Writer, et al, 1996
- DoD-73: Bell, et al, 2000
- Funded by DoD (no project number): Helmkamp, 1994; Joseph, 1997
- VA-1: Kang and Bullman, 1996; Kang and Bullman, 2001
- Funded by UK Medical Research Council: Macfarlane, et al, 2000

IV. REPRODUCTIVE HEALTH

Relevant Questions from 1996: 11, 12, 13

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?

Number of Federally-funded projects with this primary or secondary focus area
(1994 to December 31, 2000): 11

IV.A. Prevalence of birth defects in offspring of GWV, compared to an appropriate control population (1996 Question 11)

1. The rates and types of birth defects were compared among 31,000 infants born to GWV and 43,000 infants born to NDV, in 135 military hospitals in 1991-1993. (Cowan, et al, 1997) There were no differences in the rates in the offspring of male or female GWV (7.5%), compared to offspring of male or female NDV (7.6%). There were also no differences between GWV and NDV in the rates of severe birth defects (1.85%). A substudy showed that there were no significant differences in the rates of a rare, severe birth defect called Goldenhar syndrome. (Araneta, et al, 1997) These studies had two limitations: the analysis covered only live births, and not stillbirths or miscarriages; and the research was done in military hospitals, so reserve members and service members who left active-duty soon after the war were not included. A number of ongoing studies are designed to address these data gaps.

2. The prevalence of birth defects was determined 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) Birth certificate records of 99,545 live births in Hawaii between 1989 and 1993 were evaluated to identify births to military personnel. 17,182 infants were identified who were born to military parents (22% GWV and 78% NDV). There were no differences in infants born to GWV and NDV in rates of low birth weight or prematurity. 367 infants were identified with major birth defects (2% of 17,182 live births). The prevalence of birth defects was similar for GWV and NDV in the prewar period and in the postwar period. This study has a number of strengths: it included births in military and civilian hospitals; it included parents who were currently in the reserve or National Guard; and it included births to parents who had separated from the military. The authors are continuing this study, using the same methods in 5 additional states that perform active case surveillance for birth defects-Arizona, Arkansas, California, Georgia, and Iowa.

3. The final phase of the VA National Survey includes interviews and physical exams of spouses and children. This includes a complete reproductive history and pelvic exam for adult women. Adverse reproductive outcomes will be compared among GWV and NDV, including infertility, miscarriages, low birth weight, birth defects, and sexual dysfunction. The exams of veterans, spouses and children are complete, and the analysis of the study should be completed in late 2001.

4. In summary, two very large studies based on medical records have demonstrated that the rates of birth defects in the offspring of Gulf War veterans and non-deployed veterans were the same. Several ongoing studies are evaluating birth defects and other aspects of reproductive health.

IV.B. Rates of reproductive success in GWV, compared to an appropriate control group (1996 Question 12)

1. A mailed questionnaire was sent to 17,166 GWV and NDV to evaluate reproductive success through the end of 1995 (participation rate of 66%). The rates of infertility, miscarriages, prematurity, and low birth weight will be compared between GWV and NDV (Project DoD-1D). The results of this study will be published in 2001. In addition, the VA National Survey will evaluate these reproductive outcomes, as outlined above.

IV.C. Rates of sexual dysfunction in GWV, compared to an appropriate control group (1996 Question 13)

1. Three major surveys have included questions on symptoms of sexual dysfunction. In the Iowa study, there were no differences in the rates of "symptoms of sexual discomfort" among active-duty GWV and NDV. In contrast, reservists deployed to the GW reported sexual discomfort at significantly higher rates than non-deployed reservists. (Iowa, 1997) British GWV reported significantly higher rates of "sexual problems" than British NDV. (Unwin, et al, 1999) In the VA National Survey, GWV reported significantly higher rates of impotence and painful intercourse, compared to NDV. (Kang, et al, 2000) The final phase of the VA National Survey will include thorough reproductive histories of veterans and their spouses, and comprehensive physical exams, including pelvic exams. These exams will provide objective evidence whether these sexual symptoms can be medically verified.

2. The rates of cervical cytology abnormalities were compared among female Gulf War veterans and non-deployed veterans, using the results of Pap smears. (Frommelt, et al, 2000) 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 from these women were also evaluated in 1995 and 1996. 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 (no significant difference). The percentage of self-reported abnormal results among Gulf War veterans in a 1997 study was similar to the 2000 findings (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 2000 findings (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.

IV.D. Major Relevant Publications-Source of Funding, by Project Number (See bibliography for complete citations.)

- DoD-1: Cowan, et al, 1997; Araneta, et al, 1997; Araneta, et al, 2000
- DoD-39: Unwin, et al, 1999
- DoD-45: Pierce, et al, 1997
- Funded by DoD (no project number): Frommelt, et al, 2000
- HHS-1: Iowa Persian Gulf Study Group, 1997
- VA-2: Kang, et al, 2000

V. INFECTIOUS DISEASES (INCLUDING LEISHMANIASIS)

Relevant Questions from 1996: 2, 19

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

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

Number of Federally-funded projects with this primary or secondary focus area (1994 to December 31, 2000): 8

V.A. Prevalence of leishmaniasis in GWV (1996 Questions 2, 19)

1. 32 cases of leishmaniasis have been diagnosed in 697,000 GWV. (PAC, 1996) Eight DoD- and VA-funded projects have focused on the development of simple, sensitive tests for leishmaniasis that could lead to better methods of screening or diagnosis of infection, as well as new treatment methods. To date, the sensitivity of the new methods has not been validated in large human populations.

V.B. Prevalence of other infectious diseases in GWV (1996 Question 19)

V.B.1. Prevalence of infectious diseases, in general, in GWV

1. This section focuses on all infectious diseases first, and then discusses *Mycoplasma fermentans*. Serious infections are rare among GWV, based on data on mortality and hospitalizations. The mortality rates of 622,000 Gulf War veterans and 746,000 NDV were evaluated, with follow-up through December 1997. (Kang and Bullman, 2001) Death rates due to infectious diseases (ID) were very low in both GWV and NDV. There were 67 ID deaths in male GWV, compared to 233 ID deaths in male NDV (significantly lower in GWV, relative risk of 0.31). There were 2 ID deaths in female GWV, compared to 8 ID deaths in female GWV. The lower ID death rates in NDV were mainly due to lower rates of HIV infection.

2. There have been two major publications about hospitalizations in GWV and NDV. (Gray, et al, 1996; Gray, et al, 2000) The 2000 study extended the follow-up period of the 1996 study. Hospitalizations in all 697,000 GWV were compared to an equal number of NDV. Data were used from three hospital systems: DoD hospitals nationwide, VA hospitals nationwide, and all hospitals in the state of California. Data from all three hospital systems showed that GWV were significantly less likely to be hospitalized for ID than NDV.

3. The Centers for Disease Control and Prevention (CDC) performed a thorough case-control study of an Air Force National Guard unit in Lebanon, Pennsylvania. (Fukuda, et al, 1998) 490 members of this unit were deployed to the Gulf War, of which 158 participated in physical exams and several serum antibody tests and fecal tests for infectious diseases. These tests focused on important ID in the Persian Gulf region that can cause a chronic

disease. Of the 158 veterans, 8% complained of severe, chronic symptoms of fatigue, musculoskeletal pain, and/or problems with memory or depression. 54% complained of mild to moderate symptoms, and 37% did not have these symptoms (healthy). Based on the fecal tests, there were no cases of ID that would cause severe, chronic diarrhea. There were no associations between GWV with chronic symptoms vs. healthy GWV on the serum antibody tests, which could detect several endemic ID. CDC concluded that the veterans with chronic symptoms were not associated with physical examination or lab test abnormalities.

4. One study identified GWV diagnosed with ID that are endemic to the Persian Gulf region, through review of pathology specimens. (Specht, et al, 2000) The Kuwait Registry was established by DoD to act as a repository for pathology specimens, contributed by DoD and VA medical centers. Registry diagnoses were reviewed to identify endemic ID, including leishmaniasis, malaria, hepatitis A, B, and C, anthrax, and several others. Specimens were available from 2,852 Gulf War veterans with a wide variety of symptoms, from 1992 through December 1997. One patient in the Registry was diagnosed with hepatitis B (0.04%) and 15 patients were diagnosed with hepatitis C (0.58%). The rates of these two diseases were well below the rates in the general US population. No other endemic ID were identified in Registry specimens.

5. In summary, four studies have shown that the rates of infectious diseases have been low in Gulf War veterans, and significantly lower than the rates in non-deployed veterans.

V.B.2. Prevalence of *Mycoplasma fermentans* in GWV

1. 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. Two studies have evaluated the rates of infection with *Mycoplasma fermentans* among GWV. One large study compared the prevalence of antibodies to *Mycoplasma fermentans* among ill and healthy Gulf War veterans, and determined the rates of seroconversion. (Lo, et al, 2000) The cases were 718 Army GWV with chronic illnesses, who had been evaluated in Phase II of the CCEP. The controls were 2,233 GWV, who were Army veterans who had not enrolled in the CCEP. Before the war, 4.8% of the cases and 5.2% of the controls tested positive for antibodies to *Mycoplasma fermentans*. There were no differences in the rates of seroconversion after the war (1% in both groups). These results provided no evidence that infection with *Mycoplasma fermentans* was associated with the development of chronic illnesses in the cases.

2. The Navy performed a similar study, which compared the rates of antibodies to *Mycoplasma fermentans* between GWV and NDV. (Gray, et al, 1999b) *Mycoplasma* infections occurred both before the war and after the war. These infections occurred at similar rates in GWV and NDV. Also, *Mycoplasma* infections were not associated with postwar symptoms in either GWV or NDV.

3. Three studies are focused on the diagnosis and treatment *of Mycoplasma fermentans*. One recently completed study, based at Walter Reed Army Medical Center, evaluated the reproducibility of the laboratory tests used to detect the organism in human blood (Project DoD-66). The results of this study have not been published yet.

4. The second recently completed study was based at the Birmingham, Alabama VA Medical Center. It was designed to detect exposure to *Mycoplasma* or *Ureaplasma* species in white blood cells, throat swabs, and urines (Project DoD-42). At the time of the most recent progress report in late 2000, samples had been tested from 52 GWV who had medically-unexplained symptoms, 31 asymptomatic GWV, and 21 ill NDV who had applied for disability compensation. *Mycoplasma* or *Ureaplasma* species were detected frequently in urine and throat swabs, however, there were no significant differences between the three groups.

5. The third study, the Antibiotic Treatment Trial, is a multi-site clinical trial designed to determine whether long-term treatment with doxycycline leads to improvement in *Mycoplasma*-positive GWV (Projects VA-55 and DoD-119). This project will be completed in late 2001.

6. In summary, two projects have demonstrated no differences in the rates of infection with *Mycoplasma fermentans* in Gulf War veterans, compared to non-deployed veterans, either before or after the war. The Antibiotic Treatment Trial is a multi-site clinical trial designed to determine whether long-term treatment with doxycycline leads to improvement in *Mycoplasma*-positive GWV, and it will be completed in late 2001.

V.C. Major Relevant Publications-Source of Funding, by Project Number
(See bibliography for complete citations.)

- DoD-1: Gray, et al, 1996; Gray, et al, 1999b; Gray, et al, 2000
- DoD-47: Lo, et al, 2000
- Funded by DoD (no project number): Specht, et al, 2000
- HHS-2: Fukuda, et al, 1998
- VA-1: Kang and Bullman, 2001
- Funded by US Government (no project number): PAC (Presidential Advisory Committee on Gulf War Veterans' Illnesses), 1996

VI. IMMUNE FUNCTION

Relevant Questions from 1996: 10

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

Number of Federally-funded projects with this primary or secondary focus area (1994 to December 31, 2000): 14

VI.A. Prevalence of altered immune function or altered host defense among GWV, compared to an appropriate control population (1996 Question 10)

1. In summary, if there were increased rates of serious infectious diseases or autoimmune diseases in GWV, this could be an indicator of altered immune function or host defense. The evidence to date has shown that GWV have the same or significantly lower rates of these diseases, compared to NDV.

VI.A.1. Prevalence of serious infectious diseases in GWV, compared to an appropriate control population

1. Serious infections are rare among GWV, based on data on mortality and hospitalizations. The mortality rates of 622,000 Gulf War veterans and 746,000 NDV were evaluated, with follow-up through December 1997. (Kang and Bullman, 2001) Death rates due to infectious diseases (ID) were very low in both GWV and NDV. There were 67 ID deaths in male GWV, compared to 233 ID deaths in male NDV. The risk of ID deaths in GWV was only 31% of the risk in NDV (significantly lower). There were 2 ID deaths in female GWV vs. 8 ID deaths in female NDV. The lower death rates in GWV were mainly due to lower rates of HIV infection.

2. There have been two major publications about hospitalizations in GWV and NDV. (Gray, et al, 1996; Gray, et al, 2000) The 2000 study extended the follow-up period of the 1996 study. Hospitalizations in all 697,000 GWV were compared to an equal number of NDV. Data were used from three hospital systems: DoD hospitals nationwide, VA hospitals nationwide, and all hospitals in the state of California. Data from all three hospital systems showed that GWV were significantly less likely to be hospitalized for ID than NDV.

VI.A.2. Prevalence of autoimmune diseases in GWV, compared to an appropriate control population

1. Systemic lupus erythematosus (SLE) is one of the most common diseases that involve altered immune function. The rates of SLE were determined for more than 551,000 GWV and 1,479,000 NDV, including all military hospitals nationwide, with follow-up through July 1997 (six years). (Smith, et al, 2000) The rates of SLE were slightly lower in GWV (36 cases), compared to NDV (160 cases) (relative risk of 0.94).

2. Autoimmune diseases diagnosed among patients in the Comprehensive Clinical Evaluation Program (CCEP) are relevant, because this is the largest group of GWV who have received systematic, thorough medical evaluations. (Joseph, 1997) In fact, the protocol of tests for Phase II of the CCEP specifically includes blood tests for autoimmune diseases. Among the first 20,000 GWV in the CCEP, 12% underwent Phase II evaluations. Only 80 of the 20,000 were diagnosed with immune disorders (0.4%). These included 33 cases of rheumatoid arthritis, 13 cases of SLE, 13 cases of Sjogren's syndrome, and 21 cases of other diseases.

3. Three studies are performing clinical evaluations of musculoskeletal diseases, including fibromyalgia and autoimmune diseases. These are the VA National Survey, and studies in Portland, Oregon, and Iowa. (McCauley, et al, 1999a) These projects will be completed by late 2001.

4. Immune function was tested in 43 GWV with chronic fatigue syndrome and 34 healthy GWV. (Zhang, et al, 1999) Many blood tests for immune function were included, such as counts of T cells and B cells, which are types of white blood cells, and levels of cytokines, which are chemicals involved with immune function. The immune tests were within the normal range for both ill GWV and healthy GWV.

5. A completed study, based at the Birmingham, Alabama VA Medical Center, was designed to detect immune abnormalities, including cytokine levels (Project DoD-42). At the time of the most recent progress report in late 2000, samples had been tested from 52 GWV who had medically-unexplained symptoms, 31 asymptomatic GWV, and 21 ill NDV who had applied for disability compensation. There were no significant differences in several immune tests, between the three groups.

6. A similar study of immune function has begun in the United Kingdom, which focuses on cytokine levels, and which includes a larger, more representative group of GWV, NDV, and veterans who were deployed to Bosnia (Project DoD-106).

VI.B. Major Relevant Publications-Source of Funding, by Project Number
(See bibliography for complete citations.)

- DoD-1: Gray, et al, 1996; Gray, et al, 2000; Smith, et al, 2000
- Funded by DoD (no project number): Joseph, 1997
- VA-1: Kang and Bullman, 2001
- VA-5: Zhang, et al, 1999
- VA-6: McCauley, et al, 1999a

VII. OIL WELL FIRE SMOKE

Relevant Questions from 1996: 3, 14, 15

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

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?

Number of Federally-funded projects with this primary or secondary focus area
(1994 to December 31, 2000): 5

VII.A. Levels of exposures among GWV to petroleum products and combustion products (1996 Question 3)

1. Clearly, the most visible source of possible contamination to which US troops were exposed during the Gulf War was the smoke from more than 600 oil wells that were set ablaze by Iraqi forces. The fires burned from January to November 1991. In November 1998, the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) published a comprehensive review of the potential health effects of the oil well fires. This review was updated and republished in September 2000. (OSAGWI, 1998b; OSAGWI, 2000b) The results of these health assessments are briefly summarized here. Overall, the risk of long-term adverse effects from exposure to the oil well fires was assessed to be minimal.

2. The results of air quality monitoring programs conducted in 1991 indicated that the concentrations of most contaminants in the oil fire smoke were similar to concentrations measured in US cities, and did not exceed US ambient and occupational air quality standards (used for comparative purposes). (OSAGWI, 1998b; OSAGWI, 2000b) The only exception was particulate matter.

3. Air monitoring studies showed the smoke concentrations were intense in some geographical locations, but few troops were in those locations, or the troops in those locations were only exposed for brief periods (hours to days). (OSAGWI, 1998b; OSAGWI, 2000b) Short-term symptoms were reported by some troops. Some of these problems included exacerbation of existing respiratory conditions, such as asthma and bronchitis. Other reported short-term symptoms included: coughing, black mucus in nasal discharge, eye and throat irritation, and the onset of skin rashes and shortness of breath.

4. In November 1998, another comprehensive review of the scientific literature was published on the potential health effects of exposure to the oil well fire smoke. (Spektor, 1998) Even under conditions of a very conservative exposure scenario, the concentrations contained in

the smoke were much lower than the levels that are known to cause disease in the long-term, other than particulate matter.

5. In July 2000, OSAGWI completed an investigation of the potential long-term health effects of exposures to particulates during the Gulf War. (OSAGWI, 2000c) The levels of particulate matter observed in the region were high, particularly in the respirable size range, and had the potential for causing short-term symptoms. In addition, the high levels of particulates were not just the result of the oil fires, but mainly the result of natural background conditions, such as sandstorms. More than 75% of the particulates came from the high levels of sand in the desert environment. About 10 to 23% came from the oil well fires, with miscellaneous sources contributing a minor fraction. The findings were that reversible, short-term effects might have occurred, related to the high levels of particulates in the Kuwaiti Theater of Operations. However, the findings demonstrated that it was unlikely that these exposures could lead to chronic or long-term illnesses.

6. The US Army Center for Health Promotion and Preventive Medicine, and its predecessor, the US Army Environmental Hygiene Agency, performed two health risk assessments related to the oil well fires. (OSAGWI, 2000b) Modeled calculations were performed for cancer and non-cancer health outcomes (e.g., damage to the cardiopulmonary, renal, neurological, and reproductive systems). Estimates were made of the likelihood that exposed troops could experience the onset of disease, originating from their exposure to oil fire smoke. Risk levels were calculated for all US troops, and the calculated risk levels were then compared to levels determined to be safe for ambient air by the US Environmental Protection Agency. The results of the assessment indicated that in all cases, the calculated levels of risk for cancer and for non-cancer outcomes were below levels that the US EPA considers safe for the general US population.

7. In summary, the most visible source of possible contamination to which US troops were exposed during the Gulf War was the smoke from more than 600 burning oil wells. Air monitoring studies showed the smoke concentrations were intense in some geographical locations, but few troops were in those locations, or the troops in those locations were only exposed for brief periods (hours to days). A series of health risk assessments have been performed, and the overall risk of long-term adverse effects from exposure to the oil well fires has been assessed to be minimal.

VII.B. Rates of pulmonary symptoms and diagnoses reported by GWV, in comparison with an appropriate control group (1996 Question 14)

1. The mortality rates of 622,000 GVW and 746,000 NDV were evaluated, with follow-up through December 1997. (Kang and Bullman, 2001) Death rates due to respiratory diseases were very low, and were similar in GWV and NDV.

2. There have been two major publications about hospitalizations in GWV and NDV. (Gray, et al, 1996; Gray, et al, 2000) The 2000 study extended the follow-up period of the 1996 study. Hospitalizations in all 697,000 GWV were compared to an equal number of NDV. Data were used from three hospital systems: DoD hospitals nationwide, VA hospitals nationwide, and all hospitals in the state of California. Data from the DoD hospitals and California hospitals demonstrated no differences in the rates of pulmonary diagnoses between GWV

and NDV. Hospitalizations in VA hospitals for respiratory system diagnoses, such as asthma, were significantly more frequent among GWV than among NDV.

3. Four population-based studies have compared the self-reported rates of respiratory symptoms among GWV and NDV. Each of the four studies demonstrated an increase in respiratory symptoms in GWV. In 1997, the Iowa study demonstrated no differences in the reported rates of asthma and bronchitis among active-duty GWV and NDV. However, the reported rates of asthma and bronchitis were significantly higher among reserve/National Guard GWV than reserve/National Guard NDV. (Iowa, 1997) Canadian GWV reported significantly higher rates of respiratory symptoms (asthma and bronchitis) than Canadian NDV. (Goss Gilroy, 1998) British GWV reported significantly higher rates of asthma and bronchitis than British NDV. (Unwin, et al, 1999) In the VA National Survey, GWV reported significantly higher rates of bronchitis than NDV, however, there were no differences in the rates of asthma. (Kang, et al, 2000)

4. Four studies are evaluating the relationship between pulmonary symptoms and diagnoses and quantitative estimates of exposures for individual military units. The Naval Health Research Center (NHRC) has compared the rates of hospitalizations among 519,000 GWV with 7 levels of exposure to oil well fire smoke (quantitative estimates of exposure for individual units). (Smith, et al, 2001) The preliminary results show no differences in the rates of hospitalization among the 7 levels, for 15 broad ICD-9 categories of diseases or for specific pulmonary diagnoses. The NHRC is also performing a comparison among GWV with the same 7 levels of exposure, using clinical diagnoses from the two Gulf War registries (Project DoD-94).

5. Investigators in Iowa are comparing 1,900 GWV with four levels of exposure to oil well fire smoke, using quantitative estimates of exposures and symptoms of asthma and bronchitis in 1995-96 (Project HHS-1). Investigators in Boston are comparing more than 2,000 GWV from the Fort Devens cohort, with varying levels of exposure, using quantitative estimates of exposures and respiratory symptoms in 1992-93 (Project VA-7).

6. In summary, the rates of self-reported pulmonary symptoms and diagnoses have been higher in GWV than NDV in some studies, however, the rates have been similar in other studies. Five ongoing studies involve clinical evaluations, including pulmonary function tests. When these studies are completed in 2001, they will clarify whether GWV have increased rates of objective pulmonary diagnoses.

VII.C. Results of pulmonary function tests among GWV, compared to a control group (1996 Question 15)

1. Five studies involve respiratory questionnaires and pulmonary function tests among GWV, one of which has been published. In 1994-95, 527 GWV and 970 NDV were studied who were members of 14 Navy Seabee commands. (Gray, et al, 1999a) GWV reported significantly higher rates of respiratory symptoms, but there were no differences between GWV and NDV on objective pulmonary function tests.

2. Four studies are ongoing, including the VA National Survey and studies in Iowa, the United Kingdom, and Boston. The VA National Survey includes clinical evaluations to determine

the prevalence of asthma and bronchitis diagnoses in GWV and NDV. To follow-up the earlier findings of increases in respiratory symptoms, investigators in Iowa and the United Kingdom have performed pulmonary function tests on a subset of GWV and NDV in 2000. Boston investigators also performed these tests on a subset of the Fort Devens cohort. These four studies will be completed in 2001.

VII.D. Major Relevant Publications-Source of Funding, by Project Number (See bibliography for complete citations.)

- DoD-1: Gray, 1996; Gray, et al, 1999a; Gray, 2000; Smith, et al, 2001
- DoD-39: Unwin, et al, 1999
- Funded by DoD (no project number): OSAGWI, 1998b; OSAGWI, 2000b; OSAGWI, 2000c; Spektor, 1998
- HHS-1: Iowa Persian Gulf Study Group, 1997
- VA-1: Kang and Bullman, 2001
- VA-2: Kang, et al, 2000
- Funded by Canadian Department of National Defence: Goss Gilroy, 1998

VIII. CHEMICAL WEAPONS

Relevant Questions from 1996: 5, 6

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?

Number of Federally-funded projects with this primary or secondary focus area (1994 to December 31, 2000): 22

VIII.A. Exposure levels among GWV to nerve agents or mustard agent, as a result of demolitions at Khamisiyah, the allied bombing campaign, or other possible incidents of chemical weapons exposures (1996 Questions 5 and 6)

VIII.A.1. Potential exposure to chemical weapons, due to the demolitions at Khamisiyah

1. In February 1997, OSAGWI released an assessment of the potential release of chemical weapons (CW) at Khamisiyah, Iraq. (OSAGWI, 1997) However, many questions about potential exposures to US troops remained. In December 2000, OSAGWI released an updated assessment. (OSAGWI, 2000f) The overall assessment in 2000 was that US soldiers definitely destroyed many, but not all, of the chemical rockets at Khamisiyah; and that some US troops were likely exposed to very low levels of nerve agent from the demolitions on March 10, 1991. This is the only known event during the Gulf War that may have exposed large numbers of troops to chemical warfare agents, even at low concentrations.

2. Soldiers in the Army 82nd Airborne Division destroyed a large munitions depot in southern Iraq at a place called Khamisiyah on March 10, 1991. (OSAGWI, 1997; OSAWGI, 2000f) In 1996, DoD determined that United Nations weapons inspection teams had found 122 mm Iraqi rockets stored at the depot that contained sarin and cyclosarin. UN teams inspected Khamisiyah in October 1991, March 1992, and May 1996. Some of these rockets may have been among those destroyed or damaged by US troops during the demolition in March 1991.

3. The investigation of Khamisiyah determined that the exposure levels would have been too low to activate chemical detector alarms or to cause any symptoms among US troops. (CIA and DoD, 1997; OSAWGI, 2000f) Hundreds of service members have been interviewed, who were near Khamisiyah in March 1991, including medical personnel. They reported no evidence of symptoms related to CW exposure at the time of the demolitions.

4. In 1996-97, OSAGWI worked to determine the nature of the CW exposure that may have occurred and which units may have been involved. (OSAGWI, 1997; CIA and DoD, 1997) Investigations focused on the number of rockets destroyed, the amount of CW in the Iraqi

rockets, and how soldiers placed the demolition charges on the stacks of rockets. Field-testing of rocket demolitions at Dugway Proving Grounds, Utah in 1997 greatly improved the understanding of the demolition. DoD and CIA modeled the number of rockets destroyed and damaged, the amount of CW likely released, where the wind would have likely carried the CW, and the possible downwind exposure levels to nearby troops.

5. The results of this field-testing and modeling effort were published in July 1997. (OSAGWI, 1997; CIA and DoD, 1997) The model showed the extent of the potential hazard area, which is bounded by the general population limit, which is an extremely low concentration (the limit below which any member of the general population could be exposed for seven days a week for a lifetime, without experiencing adverse health effects). It is important to note that the modeling process is based on computer simulation, and not on empirical data. In 1997, 99,000 individual veterans were sent notification letters, who were assigned to units that may have been briefly exposed to extremely low levels of CW.

6. In 1997-98, OSAGWI held a series of in-depth conferences with Gulf War operations officers, to improve the knowledge of unit locations. (OSAGWI, 2000f) In all, 19 week-long conferences were held and the information obtained greatly increased the accuracy and completeness of the unit location database. The 1997 plume model was subjected to rigorous independent peer review. The comments of the scientific reviewers were incorporated to refine the modeling effort.

7. Several improvements were made to the model, which was republished in December 2000. (OSAGWI, 2000f) These include: improved weather models; an updated estimate of the amount of CW released; consideration of how long the CW would remain in the environment (including consideration of deposition and degradation); and data on cyclosarin, which was not considered in the 1997 plume model. The most influential change in 2000 was the updated personnel and unit location data. The revised 2000 model predicts that the possible exposure areas are generally smaller than those modeled in 1997. In December 2000, 101,000 individual veterans were sent notification letters, who were assigned to units that may have been briefly exposed to extremely low levels of CW. These include 66,000 individuals who also received notification letters in 1997. 33,000 individuals who received notification letters in 1997 were determined not to be under the 2000 plume, so they were sent letters advising them of their change in status.

VIII.A.2. Potential exposure to chemical weapons, due to the allied bombing campaign

1. Bombing during the air campaign could have caused the release of chemical weapons (CW) during the Gulf War. (OSAGWI, 2000e) Post-war inspections by United Nations teams and Iraqi declarations indicated that CW were present at only three locations that were bombed during the war-Muhammadiyat, Al Muthanna, and Ukhaydir. The results of OSAGWI investigations and modeling for these three sites were recently published. The conclusions of the Muhammadiyat investigation are summarized below. (OSAGWI, 2001b) The conclusions of the Al Muthanna investigation were that US forces were definitely not exposed to CW, resulting from the destruction of a bunker containing sarin-filled artillery rockets in February 1991. (OSAGWI, 2001f) The conclusions of the Ukhaydir investigation were that exposure of US forces was unlikely, resulting from damage to artillery shells

containing mustard agent, during air strikes in January and February 1991. (OSAGWI, 2001e)

2. In 1996, the Central Intelligence Agency (CIA) published a report examining the possibility of exposure of US troops to CW due to coalition bombing, and it concluded "chemical agents released by aerial bombing of CW facilities did not reach US troops in Saudi Arabia." (CIA, 1996) OSAGWI reevaluated the potential release from the ammunition storage site at Muhammadiyat because of improvements in modeling methodology and reanalysis of the characteristics of the possible CW agent release. (OSAGWI, 2001b)

3. In October 1991, United Nations inspectors determined that bombing had destroyed or damaged nerve agent and mustard agent-filled bombs at Muhammadiyat, which was located 87 miles west of Baghdad in central Iraq. (OSAGWI, 2001b) OSAGWI and CIA examined the available data to determine the type and quantity of agents released, the possible dates of release, and whether US troops were exposed. The bombing released an estimated 400 pounds of a mixture of sarin and cyclosarin nerve agents and an estimated 6,500 pounds of mustard agent.

4. The dates that the bombing caused the damage to the munitions were unknown, so OSAGWI modeled each possible date. (OSAGWI, 2001b) This included air strikes on 15 dates between January 19, 1991 and February 24, 1991. The models showed the extent of the potential hazard area, which is bounded by the general population limit, which is an extremely low concentration (the limit below which any member of the general population could be exposed for seven days a week for a lifetime, without experiencing adverse health effects). Modeling the releases indicated that the closest US forces in Saudi Arabia were 35 miles from the nerve agent hazard area. The closest US forces in Saudi Arabia were 125 miles from the mustard hazard area.

5. The overall assessment was that US forces in Saudi Arabia were definitely not exposed to CW from the bombing. (OSAGWI, 2001b) However, it is possible that 75 or fewer Special Operations Forces personnel, who were in Iraq in February 1991, may have been exposed to low levels of nerve agent on three possible dates. However, only the general vicinity of these soldiers, not their precise locations are known, therefore the potential for their exposure was assessed as indeterminate. No Special Forces were present on the possible days of mustard agent release. Other than the Khamisiyah and Muhammadiyat incidents, the only possible, documented CW exposure was the incident of indeterminate mustard agent exposure of Private Fisher on March 1, 1991. (OSAGWI, 2000d)

VIII.A.3. Potential exposure to chemical or biological weapons, due to SCUD missile attacks

1. In July 2000, OSAGWI published an interim assessment of the characteristics, capabilities, and use of Iraq's SCUD short-range ballistic missiles. This assessment was republished without changes, as a final report in February 2001. (OSAGWI, 2001c) These reports focused particularly on the number of missile attacks against the Kuwaiti Theater of Operations (KTO) and whether the missiles may have contained chemical or biological weapons.

2. 88 SCUD missiles struck in or near the KTO (46 missiles) and Israel (42 missiles). (OSAGWI, 2001c) Several other missiles failed early in flight and struck in Iraq. US Space Command registered a total of 97 launch attempts. Some veterans thought that Iraq launched more SCUD missiles than actually occurred. Often, SCUDs broke up on re-entry or after Patriot missile intercepts, and debris hit the ground in separate locations. This contributed to the impression of more attacks, along with numerous false alarms and Patriot missile fire on false targets.

3. Although Iraq had produced both chemical and biological warheads for their SCUD missiles, they did not employ them during the war. (OSAGWI, 2001c) The US threatened massive retaliation if Iraq used chemical or biological weapons. Also, technical difficulties encountered during testing of the warheads deterred Iraq from their use. No chemical or biological warheads were ever found in the debris of SCUD missiles. When SCUD missiles broke up, they often released clouds of fuel oxidizer into the air. The oxidizer, inhibited red fuming nitric acid (IRFNA), could cause a yellowish-brown or orange mist, and could cause burning skin, difficulty breathing, or nausea. Some veterans' accounts are consistent with IRFNA exposure. Lacking alternative explanations at the time, some veterans believed that the mist and accompanying symptoms meant they had been exposed to CW.

4. SCUD missiles caused millions of dollars of damage to Israeli cities and killed several Israeli civilians. (OSAGWI, 2001c) A SCUD missile was also responsible for the incident that caused the most US casualties during the war. On February 25, 1991, a warhead from a disintegrating missile fell upon a warehouse in the Dhahran suburb of Al Khobar. The warehouse served as a temporary barracks, mostly occupied by the 475th Quartermaster Detachment from Pennsylvania. 28 soldiers died and 99 were injured. The PTSD Clinical Team at the Highland Drive VA Medical Center in Pittsburgh developed an early treatment intervention program for the members of this unit. (Perconte, et al, 1993) Several members of this unit were treated for several weeks during March and April 1991 for symptoms of PTSD, depression, and increased alcohol use.

5. In summary, US soldiers definitely destroyed many, but not all, of the chemical rockets at Khamisiyah, Iraq, on March 10, 1991. DoD assessed that some US troops were likely exposed to very low levels of sarin and cyclosarin from the demolitions. No service members have reported symptoms related to nerve agent exposure at that time. This is the only known event during the Gulf War that may have exposed large numbers of troops to chemical warfare agents, even at low concentrations. It is possible, but indeterminate, that 75 or fewer Special Operations Forces personnel who were in Iraq may have been exposed to low levels of nerve agent on three possible dates in February 1991, due to the bombing of Muhammadiyat, Iraq. Other than the Khamisiyah and Muhammadiyat incidents, the only possible, documented chemical weapon exposure during the war was the incident of indeterminate mustard agent exposure of one soldier on March 1, 1991.

VIII.B. Possible health effects among GWV of low-level nerve agent exposure, compared to an appropriate control population

1. The Institute of Medicine published a comprehensive literature review of the effects of sarin and cyclosarin in September 2000. (IOM, 2000) IOM concluded there was "sufficient

evidence" of a relationship between high-level exposure to sarin and serious, short-term effects. These levels cause overt poisoning symptoms, and therefore are much higher than the levels that US troops may have experienced due to Khamisiyah. The IOM concluded there was "inadequate/insufficient evidence" to determine if there is an association between "sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent adverse long-term effects." IOM noted there were "no well-controlled studies of long-term health effects in humans exposed to sarin at doses that do not produce acute signs and symptoms."

2. Twenty-two research projects have been funded to evaluate the possible long-term effects of low-level chemical warfare exposure. Fifteen projects focus on the toxicological effects in experimental animals, including rats, mice, guinea pigs, chickens, and monkeys. Nine of these projects focus on low-level sarin exposure, alone or in combination with stress (heat stress or exercise stress), and/or pyridostigmine bromide and pesticides (DEET, permethrin, and chlorpyrifos). The health outcomes include changes in neuroanatomy, neurochemistry, and behavior. These studies have few published results, as of June 2001.

3. Four of the twenty-two projects focus on long-term effects in humans due to short-term exposure to nerve agents. One of these projects, which will be completed in 2001, focuses on the long-term effects of sarin and other nerve agents on volunteers who participated in experiments at Aberdeen Proving Grounds from the 1950s to 1970s (Project DoD-93). Three projects focus on possible exposures due to the demolitions at Khamisiyah. Scientists at the Naval Health Research Center, the Portland VA Medical Center, and the Institute of Medicine are performing these three studies.

4. In the study performed by the Naval Health Research Center, 124,487 veterans were categorized into 4 levels of estimated exposure, due to the Khamisiyah plume. (Gray, et al, 1999c) 224,804 veterans were categorized as not exposed. Hospitalization data from all DoD hospitals were evaluated through September 1995. The rates of hospitalization were evaluated for diagnoses in 15 broad ICD-9 categories and for specific neurological diagnoses, which were possible, subtle nerve agent-induced effects. There were no associations between the four groups of possibly exposed veterans and the 15 broad categories or the specific neurological diagnoses. The authors concluded that, overall, these data do not support the hypothesis that GWV are suffering post-war morbidity from subclinical nerve agent exposure.

5. The Portland VA Medical Center study performed detailed neurological and neurophysiological tests on GWV who had potential exposure to the Khamisiyah plume, compared to two control groups. (Spencer, 2001) The potentially exposed group consisted of 42 veterans who were within 50 km of Khamisiyah, including 7 individuals who witnessed the demolitions. The comparison groups included 26 GWV who were located more than 50 km of Khamisiyah, and 28 NDV. The test battery was designed to detect persistent effects of organophosphate nerve agents. There were no differences on the tests among the three groups of veterans.

6. The Institute of Medicine is performing a study of the rates of mortality, hospitalization, and self-reported symptoms in GWV with possible exposure due to Khamisiyah, compared with GWV with no exposure (Project DoD-69). This project will be completed in 2001.

7. In addition to these three funded projects focusing on Khamisiyah, there are three studies that are outgrowths of other projects, which evaluate mortality rates, clinical diagnoses, and self-reported symptoms. The mortality rates of 48,281 GWV with possible exposure due to Khamisiyah were compared with the mortality rates of 573,621 GWV with no exposure. There were no differences in mortality rates from all causes, all natural causes, accidents, or any other cause. (Kang and Bullman, 2001) GWV with possible exposure due to Khamisiyah will be compared with GWV with no exposure, using clinical diagnoses from the combined analysis of the two Gulf War registries (Project DoD-94). Based on data from the Fort Devens study, GWV with possible exposure due to Khamisiyah will be compared with GWV with no exposure, using self-reported symptoms in 1994-1996 (Project VA-4).

8. In summary, there are 6 research projects that focus on the possible long-term effects of exposures due to the demolitions at Khamisiyah, three completed studies and three that will be completed in 2001. One study demonstrated no differences in the rates or causes of hospitalizations among veterans who may have had low-level exposure due to Khamisiyah, compared to veterans who had no exposure. A second study showed no differences in the rates or causes of mortality among veterans with possible low-level exposure, compared veterans with no exposure. The third study showed no differences on sensitive neurological and neurophysiological tests among veterans with possible low-level exposure, compared to veterans with no exposure.

VIII.C. Major Relevant Publications-Source of Funding, by Project Number (See bibliography for complete citations.)

- DoD-1: Gray, et al, 1999c
- DoD-63: Spencer, 2001
- Funded by DoD (no project number): OSAGWI, 1997; OSAGWI, 2000d; OSAGWI, 2000e; OSAGWI, 2000f; OSAGWI, 2001b; OSAGWI, 2001c; OSAGWI, 2001e; OSAGWI, 2001f
- VA-1: Kang and Bullman, 2001
- Funded by VA (no project number): Perconte, et al, 1993; IOM, 2000
- Funded by the Central Intelligence Agency (no project number): CIA, 1996; CIA and DoD, 1997

IX. INTERACTIONS OF EXPOSURES (INCLUDING PYRIDOSTIGMINE BROMIDE AND PESTICIDES)

Relevant Questions from 1996: 7,17

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

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?

Number of Federally-funded projects with this primary or secondary focus area (1994 to December 31, 2000): 32

IX.A. Health effects of short-term, low-level exposures to pyridostigmine bromide and pesticides, alone or in combination (in particular, DEET and permethrin) (1996 Question 7 and 17)

IX.A.1. Overview on the Use of Pyridostigmine Bromide (PB) during the Gulf War

1. First, overviews are provided for the use of PB and pesticides. Then, a review of the completed and ongoing research is provided. PB is a drug used in the military as a pretreatment for potential nerve agent exposure. It was used by an estimated 250,000 Gulf War veterans during January and February 1991. Since 1994, DoD and VA have funded 25 research projects on the potential health effects of PB, alone or in combination with low-level sarin exposure, exposure to pesticides (DEET, permethrin, and chlorpyrifos), and various types of stressful stimuli.

2. In September 2000, the Institute of Medicine published a comprehensive literature review of the potential short-term and long-term effects of PB use. (IOM, 2000) PB has been used safely and effectively in the long-term treatment of a neurological disease, myasthenia gravis, in thousands of patients since the 1950s. The doses given in treatment are much higher than the doses given during the Gulf War. Many studies have shown that PB is safe and effective in clinical applications. The short-term side effects of doses used in clinical practice are mainly gastrointestinal, such as diarrhea, and are of short duration with no long-term residual effects. PB has been used in a variety of diagnostic tests, and no central nervous system symptoms have been reported. No CNS symptoms would be expected, since PB has not been shown to cross the blood-brain barrier under usual circumstances.

3. IOM concluded there was "inadequate/insufficient evidence" to determine whether an association exists between PB and long-term adverse health effects. (IOM, 2000) IOM noted that no reports of chronic toxicity were available related to PB use in clinical or military populations. There have not been any long-term studies that evaluated subtle health effects systematically.

4. IOM reviewed two studies of PB use in Gulf War veterans. (Haley and Kurt, 1997c; Unwin, et al, 1999) IOM concluded, "the epidemiological data do not provide evidence of a link between PB and chronic illness in Gulf War veterans." (IOM, 2000)

IX.A.2. Overview on Pesticides Used During the Gulf War

1. In January 2001, OSAGWI published a comprehensive review of pesticides used during the Gulf War and their potential health effects. (OSAGWI, 2001d) Troops used pesticides for a number of reasons. These included skin and uniform application to repel insects, as area sprays and fogs to kill flying insects, in pest strips and fly baits to attract and kill flying insects, as surface sprays, and as delousing agents applied to enemy prisoners of war to control typhus.

2. Based on a thorough analysis of the available data, OSAGWI focused their investigation on 12 pesticides of potential concern. (OSAGWI, 2001d) These 12 posed the greatest potential hazards to US service members, due to prevalence of use, toxicity, and manner of use. The 12 pesticides fall into five major categories: five organophosphate pesticides (azamethiphos, chlorpyrifos, diazinon, dichlorvos, and malathion); three carbamate pesticides (bendiocarb, methomyl, and propoxur); two pyrethroid pesticides (permethrin and d-phenothrin); one organochlorine pesticide, lindane; and one repellent, DEET. Some pesticides were used only on a limited basis, and some were used by only a very small number of US service members, such as lindane used by military police for delousing Iraqi prisoners of war. Other pesticides were widely used and available to the general military population, primarily DEET and permethrin.

3. The Environmental Protection Agency (EPA) approved all the pesticides that were obtained through the military supply system. These were considered safe for use when applicators followed instructions for use on the packaging labels. Nearly all of these 12 pesticides were available for purchase by the general public at local garden stores, and were approved by the EPA and/or the Food and Drug Administration for general use by the US public. However, some pesticides were purchased locally that have not been approved for general use by the EPA. The most prevalent locally purchased pesticide, that was not EPA-approved, was a fly bait called Snip (generic name azamethiphos).

4. There were certain groups of military personnel, totaling about 3,500 to 4,500 individuals, who were potentially at greater risk from pesticide exposure, because of their job responsibilities. (OSAGWI, 2001d) These included trained and certified pesticide applicators, field sanitation teams, and military police who conducted delousing operations. OSAGWI investigators conducted personal interviews with over 900 preventive medicine personnel, pesticide applicators, and other knowledgeable personnel, to acquire information about pesticide application and management practices during the Gulf War. There does not appear to have been an appreciable risk from exposure to pesticides to the general military population.

5. A qualitative health risk assessment (HRA) was performed to estimate the likelihood that exposures to pesticides may have been associated with short-term effects at the time of the exposure. The HRA provided an estimate of the likelihood of certain specific health effects,

and identified veteran groups who constituted high-risk populations due to their involvement with pesticides. (OSAGWI, 2001d) The HRA suggested that some pesticide applicators might have been exposed to levels of pesticides that exceeded conservatively-defined levels of concern for short-term exposures.

6. The results of the HRA alone do not prove either that overexposures occurred during deployment, or that any association exists between pesticide exposures and chronic health effects months or years after exposure. (OSAGWI, 2001d) The results of the HRA were hampered by a complete lack of sampling data on the concentrations of pesticides that may have present in the air or on surfaces. Because of this lack of data, significant uncertainties exist in the findings of the HRA. In particular, many of the assumptions that were included in the HRA were very conservative, therefore tending to overestimate exposures.

7. Eight pesticides were considered to have posed the greatest risk, including the five organophosphate pesticides, two of the three carbamates (bendiocarb and methomyl), and lindane. (OSAGWI, 2001d) DEET and permethrin were the two products used frequently as insect repellents by the general military population. DEET was applied directly to the skin. Permethrin was sprayed directly on uniforms. The HRA did not identify a risk of overexposure from DEET or permethrin.

8. Despite over 900 interviews and the review of many in-theater medical records, OSAGWI investigators identified only one documented case of an individual seeking medical care for pesticide exposure. (OSAGWI, 2001d) This individual experienced short-term, reversible health effects, which included nausea, mild headaches, and lung irritation. When he was recently interviewed, he was not experiencing any chronic adverse effects.

9. In early 2001, the Institute of Medicine began a comprehensive literature review of the potential health effects of pesticides used during the Gulf War, which will be published in late 2002.

IX.A.3. Health effects of short-term, low-level exposures to pyridostigmine bromide and pesticides, alone or in combination (in particular, DEET and permethrin) (1996 Question 7 and 17)

IX.A.4. Health effects of short-term, low-level exposures to pyridostigmine bromide and stressors, in combination (for example, heat stress or forced swimming stress)

1. Since 1994, DoD and VA have funded 32 projects focusing on the potential health effects of PB and pesticides, alone or in combination. The results of many of these projects have been published recently, and are summarized here. The key research question is whether PB can cross the blood-brain barrier. In order to cause long-term changes in brain function, PB has to be able to cross into the brain. One preliminary study in 1996 indicated that PB could cross the blood-brain barrier in mice under stressful conditions. However, several more recent studies have not replicated this finding.

2. One preliminary study in rodents 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 blood-brain barrier (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. (Telang, et al, 1999)

3. 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). The overall conclusions in a recent study were "There is no evidence that exogenous stress increases BBB permeability in mature rodents." (Sinton, et al, 2000)

4. 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, Haley, and colleagues concluded "to the extent that cross-species comparisons are valid" between humans and rodents, "the effects of stress on BBB permeability to PB are unlikely to explain the chronic CNS symptoms reported by some Gulf War veterans." (Sinton, Haley, et al, 2000) This conclusion is particularly noteworthy because it is contradictory to a previous 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 and Kurt, 1997c)

5. 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)

6. In summary, several studies have been published recently that focused on the potential health effects of pyridostigmine bromide (PB) and pesticides, alone or in combination. The key research question is whether PB can cross the blood-brain barrier (BBB). Several studies have evaluated whether other chemicals, such as pesticides, or stressful stimuli, such as heat stress, can increase the permeability of the BBB, and can therefore enhance penetration of PB into the brain. All these recent studies have reached the same conclusion, that other chemicals or stressful stimuli do not increase the permeability of the BBB to PB, and that PB does not penetrate the brain, even at lethal levels. If PB does not cross the BBB, it is very unlikely to cause changes in brain function.

IX.C. Major Relevant Publications-Source of Funding, by Project Number (See bibliography for complete citations.)

- DoD-39: Unwin, et al, 1999
- Funded by DoD (no project number): OSAGWI, 2001d; White House, 2000
- Funded by VA (no project number): IOM, 2000
- Funded by the Perot Foundation: Haley and Kurt, 1997c; Sinton, Haley, et al, 2000
- Research in US, not federally funded: Telang, et al, 1999; Chaney, et al, 1999; Chaney, et al, 2000
- Research in France: Lallement, et al, 1998
- Research in Israel: Friedman, et al, 1996; Grauer, et al, 2000

X. ENVIRONMENTAL TOXICOLOGY (INCLUDING DEPLETED URANIUM, BIOLOGICAL WARFARE AGENTS, AND VACCINES)

Relevant Questions from 1996: 4

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?

Number of Federally-funded projects with this primary or secondary focus area (1994 to December 31, 2000): 5

Note: Several environmental or occupational exposures have been evaluated as potential causes of illnesses in GWV. These include: infectious diseases, vaccines, oil well fire smoke, depleted uranium, biological warfare agents, chemical weapons, pyridostigmine bromide, and pesticides. The evidence for each of these exposures is summarized in other sections, except for depleted uranium, biological warfare agents, and vaccines, which are summarized here.

X.A. Potential exposure levels among GWV to depleted uranium, and the possible health effects (1996 Question 4)

X.A.1. Potential exposures among GWV to depleted uranium

1. OSAGWI released an updated Environmental Exposure Report on depleted uranium (DU) in December 2000, focusing on the potential exposures of US service members during the Gulf War. (OSAGWI, 2000a) Based on the scientific evidence to date, the report concludes it is unlikely that DU exposure is a cause of the undiagnosed illnesses experienced by some Gulf War veterans. The first interim report about DU was published in August 1998. (OSAGWI, 1998a)

2. The Gulf War was the first conflict involving battlefield use of armor-piercing munitions and reinforced tank armor incorporating depleted uranium (DU). Depleted uranium played a key role in US forces' overwhelming success during the Gulf War. This very dense metal is a by-product of the process by which natural uranium is "enriched" to produce reactor fuel and nuclear weapons components. The leftover uranium, 40% less radioactive than natural uranium, is called "depleted uranium," or DU. At high concentrations, DU can cause chemical toxicity, which is identical in all forms of uranium, and which is similar to other heavy metals, such as lead. The extreme density of the metal and its self-sharpening properties make DU a formidable weapon. Its projectiles slice through thicker, tougher armor at greater ranges than other high-velocity rounds.

3. OSAGWI investigators interviewed hundreds of Gulf War combatants and eyewitnesses, reconstructed numerous operations, consulted with subject matter experts, and researched the most current body of knowledge about DU's health effects and environmental impact. (OSAGWI, 2000a) The investigation classifies possible DU exposures into three levels (I, II,

and III), encompassing 13 separate activities or incidents. These levels were derived from initial assessments of the exposures' potential relative risks, decreasing from Level I to Level III.

4. Level I includes incidents in which US tanks mistakenly fired DU armor-piercing rounds into other US combat vehicles, exposing surviving crew in those vehicles to wounds from DU fragments and/or inhaled and ingested particles formed when DU munitions penetrate armor, especially tank armor (104 exposed individuals). (OSAGWI, 2000a) During these friendly-fire incidents, personnel rushing to evacuate and rescue fellow soldiers from stricken vehicles also may have been directly exposed to DU (30 to 60 exposed individuals). OSAGWI investigators have conducted personal interviews with nearly all of the 104 individuals who were directly involved in the friendly fire incidents.

5. Level II exposures to DU occurred after combat, when explosive ordnance disposal (EOD) personnel entered DU-struck vehicles to remove unexploded munitions (10 to 20 exposed individuals). (OSAGWI, 2000a) In addition to EOD personnel, battle damage assessment teams (BDAT), radiation control (RADCON) teams, and salvage crews worked in and on the damaged or destroyed vehicles as they were processed for repair or disposal (at most, 150 exposed individuals). This group also includes personnel involved in cleanup and recovery operations in the North Compound of Camp Doha, Kuwait, after a July 1991 motor pool fire in which DU munitions, among others, detonated and burned (more than 600 individuals). Level II includes these personnel and others who may have come into direct contact with dust residue from expended DU rounds.

6. Level III includes personnel whose exposure to DU was short-term and generally very low. (OSAGWI, 2000a) Exposures may have occurred as personnel passed through and inhaled smoke from burning DU, casually handled spent DU penetrators, or briefly entered DU-struck vehicles on the battlefield or in salvage yards.

X.A.2. Potential health effects of depleted uranium among GWV

1. Based on data developed to date, OSAGWI concluded that, while DU could pose a chemical hazard at high intakes, no Gulf War veterans experienced intakes high enough to cause health effects. (OSAGWI, 2000a) Furthermore, the available evidence indicates that due to DU's low-level radioactivity, adverse radiological health effects are not expected. The available scientific and medical evidence to date does not support claims that DU caused or is causing illnesses in Gulf War veterans. Nevertheless, further medical follow-up is warranted for soldiers with embedded DU fragments, which DoD and VA have committed to continue indefinitely.

2. Since 1993, the Baltimore VA Medical Center has monitored 33 veterans seriously injured in friendly-fire incidents involving depleted uranium. (Hooper, et al, 1999; McDiarmid, et al, 2000) The VA is following the group very carefully, administering a broad battery of medical tests to determine if the embedded DU fragments are causing any health problems. While these veterans have persistent impairments due to their wartime injuries, the Baltimore researchers report that the veterans are not demonstrating adverse effects from DU's chemical or radiological toxicity. About half of the 33 veterans still have DU fragments in their bodies, and they have demonstrated persistent elevated concentrations of urinary

uranium. The veterans without retained DU fragments have not shown higher than normal levels of urinary uranium. To date, no adverse effects in the kidney have been detected. In 1999, the Baltimore VA evaluated 30 additional veterans involved in friendly-fire incidents, including 4 with suspected embedded DU fragments. (OSAGWI, 2000a) While there has been no clinical evidence of illness associated with DU exposure to date, the veterans involved in friendly fire will remain under medical surveillance indefinitely.

3. In August 1998, DoD and VA extended the medical follow-up program to evaluate all individuals who were in or on vehicles struck by friendly fire, as well as those who worked around DU-struck vehicles or burned vehicles containing DU (Level I and Level II). (OSAGWI, 2000a) The follow-up program guidelines called for OSAGWI to notify these veterans of their exposures and offer a medical evaluation. To date, OSAGWI has notified more than 200 Level I and Level II veterans about this follow-up program.

4. As an extension of the two Gulf War Registries, DoD and VA initiated a program in 1998 to perform a DU medical examination for any concerned Gulf War veteran who requests it. This includes a physical exam, a questionnaire for DU exposure, and a 24-hour urine sample to measure urinary uranium. As of late 2000, 398 veterans have received this exam. The results were recently published for the first 169 veterans who volunteered for this expanded program in August 1998 to December 1999. (McDiarmid, et al, 2001) Only three individuals had validated, elevated concentrations of uranium in their urine. Of these three individuals, one person probably had retained DU metal fragments from a friendly fire incident. The sources of the elevated uranium levels in the other two persons are unknown; in fact, one of them was not even a Gulf War veteran. The authors concluded that elevated urinary uranium levels were unlikely to be observed, except for those veterans with retained DU metal fragments. They stated: "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."

5. DoD has funded five toxicology projects to investigate the health effects of DU in experimental animals. The Armed Forces Radiobiology Research Institute has been investigating the health effects of embedded DU pellets in rats since 1994. One important finding has been that there was no detectable kidney toxicity in these rats, even at very high concentrations of urinary uranium. (Pellmar, et al, 1999a; Pellmar, et al, 1999b)

6. Three major scientific reviews of the toxicology of uranium and depleted uranium were published in 1999 and 2000. The first was the comprehensive medical literature review on the potential health effects of DU, published by RAND in April 1999. (Harley, et al, 1999) The second review, dated September 1999, is the *Toxicological Profile for Uranium (Update),* published by the Agency for Toxic Substances and Disease Registry (ATSDR), which is part of the Department of Health and Human Services. (ATSDR, 1999) ATSDR toxicological profiles are recognized internationally as an authoritative source of information about human and environmental effects of hazardous chemicals. The third review was *Gulf War and Health: Volume 1, Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines*, recently published by the Institute of Medicine. (IOM, 2000) These three reports provide comprehensive assessments of the chemical and radiological effects of uranium on health.

7. RAND concluded that the medical literature contains no evidence of radiological health effects resulting from exposure to natural uranium or depleted uranium. (Harley, et al, 1999) RAND also concluded that, while uranium in large doses can cause changes in kidney function, no increases in kidney disease have been observed in relatively large occupational populations chronically exposed to natural uranium. The RAND study also cited the absence of kidney effects in friendly fire victims with embedded DU fragments in the Baltimore VA follow-up program, despite the presence of elevated urine uranium levels. The ATSDR profile concluded that, because of scientific evidence and the low radioactivity of natural and depleted uranium, it expects no radiological health hazard from inhalation, dermal, or oral exposure to natural or depleted uranium. (ATSDR, 1999)

8. In September 2000, the Institute of Medicine (IOM) released its report on depleted uranium. In particular, IOM focused on two concerns often raised about uranium exposures: renal dysfunction and lung cancer. (IOM, 2000) IOM concluded that there was "limited/suggestive evidence of no association" between uranium exposure and renal dysfunction, and between uranium exposure and lung cancer (at cumulative exposures less than 20 rems) (a rem is a unit of radiation dose). Twenty rems are at least four times higher than the highest radiological doses estimated for Gulf War veterans. (OSAGWI, 2000a) The IOM report also stated the data were inadequate or insufficient to determine whether exposure to uranium is associated with a variety of other chronic health conditions, including bone cancer, lung cancer (at cumulative exposures greater than 20 rems), lymphatic cancer, nervous system disease, and nonmalignant respiratory disease.

9. In summary, because of the scientific evidence to date, and the low radioactivity of natural and depleted uranium, no radiological health hazard is expected from inhalation, dermal, or oral exposure to natural or depleted uranium. While depleted uranium (DU) could theoretically cause heavy metal toxicity at very high levels, in particular kidney dysfunction, no Gulf War veterans experienced intakes high enough to cause adverse health effects. The available scientific and medical evidence to date does not support concerns that DU has caused or is causing illnesses in Gulf War veterans. A total of 104 individuals were exposed to DU in friendly fire incidents, some of whom have retained metallic fragments. While there has been no clinical evidence of illness associated with DU exposure to date, the veterans involved in friendly fire will remain under medical surveillance indefinitely.

X.B. Potential exposures of GWV to biological warfare agents (1996 Question 4)

1. In October 2000, OSAGWI published an interim assessment of the potential use of biological weapons (BW) during the Gulf War. This assessment was republished without changes, as a final report in February 2001. (OSAGWI, 2001a) Iraq had used CW in the Iran-Iraq War. During the Gulf War, it was suspected that Iraq was developing a capability to use BW, including anthrax and botulinum toxin. The purpose of the investigation was to explain Iraq's program to develop BW, to identify the actions that US forces took during the war to detect and report BW exposures, and to assess the possibility that Iraq actually used BW agents. The overall conclusion was that there was no evidence that Iraq used BW agents during the Gulf War.

2. OSAGWI reviewed classified and unclassified documents from each branch of service, and it reviewed reports of the United Nations inspection teams. (OSAGWI, 2001a) These reports described post-war inspections of suspected BW production and storage sites. OSAGWI reviewed reports of units specializing in various aspects of enemy use of BW, and interviewed personnel who served in these units, who collected suspect samples, and transported them to the US for further analysis. They also interviewed scientists who examined the results of these analyses at the US Army Medical Research Institute of Infectious Diseases.

3. During the war, DoD developed a system to monitor, evaluate, and transport possible BW samples. (OSAGWI, 2001a) All the documentation and interviews provided a consistent result-the total absence of disease patterns, or even a case of a single individual, associated with BW agents. However, the use of BW cannot be completely ruled out, because air sampling for BW was not conducted continuously, nor did it cover the entire battlefield.

X.C. Potential health effects of vaccines among GWV, compared to a control group (1996 Question 4)

X.C.1. Use of vaccines during the Gulf War

1. In December 2000, OSAGWI published an overview of the use of vaccines during the Gulf War. (OSAGWI, 2000g) This overview provides information on vaccines administered to maintain general readiness ("routine" vaccines), as well as vaccines chosen for specific use during the Gulf War, including vaccines against biological warfare (BW) agents. Because of its varied missions, the military employs various vaccines against "routine" infectious diseases, as well as infectious diseases that are endemic in foreign countries. The report also discusses adverse reactions associated with vaccines, information that was provided to service members during the war, and the use of investigational vaccines.

2. Many of the "routine" vaccines used by the military are also widely used in the civilian community (such as, polio, measles, mumps, rubella, influenza, tetanus, and diphtheria). (OSAGWI, 2000g) The decisions to use specific vaccines during the Gulf War were based on assessments of the infectious diseases that personnel were likely to encounter. Specific vaccines recommended during deployment to the Gulf War included meningococcal, typhoid, and yellow fever vaccines, and immune globulin to protect against hepatitis A. The very low numbers of reported casualties from infectious diseases were partially due to the effectiveness of the vaccines given to service members before and during deployment. There was only one death due to infectious disease during the war, a case of meningococcal meningitis. (PAC, 1996)

3. During the Gulf War, anthrax vaccine and botulinum toxoid vaccine were used to protect US forces against the threat of BW use. (OSAGWI, 2000g) About 150,000 service members received one or more doses of anthrax vaccine and about 8,000 received one or more doses of botulinum toxoid. Use of these vaccines during the war was characterized by several difficult issues, including: insufficient quantities to protect all forces at risk; prioritization of military units for vaccination because of limited availability; use of the investigational botulinum toxoid vaccine; provision of adequate information about the vaccines to service members; and recording vaccines in health records.

4. Operational security concerns prevented many service members from receiving information about the BW vaccines, why they were being given, and possible side effects. (OSAGWI, 2000g) There was a great deal of misinformation about the anthrax vaccine, for example, that it was not approved by the Food and Drug Administration (FDA). In reality, the vaccine was approved and licensed by the FDA in 1970. The concerns raised by some GWV about the safety of the anthrax vaccine have continued, because DoD began a program to administer the vaccine to all US service members in 1998.

5. Uncertain guidance about how to document these vaccines contributed further to service members' concerns about the vaccines. (OSAGWI, 2000g) Inadequate medical record keeping, especially for the BW vaccines, has made it very difficult to determine which vaccines were given to individual service members. This has complicated research on the possible association between vaccines and illnesses in Gulf War veterans.

X.C.2. Potential health effects of vaccines among GWV

1. In September 2000, the Institute of Medicine published a review of the potential short-term and long-term health effects of the anthrax vaccine, the botulinum toxoid vaccine, and multiple vaccines given concurrently. (IOM, 2000) IOM determined that there was "sufficient evidence" of an association between the anthrax vaccine and the botulinum toxoid vaccine, and transient, short-term local and systemic effects. IOM reached contrasting conclusions about the long-term effects of the anthrax vaccine, the botulinum toxoid vaccine and multiple vaccines given concurrently. In all three, IOM concluded that there was "inadequate/insufficient" evidence to determine whether an association existed between the vaccines and long-term adverse health effects. Studies of these vaccines have not used active surveillance to systematically evaluate long-term health outcomes. Unfortunately, this situation is typical of all but a few vaccines.

2. IOM summarized several completed and ongoing human studies that are following small groups of anthrax vaccine recipients, almost all of which are unpublished. (IOM, 2000) IOM strongly urged the DoD scientists who are conducting these studies to submit their results to peer-reviewed journals for publication. Also, IOM started a new two-year study in 2000 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.

3. The Centers for Disease Control and Prevention (CDC) performed a thorough case-control study of an Air Force National Guard unit in Lebanon, Pennsylvania. (Fukuda, et al, 1998) 490 members of this unit were deployed to the Gulf War, of whom 158 participated in physical exams and several serum antibody tests. These tests focused on antibodies to the two BW vaccines and to important infectious diseases in the Persian Gulf region that can cause chronic diseases. Of the 158 veterans, 8% complained of severe, chronic symptoms of fatigue, musculoskeletal pain, and/or problems with memory or depression. 54% complained of mild to moderate symptoms, and 37% did not have these symptoms (healthy). Ten of the 158 individuals had antibodies to the botulinum toxin, and 14 of the 158 individuals had antibodies to the anthrax protective antigen. There were no differences in the rates of positive antibodies between the ill and healthy veterans. The authors concluded there was no

association between the vaccines and the development of a chronic illness, in this unit with a high proportion of ill veterans.

4. In 1997-98, a mailed survey was conducted among a randomly selected sample of 3,284 British GWV. (Unwin, et al, 1999) A more detailed analysis was performed 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 used data only from 923 veterans who reported that they still had their vaccine records (28%). The associations with six health outcomes were evaluated. Multiple vaccines received before deployment were associated with only one of the six health outcomes (posttraumatic stress reaction). In contrast, five of the six outcomes were associated with multiple vaccines received during deployment (all but posttraumatic stress reaction). The strongest association was for the CDC definition of "chronic multisymptom illness," which was based on the working case definition developed in the CDC Air Force study. (Fukuda, et al, 1998) Receiving the anthrax vaccine was not associated with the "chronic multisymptom illness," whether given before or during deployment. 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 authors are continuing their study, using a case-control design comparing healthy and ill GWV, and relying on Ministry of Defence medical records to validate vaccine use. (Hotopf, et al, 2001)

5. In 1998, a second mailed survey was conducted among a separate group of 7,878 randomly selected British GWV. (Cherry, et al, 2001a; Cherry, et al, 2001b) Questionnaires included data on 95 symptoms and several potential environmental exposures. Factor analysis was performed, which yielded 7 different clusters of symptoms, which were named "psychological, peripheral, gastrointestinal, respiratory," etc. Questions were included about the number and type of vaccines given before or during deployment, and whether or not the veteran had kept his vaccine records. There were no associations between the number of vaccines received and 6 of the 7 clusters of symptoms. There was a significant association between the number of vaccines received and one cluster, named "peripheral," which included symptoms of skin rashes and peripheral neuropathy. This association between the number of vaccines and the "peripheral" cluster of symptoms was consistent in the group of veterans who kept their vaccine records (2,173 veterans), and in the group who had not (5,705 veterans). This association with the "peripheral" cluster was the same, whether the vaccines were given before deployment or during deployment. Because the general designs of the Hotopf study and the Cherry study were similar, there is no obvious explanation why their results were so different. Both authors raised the issue of potential recall bias, because vaccines had become a major focus of concern among British GWV by the time of these studies in 1997-98.

6. DoD has funded more than 50 studies examining the safety and effectiveness of the anthrax vaccine. (White House, 2000) An important example is a long-term study of the participants in the Anthrax Vaccine Immunization Program (AVIP), which was funded in 2000 (DoD-99). Hospitalizations in DoD hospitals nationwide will be linked with data on AVIP participants. This surveillance system should ensure early detection of any associations

between the vaccine and serious health effects that require hospitalization during the 42 days after vaccination.

7. In 2000, CDC began a large collaborative study with DoD to evaluate the safety and effectiveness of vaccines used against biological weapons, especially the anthrax vaccine. (White House, 2000) 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 booster injections in the series; and changing the route of administration from subcutaneous to intramuscular.

8. In summary, during the Gulf War, several "routine" vaccines were administered to service members, such as influenza and tetanus vaccines, as well as vaccines against biological warfare agents. The very low numbers of reported casualties from infectious diseases were partially due to the effectiveness of the vaccines given to service members before and during deployment. About 150,000 service members received the anthrax vaccine. There is inadequate evidence to determine if this vaccine can cause long-term adverse effects, because studies of this vaccine have not used active surveillance to systematically evaluate long-term health outcomes. DoD and CDC have several ongoing studies to evaluate the potential long-term effects of the anthrax vaccine.

X.D. Major Relevant Publications-Source of Funding, by Project Number
(See bibliography for complete citations.)

- DoD-7A: Pellmar, et al, 1999a; Pellmar, et al, 1999b

- DoD-39: Unwin, et al, 1999; Hotopf, et al, 2000; Shaheen, 2000; Bolton, et al, 2001; Hotopf, et al, 2001

- Funded by DoD (no project number): OSAGWI, 1998a; OSAGWI, 2000a; OSAGWI, 2000g; OSAGWI, 2001a; Harley, et al, 1999; White House, 2000

- HHS-2: Fukuda, et al, 1998

- Funded by the Department of Health and Human Services (no project number): ATSDR, 1999

- Funded by VA and DoD (no project number): Hooper, et al, 1999; McDiarmid, et al, 2000; McDiarmid, et al, 2001

- Funded by VA (no project number): IOM, 2000

- Funded by the US Government (no project number): PAC (Presidential Advisory Committee on Gulf War Veterans' Illnesses), 1996

- Funded by UK Medical Research Council: Cherry, et al, 2001a; Cherry, et al, 2001b

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